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Free-Radical Rearrangements. II. Ketones and Esters from the Reactions of Aldehydes with Peroxides[1]

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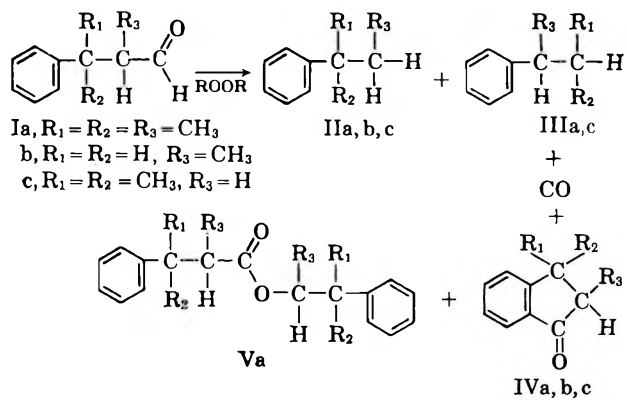
Striking changes occur when the reactions of *t*-alkyl peroxides with aralkanals are carried out at 100°. Carbonyl-containing products are formed indicating that the reactions of intermediate aralkanoyl radicals become more important at the lower temperature. For example, the reaction of *t*-amyl peroxide with 4-methyl-4-phenylpentanal (VI) at 100° gives 18% 4,4-dimethyl-1-tetralone (VIII) and 18% 4-methylvalerophenone (IX) and only 30% of the product of decarbonylation, 3-methyl-3-phenylbutane (VII). Structures with strong steric interactions have a similar effect. The reaction of 2,3-dimethyl-3-phenylbutanal (Ia) with *t*-butyl peroxide even at 140° produces 2,3-dimethyl-3-phenylbutyl 2,3-dimethyl-3-phenylbutyrate (Va, 67%), 2,3,3-trimethyl-1-indanone (IVa, 21%), and products of decarbonylation with partial rearrangement (7%)—carbon monoxide, 2-methyl-2-phenylbutane (IIa), and 2-methyl-3-phenylbutane (IIIa).

Previous studies of the free-radical reactions of aralkanals with *t*-butyl peroxide have stressed their decarbonylation to give aralkanes with their intermediate free-radical rearrangement (1,2-shift of aryl groups)[2-4] that is dominant above 130°. The influence of reaction temperature[2d,4a,d] and reactant concentrations,[2d,4d] as well as conformational[4b,c] and other structural effects,[2b,c,3a,b,4a,d] on the extent of rearrangement have been considered. In two prior studies, the formation of a tetralin[3a] and an indanone[4a] as minor products has indicated that intramolecular free-radical alkylation or acylation also occurs, and an example of 1,4-rearrangement has been observed.[3a]

The observation that the sterically congested aldehyde Ia with *t*-butyl peroxide, even at 140°, gives the tetralone VIa and its Tischenko ester Va as dominant products encouraged study of these reactions under conditions planned to favor the formation of such carbonyl-containing products. Previous research[5] with free-radical reactions of aldehydes and ketones has shown that yields of carbonyl products are enhanced at lower reaction temperatures as a consequence of the decreased rates of decarbonylation of intermediate alkanoyl radicals. Accordingly, reactions of the 3- and 4-phenyl alkanals Ib, Ic, and VII with *t*-amyl peroxide at 100° have been found (see Table I) to give increased yields of ketonic products, but esters were not observed (even qualitative tests were negative).



At 100° with *t*-amyl peroxide, 4-methyl-4-phenylpentanal (VI) gives 4,4-dimethyl-1-tetralone (VIII) and decarbonylation product VII. An interesting product of rearrangement, 4-methylvalerophenone (IX), also is formed (see p. 1664, col. 1).

In all experiments, carbon monoxide was obtained in a yield equal to that of the alkyl benzene product, and all reactions were continued until its evolution ceased. The time required to complete the reaction was longer, and the conversions of aldehyde to products were lower in the experiments at 100° (*cf.* experiments 2 and 3, and 4 and 5, Table I). Analysis of distillation

(1) W. H. Urry, D. J. Trecker, and H. D. Hartzler, Abstracts of Papers, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961, p. 75Q.

(2) (a) S. Winstein and F. H. Seubold, *J. Am. Chem. Soc.*, **69**, 2916 (1947); (b) W. H. Urry and N. Nicolaides, *ibid.*, **74**, 5163 (1952); (c) D. Y. Curtin and M. J. Hurwitz, *ibid.*, **74**, 5381 (1952); (d) F. H. Seubold, *ibid.*, **75**, 2532 (1953).

(3) (a) S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, **12**, 138 (1956); (b) L. H. Slaugh, *J. Am. Chem. Soc.*, **81**, 2262 (1959).

(4) (a) D. Y. Curtin and J. C. Kauer, *J. Org. Chem.*, **25**, 880 (1960); (b) J. W. Wilt and H. Philip, *ibid.*, **24**, 441 (1959); **25**, 891 (1960); (c) J. W. Wilt and C. A. Schneider, *ibid.*, **26**, 4196 (1961); (d) C. Rüchardt, *Ber.*, **94**, 2599 (1961).

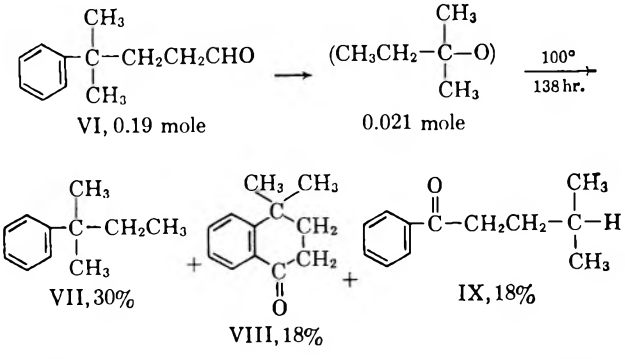
(5) (a) C. H. Bamford and R. G. W. Norrish, *J. Chem. Soc.*, 1531, 1544 (1938); (b) R. Cramer, *J. Am. Chem. Soc.*, **79**, 6215 (1957); (c) F. E. Blacet and J. G. Calvert, *ibid.*, **73**, 667 (1951).

TABLE I

REACTION OF ARALKANALS WITH *t*-ALKYL PEROXIDES[a]

Expt.	Aldehyde (mole)	Peroxide[b]	Reaction time, hr.	% conversion	% yields[c] Hydrocarbon	Ketone	Other
1	Ia (0.095)	TBP	20	58	7, IIa, IIIa	21, IVa	67, Va
2	Ib (0.17)	TAP	84	32	81, IIb	6, IVb	*d*
3	Ib (0.058)	TBP	27	70	98, IIb	2, IVb	*d*
4	Ic (0.29)	TAP	24	58	62, IIc; 38, IIIc	5, IVc	*d*
5	Ic[e]	TBP		71	47, IIc; 53, IIIc	*f*	
6	VII (0.188)	TAP	138	58	30, VII	18, VIII	18, IX
7	Ia (0.053)[g]	TBP	48	75	8, IIa; 19, IIIa	*f*	46, Va
8	Ic[h]	TBP		57	15.9, IIc; 80.6, IIIc[i]	*f*	

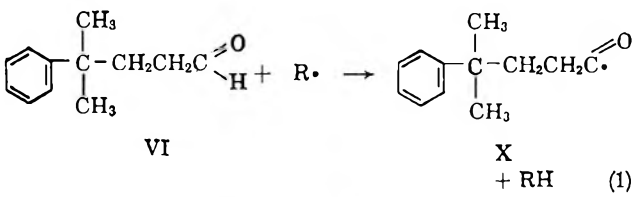
[a] Experiments 1 to 6 without, and 7 and 8 with solvents. [b] In all experiments, approximately 10 mole % of peroxide was used: TAP denotes *t*-amyl peroxide at 100°, and TBP, *t*-butyl peroxide at 140°. [c] Based upon aldehyde consumed. [d] Corresponding 1,2-diketone was shown to be present in distillation residues. [e] Data from ref. 2d. [f] Ketone product was not isolated. [g] Ia was 0.90 *M* in chlorobenzene, 23 mole % *t*-butyl peroxide was used, and reaction temperature was 130°. [h] Data from ref. 4d. Ic was 1.01 *M* in *o*-dichlorobenzene, and reaction temperature was 129.7°. [i] Product contained 3–4% phenylisobutenes.

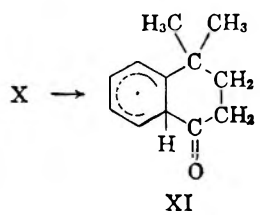


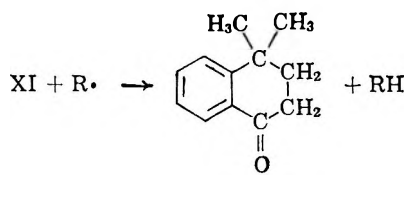
residues showed that they contained the expected 1,2-diketones (RCHO → RCOCOR).

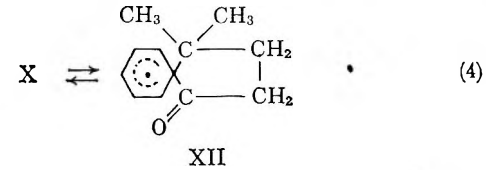
The free-radical chain reaction mechanism proposed[2-4] for this reaction must be supplemented with unit reactions of intermediate aralkanoyl radicals resulting in the formation of the ketonic products important at lower temperatures.

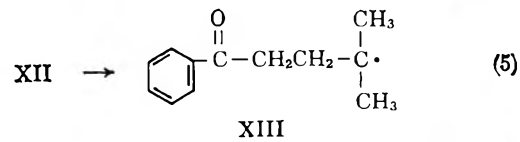
In this reaction of VI, the aralkanoyl radical X undergoes intramolecular free-radical acylation at either adjacent *ortho* position to give the intermediate radical XI (eq. 2, Ar_6^2 ring closure[3a]) that, when attacked by another free radical as in reaction 3, completes the formation of the tetralone VIII. Alternatively, the radical X effects ring closure to the 1-position (Ar_5^1) to give the spiro radical XII. Subsequent ring opening of XII may occur to regenerate X, but presumably reaction 5 is favored since the transition state leading to the more stable tertiary radical XIII is of lower energy. Reaction of XIII with another molecule of aldehyde gives 4-methylvalerophenone (IX) and another aralkanoyl radical X to continue the reaction chain.

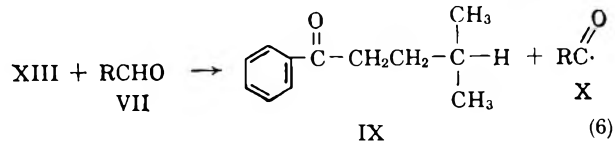










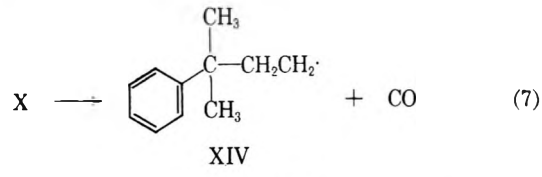


Indanones[6] are formed in the reactions of aldehydes Ia, Ib, and Ic by a reaction sequence analogous to reactions 2 and 3. However, tetralones are obtained in higher yield than indanones when the reactions of homologous aldehydes are compared (*cf.* experiments 4 and 6, Table I). Yields of indanones are greater in the reactions of the more highly substituted 3-phenyl alkanals (*cf.* experiments 1 and 2 with 4, Table I) with a methyl group on the 2-carbon atom being as effective in increasing indanone formation as two methyl groups on the 3-carbon atom.

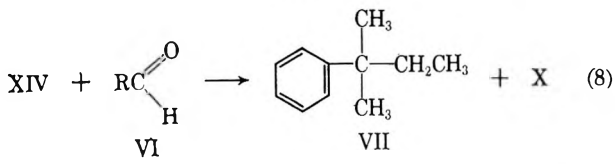
Even at 100° with Ib, Ic, and VII, decarbonylation of the intermediate aralkanoyl radicals is the dominant reaction.

No 3,3-dimethylindane is formed by XIV *via* intramolecular free-radical alkylation at its *ortho* position (the vapor phase chromatogram of the reaction product of 6, Table I, showed none, while the peak due to this

(6) Two such examples have been reported previously: 3,3-diphenylindanone (9%) from the reaction of 3,3,3-triphenylpropanal with benzoyl peroxide at 80°[4a]; and fluorenone from the reaction of 2-phenylbenzaldehyde with *t*-butyl peroxide at 140°. D. P. Denney and P. P. Kleinchuk, *J. Am. Chem. Soc.*, **80**, 3289 (1958).



XIV



VI VII

indane was visible in the chromatogram of a 1% solution of it in VII). However, the analogous formation of tetralins from 4-phenylbutyl radicals is well known.[3a,7] These observations, and the fact mentioned above that tetralones are obtained in higher yields than indanones (*cf.* 1 and 4, Table I), suggest that six-membered ring intermediates (such as XI) form more readily than the corresponding five-membered ring ones. Indanes are formed, however, in the reaction of alkylbenzenes with olefins at 400–485°, presumably *via* substituted 3-phenylpropyl radicals.[8]

That indanones are formed at 100–140° and indanes are not suggests that 3-phenylpropanoyl radicals undergo the ring-closure reaction more readily than 3-phenylpropyl radicals. An attractive hypothesis is that overlap of the π-orbitals of the carbonyl group of the former with those of the phenyl ring permits a transition state of lower energy than that for the ring closure of 3-phenylpropyl radicals. Another possibility is that the latter radicals undergo the competing attack upon aldehyde molecules (reaction 8) at a much faster rate than that of their ring closure.

Another limitation of the versatility of radical XIV is that it does not undergo 1,3-rearrangement. No 2-methyl-4-phenylbutane is observed (experiment 6, Table I). In contrast, the 1,2-shift is a common reaction of 2-phenylethyl radicals, and the 1,4-shift of a 4-phenylbutyl radical, 4-methyl-4-phenylpentyl, has been postulated[3a] for the formation of 2-methyl-5-phenylpentane in the reaction of *t*-butyl peroxide with 5-methyl-5-phenylhexanal.

With aldehyde Ic at 100°, the decarbonylation product contained 62% of IIc and 38% of the product of rearrangement, IIIc. This extent of rearrangement, that is lower than observed before,[2a,d,4d] may be attributed to two factors. During this reaction, the average concentration of Ic was higher than in former studies as a consequence of its low conversion (58%). Hence, the competing attack of the 2-methyl-2-phenylpropyl radical upon aldehyde prior to its rearrangement is favored. Further, Rüchardt[4d] has shown that the ratios of the rates of these competing reactions, rearrangement *vs.* attack upon aldehyde (Rüchardt's k_4/k_5), are 2.76 at 129.7° and 3.25 at 144.5°. It is likely that this rate ratio is lower ($k_4/k_5 \sim 2$) at 100°.

Even though the 2-phenylethyl radical undergoes 3.3–5.1% rearrangement in this reaction of 3-phenylpropanal (1 *M* in chlorobenzene),[3b] the extent of rearrangement of such radicals (100% with Ph_3CCH_2·)[2c] seems to depend upon the degree to which the rearranged radical is more stable than the unrearranged one. The rearrangement tendency of the 1,2-dimethyl-2-phenylpropyl radical (experiment 7, Table I, secondary radical rearranging to a tertiary one) is only a little less than that of the 2-methyl-2-phenylpropyl radical (primary giving a tertiary radical). This aspect of the reaction of *t*-butyl peroxide with aldehyde Ia was studied in chlorobenzene (0.90 *M* aldehyde) at 130°. With the lower aldehyde concentration, 27% of decarbonylation product was obtained. It contained 70% 2-methyl-3-phenylbutane (IIIa, rearrangement product) and 30% 2-methyl-2-phenylbutane (IIa). In a study of this reaction of Ic (experiment 8, Table I) at 129.7° in *o*-dichlorobenzene, Rüchardt[4d] found 80.6% of the rearrangement product IIIc, at an aldehyde concentration of 1.01, and 81.8% of it at 0.70 *M*.

In these reactions at 100°, chain-breaking events are profoundly changed. 1,2-Diketones were found to be present in distillation residues to suggest that dimerization, and probably cross dimerization, of both aralkyl and aralkanoyl radicals occurs. Most interesting is the fact that the formation of indanones and tetralones becomes an important chain-breaking reaction under these conditions. In the formation of each molecule of these products (reactions 2 and 3), two radicals are consumed. To illustrate the importance of such reactions, the yields of these cyclic ketones, based upon *t*-alkyl peroxide used, are listed in Table II.

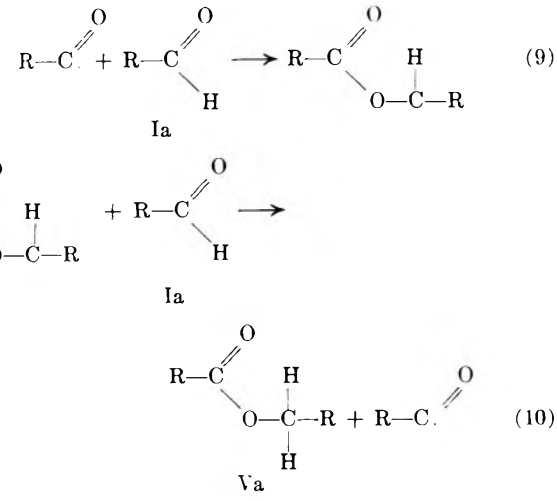
TABLE II

Aldehyde (reaction temperature, °C.)	Ketone (% yield, based upon peroxide used)
Ib (140)	2-Methyl-1-indanone (9.3)
Ib (100)	2-Methyl-1-indanone (18)
Ic (100)	3,3-Dimethyl-1-indanone (23)
Ia (140)	2,3,3-Trimethyl-1-indanone (80)
VII (100)	4,4-Dimethyl-1-tetralone (90)

Even at 140° with Ia, this sequence is the dominant chain termination, but it is less important with Ib. With all of the aldehydes studied, its importance is increased at 100°. With Ia at 140° or VII at 100°, ring closure to form the indanone or tetralone is so efficient that little chain breaking occurs *via* other reactions.

The absence of esters among the products of the other reactions in this study emphasizes the uniqueness of the reaction of Ia with *t*-butyl peroxide at 140° to give 67% of the ester Va and 21% of IVa with only 7% of the products of decarbonylation and rearrangement—carbon monoxide, IIa, and IIIa. Va probably is formed by the two-step chain mechanism (reactions 9 and 10) in which aralkanoyl radical attack on the aldehyde carbonyl function involves addition to the oxygen atom. The limited number of prior examples of such presumed acyl radical addition to the carbonyl group involve obvious steric effects or resonance stabilization of the intermediate radical (enolate or benzyl radicals are formed). This type of reaction step is proposed[9] as part of a chain sequence for the photochemical reaction of benzaldehyde with phenanthraquinone to give the monobenzoate ester of phenanthracene-9,10-diol.[10]

(7) D. F. DeTar and C. Weiss, *J. Am. Chem. Soc.*, **78**, 4296 (1956).
(8) H. Pine and J. T. Arrigo, *ibid.*, **79**, 4958 (1957).
(9) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 238 (1953).
(10) (a) R. Klinger, *Ann.*, **249**, 137 (1888); (b) A. E. Schönberg and H. Moubasher, *J. Chem. Soc.*, 1430 (1939); (c) A. E. Schönberg, N. Latif, R. Moubasher, and A. Sina, *ibid.*, 1364 (1961).

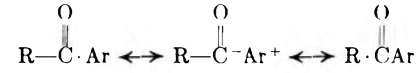


The quantum yield of this reaction is not known and it may be a nonchain photochemical process. Similar reaction steps have been proposed in the nonchain radical reactions: (1) perfluoro acid chlorides and nickel carbonyl with perfluoro 1,2-diketones to give the perfluoroenediol diesters[11]; (2) benzoyl peroxide with benzaldehyde to give *meso*[12] and *dl*[13] *sym*-diphenylethyleneglycol dibenzoate; and (3) *t*-butyl peroxide with benzaldehyde in pyridine to give 4-(α-benzoyloxybenzyl)pyridine.[14] The recently studied vapor phase photolysis of butanal to give *sym*-tripropyltrioxane (81%),[15] and of 3,4-hexanedione in propanal to give 4-oxo-3-hexanolpropionate[16] (54%), may again be reactions of photochemically excited states.

Free-radical, chain-addition reactions in which it is postulated that intermediate acyl radicals add to olefins[17] to give ketones and to azo compounds to give substituted hydrazines[18] as the eventual products are well known.

Steric effects and the tendency of radicals to form π-complexes with aromatic substances are probably responsible for the above reaction of Ia to give the ester Va and the indanone IVa, and for its diminished decarbonylation reaction. Study of the molecular model of the 2,3-dimethyl-3-phenylbutanoyl radical (from Ia) indicates that its most stable conformation is that in which the 2-methyl group is staggered between the two methyl groups on the 3-carbon atom. In this conformation, the acyl radical is forced toward one side of the phenyl ring. Hence, this radical may be stabilized against decarbonylation by π-complex formation. Addition of this radical to the oxygen atom of another aldehyde molecule on the side of the acyl group away from the phenyl ring (reaction 9) would lead to the ester-forming reaction, and formation of the σ-bond to the *ortho* carbon of the phenyl ring would lead to the formation of indanone product.

This intramolecular stabilization of intermediate acyl radical by π-complex formation is the converse of a suggestion by Walling[19] that such π-complex formation by *t*-butoxy radicals give enhanced β-scission. It is reasonable that a partial negative charge on oxygen atom in the *t*-butoxy aromatic complex should lower the energy of the transition state for β-scission to give acetone and a methyl radical. On the other hand, similar complex formation by alkanoyl radicals may be represented as follows.



The partial negative charge on the carbonyl carbon of the complex may stabilize it against α-scission decarbonylation.

The decarbonylation of two aliphatic aldehydes, 2,3,3-trimethylbutanal and cyclopropylacetaldehyde, have given interesting results. With the former, only 2,2-dimethylbutane and carbon monoxide were obtained to indicate that there is no comparable rearrangement of aliphatic free radicals with a quaternary carbon atom. The peroxide-induced reaction of cyclopropylacetaldehyde gave only 1-butene and carbon monoxide. It is apparent that the intermediate cyclopropylcarbinyl radical undergoes a ring-opening reaction as a consequence of the strain in the cyclopropyl ring to give the but-3-enyl radical that abstracts the aldehydic hydrogen of another aldehyde molecule to give 1-butene.

Experimental

Preparation of VI.—The Grignard reagent was prepared from 1-chloro-2-methyl-2-phenylpropane (570.3 g., 3.37 moles, b.p. 65° at 2 mm., $n^{20}D$ 1.5250; prepared in 61% yield by the method of Whitmore)[20] with magnesium turnings (87.5 g., 3.65 g.-atoms) in anhydrous ether (950 ml.). Treatment of the reaction mixture with a large excess of Dry Ice and its acid hydrolysis gave 3-methyl-3-phenylbutanoic acid (493 g., 2.77 moles, m.p. 57–58°,[21] 82% yield). Reduction[22] of this acid with lithium aluminum hydride (119.8 g., 3.16 moles) in anhydrous ether (3.5 l.) gave 3-methyl-3-phenylbutanol (378.8 g., 2.31 moles, b.p. 137° at 16 mm., $n^{20}D$ 1.5228, 91% yield).

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.4; H, 9.8. Found: C, 80.7; H, 9.8.

3-Methyl-3-phenylbutanol (378.4 g., 2.31 moles) with thionyl chloride (550 g., 4.60 moles; Matheson Coleman and Bell) gave 1-chloro-3-methyl-3-phenylbutane (314.7 g., 1.72 moles, b.p. 123° at 18 mm., $n^{20}D$ 1.5194, 75% yield). The Grignard reagent from this chloride (274 g., 1.5 moles) with magnesium turnings (40 g., 1.7 g.-atoms) in anhydrous ether (850 ml.) was treated with ethyl orthoformate (333 g., 2.25 moles) in anhydrous ether (370 ml.). Hydrolysis of the resulting acetal with sulfuric acid solution (5 *M*, 500 ml.), ether extraction, drying (sodium sulfate), and distillation gave VI (101 g., 0.57 mole, b.p. 123° a 10 mm., $n^{20}D$ 1.5109, 38% yield). Its 2,4-dinitrophenylhydrazone (m.p. 81° from ethanol) was prepared.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.7; H, 5.7; N, 15.7. Found: C, 60.4; H, 5.9; N, 15.8.

Reaction of VI with *t*-Amyl Peroxide.—In a nitrogen atmosphere, a solution containing VI (33.0 g., 0.188 mole) and the peroxide (3.6 g., 0.021 mole) was held at 100° for 138 hr. in a three-necked flask (50 ml.) equipped with a thermometer, a

(11) J. Drysdale and D. D. Coffman, *J. Am. Chem. Soc.*, **82**, 5111 (1960).
(12) F. F. Rust, F. H. Seubold, and W. E. Vaughan, *ibid.*, **70**, 3258 (1948).
(13) A. L. J. Beckwith and G. W. Evans, *J. Chem. Soc.*, 130 (1962).
(14) M. S. Kharasch, O. Schwartz, M. Zimmerman, and W. Nudenberg, *J. Org. Chem.*, **18**, 1051 (1953).
(15) D. J. Trecker, Doctoral dissertation, University of Chicago, Chicago, Ill., 1962.
(16) W. H. Urry and D. J. Trecker, *J. Am. Chem. Soc.*, **84**, 118 (1962).
(17) (a) M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949); (b) J. D. LaZerte and R. J. Koshar, *J. Am. Chem. Soc.*, **77**, 910 (1955); (c) T. M. Patrick, Jr., *J. Org. Chem.*, **17**, 1009 (1952); (d) R. L. Huang, *J. Chem. Soc.*, 1794 (1956); (e) T. M. Patrick, Jr., *J. Am. Chem. Soc.*, **17**, 1269 (1952).
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(19) (a) C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **85**, 1593 (1963); (b) C. Walling and P. Wagner, *ibid.*, **85**, 2333 (1963).
(20) F. C. Whitmore, C. A. Weisgerber, and A. C. Shabica, Jr., *ibid.*, **65**, 1469 (1943).
(21) A. Hoffman, *ibid.*, **51**, 2545 (1929).
(22) R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 2548 (1947).

nitrogen inlet tube, and a condenser (attached through a −80° trap to a Precision wet test meter). Carbon monoxide (0.85 l., 18%) was evolved.

Fractional distillation of the reaction mixture through a 3-ft. Podbielniak Heli-Grid column gave VII (4.4 g., 0.03 mole, b.p. 63–66° at 10 mm., $n^{20}D$ 1.4995, 30% yield); unchanged VI (1.9 g., 0.011 mole, b.p. 123° at 10 mm., $n^{20}D$ 1.5109); and a mixture of carbonyl compounds (12.7 g., b.p. 123–127° at 10 mm., $n^{20}D$ 1.5149, infrared at 1725 and 1675 cm.$^{-1}$). Distillation then was continued in a molecular still to give another such mixture (6.0 g.; infrared at 1720, 1690 and 1675 cm.$^{-1}$). Quantitative analysis of these carbonyl-containing fractions by chromatography of a mixture of their 2,4-dinitrophenylhydrazones on silicic acid[23] gave unchanged VI (12.0 g., 0.068 mole, total recovery 42%), VIII (3.4 g., 0.020 mole, 17.5% yield), and IX (3.3 g., 0.019 mole, 17.5% yield).

A distillation residue (6.2 g., infrared at 1710 cm.$^{-1}$, no hydroxyl) remained, and part of it (1.0 g.) was chromatographed on neutral alumina. The first two fractions contained 2,9-dimethyl-2,9-diphenyl-5,6-decanedione (positive 2,4-dinitrophenylhydrazine and periodic acid tests; hydroxylamine–ferric chloride test for ester was negative; carbonyl content 105%, based on one carbonyl function per molecule as determined by the hydroxylamine hydrochloride method).[24]

Anal. Calcd. for $C_{24}H_{30}O_2$: mol. wt., 350. Found: mol. wt., 355.

Treatment of this residue with aqueous periodic acid gave 4-methyl-4-phenylpentanoic acid (melting point of its anilide, 165–166°; melting point of mixture with authentic sample, 166–167°).

VII was identified further by the preparation of its *p*-sulfonamide (m.p. 85–86°,[25] melting point of mixture with an authentic sample was undepressed). 1,1-Dimethylindane (b.p. 85° at 20 mm., $n^{20}D$ 1.5150; prepared according to Bogert and Davidson)[26] was not a product of this reaction. This hydrocarbon and VII are separated by the v.p.c. method used (Fisher–Gulf partitioner; 11-ft. column packed with tricresyl phosphate on firebrick; isothermal, 120°; helium flow, 100 ml. per min.), but the chromatogram of the reaction product had no peak due to this indane.

The mixture of the three 2,4-dinitrophenylhydrazones obtained from the carbonyl-containing fractions was triturated with boiling ethanol, and the insoluble 2,4-dinitrophenylhydrazone of VIII (m.p. 224–226°; mixture melting point with authentic sample, 223–225°) was separated by filtration of the hot mixture.

Anal. Calcd. for $C_{18}H_{18}O_4N_4$: C, 61.0; H, 5.1; N, 15.8. Found: C, 61.1; H, 5.2; N, 15.9.

The 2,4-dinitrophenylhydrazone of IX (m.p. 177–179°, undepressed with a mixture with an authentic sample) recrystallized from the ethanol solution.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.7; H, 5.6; N, 15.7. Found: C, 60.7; H, 5.6; N, 15.5.

This derivative also gave the same X-ray diffraction pattern as an authentic sample [*d* 10.0 Å. (s); 7.5 Å. (w); 5.5 Å. (s); 4.8 Å. (m); 4.2 Å. (s); 3.5 Å. (m); 3.0 Å. (w); and 2.0 Å. (w)].[27]

IX (20.0 g., 0.11 mole, b.p. 143–145° at 20 mm., $n^{20}D$ 1.5100,[24] 61% yield) was prepared by the reaction of 4-methylpentanoyl chloride (25.0 g., 0.19 mole, Eastman) with benzene (141 g., 1.8 moles) and aluminum chloride (30.0 g., 0.23 mole). After a 17-hr. reaction period, additional aluminum chloride (30.0 g., 0.23 mole) was added and stirring was continued for 2 hr. Its oxime (m.p. 70–71° from ethanol)[28] and its 2,4-dinitrophenylhydrazone (m.p. 180–181°) were prepared.

VIII was prepared by the reaction of 4-methyl-4-phenylpentanoic acid (17.6 g., 0.09 mole) in carbon disulfide (175 ml.) with phosphorus pentachloride (15.8 g.; 0.09 mole; Matheson Coleman and Bell) under vigorous stirring for 2 hr., and then aluminum chloride (30 g., 0.225 mole, Mallinckrodt A.R.) was added and the mixture was held at reflux for 2.5 hr. After hydrolysis of the reaction mixture with cold dilute hydrochloric acid, distillation gave VIII (3.17 g., 0.21 mole, b.p. 127–128° at 7 mm., $n^{20}D$ 1.5502,[29] 24% yield). Its 2,4-dinitrophenylhydrazone (m.p. 125–126° from ethyl acetate), and its semicarbazone (m.p. 203–204° from aqueous ethanol) were prepared.

Preparation of Ic.—This aldehyde (46.3 g., 0.29 mole, b.p. 83–85° at 3 mm., $n^{20}D$ 1.5148, 29% yield, 2,4-dinitrophenylhydrazone m.p. 120–122°) was prepared by the hydrolysis of its acetal with hydrochloric acid solution (5 *N*, 400 ml.). The acetal was prepared by the reaction of the Grignard reaction from 1-chloro-2-methyl-2-phenylpropane (170.0 g., 1.01 mole, b.p. 75° at 3 mm., $n^{20}D$ 1.5252; prepared in 88% yield by the method of Kharasch and Brown)[30] with magnesium turnings (25.9 g., 1.11 g.-atoms) in ether (400 ml.) with ethyl orthoformate (148.0 g., 1.00 mole) in ether (150 ml.). The crude Ic from the acetal hydrolysis was treated with a saturated solution of sodium bisulfite. The precipitated bisulfite addition product was separated on a filter and was washed thoroughly with ether. Ic was recovered by treating the addition product with hydrochloric acid solution (1 *N*, 200 ml.).

Reaction of Ic with *t*-Amyl Peroxide.—In the apparatus previously described, Ic (46.3 g., 0.29 mole) and *t*-amyl peroxide (5.6 g., 0.032 mole) were held at a temperature of 100° for 24 hr. (swept with nitrogen). During this time, carbon monoxide (3.4 l., 52%) was evolved.

The gas chromatography (apparatus described above; isothermal, 220°) of the reaction mixture indicated that it contained 2-methyl-2-butanol and 2-butanone, a mixture of butylbenzenes (48.5%; retention time, 5 min.), unchanged Ic (42% recovered; retention time, 22 min.), and IVc (2.5%; retention time, 30 min.). Fractional distillation through a 3-ft. Podbielniak Heli-Grid column gave the following products: a mixture of 2-methyl-2-butanol and 2-butanone (5.0 g., b.p. 55–90°, $n^{20}D$ 1.4918); a mixture of butylbenzenes (21.9 g., 0.163 mole, b.p. 58–60° at 20 mm., $n^{20}D$ 1.4918–1.4873), shown to contain 62% IIc (13.8 g., 0.103 mole, 57% yield) and 39% IIIc (8.1 g., 0.060 mole, 33% yield) by comparison of the refractive index of each fraction obtained with a graph (refractive indices *vs.* per cent composition) from the known butylbenzenes (infrared spectra of fractions were identical with mixtures of the indicated composition); a mixture of carbonyl compounds (10.7 g., b.p. 60° at 1 mm., $n^{20}D$ 1.5172) that contained unchanged Ic (9.5 g., 0.059 mole) and IVc (1.2 g., 0.007 mole, 5% yield); and a viscous residue (6.0 g., negative hydroxylamine–hydrochloride test, positive periodic acid test) that contained 2,7-dimethyl-2,7-diphenyl-4,5-octanedione.

Anal. Calcd. for $C_{22}H_{26}O_2$: mol. wt., 322. Found: mol. wt., 319.

The known *p*-sulfonamides[25] were prepared from the IIc (m.p. 134–136°) and the IIIc (m.p. 86–87°, mixture melting points with authentic samples were not depressed). A mixture of 2,4-dinitrophenylhydrazones was prepared from the above carbonyl fraction and the hydrazone of IVc (m.p. 265–267°, red crystals)[31] was obtained pure by trituration with boiling ethanol. Authentic IVc (1.6 g., 0.01 mole, b.p. 125° at 21 mm., $n^{20}D$ 1.5408, 63% yield) was prepared by the reaction of aluminum chloride (2.7 g., 0.020 mole) under reflux for 2.5 hr. with a mixture obtained from 3-methyl-3-phenylbutanoic acid (2.6 g., 0.016 mole) and phosphorus pentachloride (3.4 g., 0.016 mole) in ligroin (20 ml., 90–100°) that had been stirred for 2 hr. Its semicarbazone (m.p. 205–207°),[31] and its 2,4-dinitrophenylhydrazone (m.p. 268° from ethyl acetate,[31] mixture melting point with above derivative showed no depression) were prepared.

Separation of the above 2,4-dinitrophenylhydrazone mixture with column chromatography on a 2:1 mixture of activated silicic acid and Celite (156-A)[23] gave the 2,4-dinitrophenylhydrazone of 3-methyl-3-phenylbutanal (m.p. 121–122°).[29] The reaction of the residue from the above distillation with an aqueous solution of periodic acid gave 3-methyl-3-phenylbutanoic acid (m.p. 56–57°).[21]

Preparation of Ib.—1-Phenyl-2-propanol (478.8 g., 3.53 moles, b.p. 95° at 7 mm., $n^{20}D$ 1.5241; prepared in 47% yield by

(23) B. E. Gordon, F. Wopate, Jr., H. D. Burnham, and L. C. Jones, Jr. *Anal. Chem.*, **23**, 1754 (1951).

(24) W. T. Smith, Jr., and R. L. Shriner, "The Examination of New Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 85.

(25) E. H. Huntress and J. S. Autenreith, *J. Am. Chem. Soc.*, **63**, 3446 (1941).

(26) M. T. Bogert and D. Davidson, *ibid.*, **56**, 187 (1934).

(27) North American Philips Powder Camera with Strouman's arrangement, 57.3-mm. radius. The photographs were made by M. E. Lipschutz, Enrico Fermi Institute, University of Chicago.

(28) R. L. Shriner and T. A. Turner, *J. Am. Chem. Soc.*, **53**, 1267 (1930).

(29) S. J. Lapporte Doctoral dissertation, University of California at Los Angeles, 1956, pp. 183–188.

(30) M. S. Kharasch and H. C. Brown, Jr., *J. Am. Chem. Soc.*, **61**, 2143 (1939).

(31) G. Baddeley and R. Williamson, *J. Chem. Soc.*, 4653 (1956).

the method of Huston and Bostwick)[32] with thionyl chloride (905 g., 7.06 moles) gave 1-phenyl-2-chloropropane (386.9 g., 2.51 moles, b.p. 94° at 17 mm., $n^{22}D$ 1.5196,[33] 71% yield). Ethyl orthoformate (296 g., 2.00 moles, Eastman) in anhydrous ether (400 ml.) was treated with the Grignard reagent prepared from the 1-phenyl-2-chloropropane (309.7 g., 2.00 moles) with magnesium turnings (53.5 g., 2.20 g.-atoms) in ether (950 ml.). The product acetal was hydrolyzed with hydrochloric acid (5 *N*, 200 ml.). The aldehyde–sodium bisulfite addition product was prepared. Its treatment with hydrochloric acid (1 *N*) gave Ib (57.0 g., 0.62 mole, b.p. 89–90° at 6 mm.,[34a] $n^{20}D$ 1.5141, 31%). Its semicarbazone (m.p. 121–122°)[34a] and its 2,4-dinitrophenylhydrazone (m.p. 116–117°) were prepared.

Reaction of Ib with *t*-Amyl Peroxide.—Ib (25.0 g., 0.17 mole) and the peroxide (3.3 g., 0.019 mole, b.p. 51° at 13 mm., $n^{20}D$ 1.4087) were held at 100° for 84 hr. in the apparatus described above.

During this reaction period, carbon monoxide (1.25 l., S.C.,[34b] 29% yield) was given off. Gas chromatographic analysis (Perkin-Elmer vapor fractometer, Model 154; 12-ft. column, 35% by weight Dow-Corning silicon oil no. 710 on 30–80-mesh firebrick; isothermal, 173°; helium flow, 100 ml. per min.) indicated peroxide decomposition products (2-methyl-2-butanol and 2-butanone); IIb (26%; retention time, 5 min.); unchanged Ib (72%; retention time, 23 min.); and IVb (2%; retention time, 37 min.). Authentic samples gave the same retention times. A known mixture of 2-phenylpropane (retention time, 4.5 min.) and IIb (retention time, 5.0 min.) was separated by this analysis. Hence, 2-phenylpropane is not a product of this reaction. Similarly, 2-methylpropiophenone (retention time, 25 min.) was shown to be absent from the product.

Fractional distillation (the Podbielniak Heli-Grid column, 50-plate) of this reaction mixture gave (1) a mixture of 2-methyl-2-butanol and 2-butanone (3.2 g., b.p. 55–90°); (2) IIb (5.0 g., 0.042 mole, b.p. 53° at 15 mm., $n^{20}D$ 1.4740, 81% yield); (3) a mixture of carbonyl compounds (b.p. 90–95° at 7 mm., $n^{20}D$ 1.5120, infrared at 1725 and 1690 cm.$^{-1}$) composed of Ib (17.1 g., 0.115 mole, 68% recovered) and IVb (0.5 g., 0.032 mole, 6%); and (4) a dark viscous residue (2.0 g., mol. wt. 325, infrared at 1705 cm.$^{-1}$ with no hydroxyl absorption, positive periodic acid test, and negative hydroxyl amine–ferric chloride ester test).

IIb gave its *p*-sulfonamide (m.p. 108–109°, mixture melting point with authentic sample the same).[25] Fraction 3 gave a mixture of 2,4-dinitrophenylhydrazones (red and yellow crystals). The red needles of the 2,4-dinitrophenylhydrazone of IVb (m.p. 201–203° from ethanol–ethyl acetate, m.m.p. 204–205°) were obtained by filtration when the mixture was triturated with boiling ethanol.

Anal. Calcd. for $C_{16}H_{14}N_4O_4$: N, 17.2. Found: N, 17.4.

The 2,4-dinitrophenylhydrazone of Ib (m.p. 116–117°) recrystallized as the ethanol solution cooled. IVb (13.4 g., 0.092 mole, b.p. 108° at 9 mm., $n^{20}D$ 1.5550, 62% yield, semicarbazone m.p. 198–199°,[35] *p*-nitrophenylhydrazone m.p. 165–166°,[36] and 2,4-dinitrophenylhydrazone m.p. 207–208°) was prepared otherwise from the reaction of 2-methyl-3-phenylpropanoyl chloride (from the acid, 24.6 g., 0.15 mole, and phosphorus pentachloride, 31.2 g., 0.15 mole, in ligroin, 90°, 175 ml.) and aluminum chloride (40.0 g., 0.30 mole) at reflux for 2 hr. The 2-methyl-3-phenylpropanoic acid (59.1 g., 0.36 mole, b.p. 146° at 7 mm.,[37] $n^{20}D$ 1.5186, 72% yield, amide m.p. 106°)[38] was prepared by the carbonation of the Grignard reagent obtained from 1-phenyl-2-chloropropane (77.2 g., 0.50 mole) with magnesium turnings (13.3 g., 0.55 g.-atom) in anhydrous ether (160 ml.).

Reaction of Ib with *t*-Butyl Peroxide.—Ib (8.5 g., 0.058 mole) and the peroxide (0.93 g., 0.0063 mole, b.p. 42° at 58 mm., $n^{20}D$ 1.3889) were brought into reaction as previously described except that the reaction temperature was held at 140° for 27 hr. Gas (1.15 l., S.C.,[34b] 79%, carbon monoxide) was evolved. Chromatographic analysis, as before, showed (a) 2-methyl-2-propanol and acetone; (b) IIb (69%; retention time, 5 min.); (c) Ib (30% unchanged; retention time, 23 min.); and (d) IVb (1%; retention time, 37 min.).

Preparation of Ia.—This aldehyde was prepared by procedures as described above, from 2-bromo-3-methyl-3-phenylbutane. Bromine (48 g., 0.30 mole) was added in six portions to 2-methyl-2-phenylbutane[39] (160.0 g., 1.08 mole, $n^{20}D$ 1.4960; purified by a previous bromination to remove 2-methyl-3-phenylbutane present)[40] irradiated with a 150-w. flood lamp for 6 hr. (50–60°). After a short induction period (20 min.), hydrogen bromide was evolved. After 6 hr., residual hydrogen bromide and bromine were removed through an aspirator as nitrogen was bubbled through the reaction mixture. Distillation gave unchanged 2-methyl-2-phenylbutane (123.9 g., b.p. 40–42° at 2 mm., $n^{20}D$ 1.4958) and 2-bromo-3-methyl-3-phenylbutane (38.6 g., b.p. 78–80° at 2 mm., $n^{20}D$ 1.5425, 71% yield based upon amylbenzene consumed).

Anal. Calcd. for $C_{11}H_{15}Br$: Br, 35.2. Found: Br, 35.1.

A residue (12.6 g.) of polybromides remained. This bromide was identified further by carbonation of its Grignard reagent to give 2,3-dimethyl-3-phenylbutanoic acid (m.p. 104–105° from aqueous ethanol; 91% yield).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.0; H, 8.4. Found: C, 75.1; H, 8.5.

In addition this bromide was hydrogenated over palladium on calcium carbonate to give only 2-methyl-2-phenylbutane.

The Grignard reagent was prepared by the reaction of 2-methyl-2-phenyl-3-bromobutane (68 g., 0.30 mole, $n^{20}D$ 1.5392) with magnesium (7.2 g.) in anhydrous ether (100 ml.). After the formation of the Grignard reagent was complete (addition of the halide, 2.5 hr.; reflux, 45 min.), ethyl orthoformate (redistilled Eastman, 44.0 g., 0.30 mole, $n^{20}D$ 1.3920) in anhydrous ether (80 ml.) was added (over 20 min.; reflux, 12 hr.).

Work-up of the reaction mixture with hydrolysis of the acetal by hydrochloric acid and purification of the aldehyde through its bisulfite addition product were done as described above. Ia (29.4 g., 0.17 mole, 56% yield, b.p. 53–55° at 0.3 mm., $n^{20}D$ 1.5289) was obtained by distillation.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.8; H, 9.2. Found: C, 81.3; H, 9.0.

Its 2,4-dinitrophenylhydrazone (m.p. 223–224° from ethyl acetate), and its semicarbazone (m.p. 195–196° from aqueous ethanol) were prepared.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: N, 15.7. Found: N, 15.4.

The Reaction of Ia with *t*-Butyl Peroxide.—A solution of the peroxide (1.6 g., 0.011 mole) in Ia (16.7 g., 0.095 mole) was heated at 140° under a nitrogen atmosphere for 20 hr. After 12 hr., additional peroxide (0.5 g., 0.003 mole) was added. Little carbon monoxide (200 ml.) was evolved.

The reaction product was separated by fractional distillation to give a distillate (7.5 g., b.p. 70–75° at 1 mm.) and a viscous residue (8.4 g., infrared at 730 and 1690 cm.$^{-1}$). Analysis of the distillate (v.p.c., F & M, Model 500, temperature-programmed gas chromatograph, 2-ft. silicone rubber column; isothermal, 175°; helium flow, 100 ml. per min.) indicated a mixture of amylbenzenes (retention time, 1.7 min.; 0.5 g.; 0.004 mole; 7.2%) and unchanged Ia (retention time, 5.3 min.; 7.0 g.; 0.040 mole; 58% conversion). Recrystallization of the residue from ethanol gave Va (6.5 g., 0.018 mole, m.p. 186–187°, 67% yield).

Anal. Calcd. for $C_{24}H_{30}O_2$: C, 81.8; H, 9.1. Found: C, 81.4; H, 8.9.

Va was hydrolyzed with aqueous alcoholic potassium hydroxide solution (0.86 *N*; reflux, 24 hr.). The ethanol was removed under vacuum, and 2,3-dimethyl-3-phenylbutyric acid (m.p. 103.5–104.5° after sublimation; mixture melting point with authentic acid prepared as above, 104–105°) precipitated when the basic solution was made acidic. From the ether extract, 2,3-dimethyl-3-phenylbutanol (m.p. 108–109° from aqueous ethanol) was isolated.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.8; H, 10.2. Found: C, 80.7; H, 10.0.

An authentic sample of this alcohol (m.p. 108–109°, mixture melting point not depressed) was prepared by the reduction of the above aldehyde with lithium aluminum hydride.

(32) R. C. Huston and O. O. Bostwick, *J. Org. Chem.*, **13**, 334 (1948).

(33) J. Kenyon, H. Phillips, and V. P. Pittman, *J. Chem. Soc.*, 1084 (1935).

(34) (a) M. Ramart-Lucas and L. Labaune, *Ann. Chem.*, **16**, 292 (1931). (b) Standard conditions.

(35) E. A. Speight, A. Stevenson, and J. F. Thorpe, *J. Chem. Soc.*, **125**, 2191 (1924).

(36) R. Kishner, *J. Russ. Phys. Chem. Soc.*, **46**, 1413 (1914).

(37) F. S. Kipping and G. Clarke, *J. Chem. Soc.*, **83**, 915 (1903).

(38) E. H. Woodruff and T. W. Conger, *J. Am. Chem. Soc.*, **60**, 465 (1938).

(39) M. Inatome, K. W. Greenlee, J. N. Derfer, and C. E. Boord, *ibid.*, **74**, 292 (1952).

(40) H. D. Hartzler, Doctoral dissertation, University of Chicago, Chicago, Ill., Aug., 1957, p. 34.

The ethanolic filtrate from the recrystallization of Va contained IVa (2.0 g., 0.011 mole, 21% yield). It was converted to its 2,4-dinitrophenylhydrazone [m.p. 75–77°, mixture melting point undepressed; ultraviolet spectrum was λ_{max} 390 μ (ϵ_{max} 1.92 × 10^4), and 266 (1.18 × 10^4)]. Authentic IVa was obtained from the reaction of 2,3-dimethyl-3-phenylbutanoic acid (5.0 g., 0.026 mole, prepared as above) with phosphorus pentachloride (5.5 g.; 0.026 mole; reflux, 1 hr.), and then aluminum chloride (6.9 g., 0.052 mole; reflux, 2 hr.) was added. Work-up of the reaction mixture with cold, dilute hydrochloric acid, drying, and then distillation gave IVa (3.2 g., 0.018 mole, b.p. 130–134° at 1 mm., n^{20}D 1.5437, infrared at 1690 cm.$^{-1}$). Its 2,4-dinitrophenylhydrazone (m.p. 76–77° from ethanol) was prepared.

Anal. Calcd. for $C_{18}H_{18}N_4O_4$: N, 15.8. Found: N, 15.3.

To study the amylbenzenes obtained in the reaction of Ia with *t*-butyl peroxide, reaction conditions were modified. A solution containing Ia (9.3 g., 0.053 mole, n^{20}D 1.5287), the peroxide (1.02 g., 0.007 mole, n^{20}D 1.3893), and redistilled chlorobenzene (50 ml., n^{20}D 1.5248) was held at 130° for 24 hr. Then more peroxide (0.96 g.) was added, and the reaction was continued for another 24 hr. Carbon monoxide (515 ml., S.C.) was evolved.

The reaction mixture was distilled to give chlorobenzene (54.8 g., b.p. 71–72° at 112 mm., n^{20}D 1.5248); a mixture of hydrocarbons (2.18 g., b.p. 62–68° at 20 mm., n^{20}D 1.4931); and a residue (5.8 g.) from which Ia (4.3 g., m.p. 184–186°) was obtained. The infrared spectrum of the mixture of hydrocarbons was identical with a mixture of IIa (30%) and IIIa (70%). A mixture of *p*-benzamido derivatives was prepared from the hydrocarbon mixture (m.p. 104–118°). 2-Methyl-3-(*p*-benzamidophenyl)butane (m.p. 138–141°, after nine recrystallizations from aqueous ethanol; mixture melting point with authentic sample, 139–141°) was obtained.

Preparation of 2,3,3-Trimethylbutanal.—The Grignard reagent prepared from 2-chloro-3,3-dimethylbutane (56.0 g., 0.46 mole, n^{20}D 1.4180,[41] obtained by careful fractional distillation of the mixture products from the photochemical chlorination of 2,2-dimethylbutane)[42] with magnesium (12 g., 0.5 g.-atom) in anhydrous ether (125 ml.; addition, 4 hr.; reflux, 45 min.) was treated with ethyl orthoformate (Eastman, 96.0 g., 0.46 mole, b.p. 80° at 89 mm., n^{20}D 1.3920) in anhydrous ether (100 ml.; reflux, 16 hr.). The acetal product was hydrolyzed with hydrochloric acid, and the aldehyde formed was purified *via* the aldehyde–bisulfite addition product. The latter was treated with sodium carbonate solution, and the mixture was extracted with ether. The ether solution (dried over sodium sulfate) was distilled to give 2,3,3-trimethylbutanal (13.1 g., 0.11 mole, b.p. 66–68° at 69 mm., n^{20}D 1.4125).

Anal. Calcd. for $C_7H_{14}O$: C, 73.6; H, 12.4. Found: C, 72.9; H, 12.2.

Its 2,4-dinitrophenylhydrazone (m.p. 126–127° from aqueous ethanol) was prepared.

Anal. Calcd. for $C_{13}H_{18}N_4O_4$: N, 19.0. Found: N, 18.8.

Reaction of 2,3,3-Trimethylbutanal with *t*-Butyl Peroxide.—A solution containing this aldehyde (3.54 g., 0.031 mole) and peroxide (0.56 g., 0.004 mole, b.p. 45° at 72 mm., n^{20}D 1.3889) was heated at 130° for 24 hr. Carbon monoxide (563 ml. S.C. 80% yield) was evolved. 2,2-Dimethylbutane (2.2 g., n^{20}D 1.3684,[43] 83% yield) was obtained by distillation of the reaction mixture and the contents of the −80° trap. Its infrared spectrum was identical with that of an authentic sample (Phillips 99% pure neohexane).

Preparation of Cyclopropyl Acetaldehyde.—Cyclopropanecarboxylic acid (51.6 g., 0.60 mole, prepared from γ-chlorobutyronitrile)[44] with thionyl chloride (84 g., 0.70 mole) gave cyclopropane carbonyl chloride (52.3 g., 0.50 mole, 83% yield).[45] This acid chloride (14.4 g., 0.14 mole) in ether (50 ml.) was added over a period of 45 min. to a stirred solution of diazomethane (0°, from 70 g. of nitrosomethylurea)[46] in anhydrous ether (700 ml.). The crude diazo ketone obtained by distillation of the reaction mixture was dissolved in absolute ethanol (200 ml.), and this solution was irradiated with a mercury resonance lamp. Over a period of 2 days, nitrogen (2.98 l., S.C., 0.133 mole) was collected. Distillation of the reaction mixture gave ethyl cyclopropylacetate (13.9 g., 0.11 mole, b.p. 86–88° at 75 mm., n^{20}D 1.4240).

Ethyl cyclopropylacetate (18 g., 0.14 mole) in anhydrous ether (50 ml.) was treated with an ether solution (100 ml.) of lithium aluminum hydride (5.0 g., 0.13 mole; addition, 45 min.; reflux, 2 hr.). Work-up gave 2-cyclopropylethanol (11.1 g.; 0.13 mole; b.p. 88–90° at 100 mm.; n^{20}D 1.4344; 93%; infrared at 3320, 3060, and 1050 cm.$^{-1}$).

Anal. Calcd. for $C_5H_{10}O$: C, 69.8; H, 11.6. Found: C, 69.4; H, 11.8.

The phenylurethane (m.p. 57–58° from aqueous ethanol), and α-naphthylurethane (m.p. 81–82° from 60° ligroin) of this alcohol were prepared.

Anal. Calcd. for $C_{12}H_{15}NO_2$: N, 6.9. Found: N, 6.9.

Anal. Calcd. for $C_{16}H_{17}NO_2$: N, 5.5. Found: N, 5.9.

2-Cyclopropylethanol (9.0 g., 0.10 mole) in anhydrous pyridine (40 ml., Baker) was oxidized with chromic anhydride–pyridine complex (120 ml.; prepared from anhydrous chromic anhydride, 12 g., and pyridine, 120 ml.).[47] After the reaction mixture had been allowed to stand for 12 hr., it was made acidic with dilute hydrochloric acid. It was then extracted with ether, and the ether solution (dried over sodium sulfate) was distilled to give cyclopropylacetaldehyde (4.03 g., 0.048 mole, b.p. 69–75° at 166 mm., n^{20}D 1.3891, 48% yield) and unchanged 2-cyclopropylethanol (4.01 g., b.p. 78–90° at 160 mm., n^{20}D 1.4290, 45% recovery).

Anal. Calcd. for C_5H_8O: C, 71.4; H, 9.5. Found: C, 70.8; H, 10.0.

The 2,4-dinitrophenylhydrazone of this aldehyde (m.p. 118–119° from aqueous ethanol) was prepared.

Anal. Calcd. for $C_{11}H_{12}N_4O_4$: N, 21.2. Found: N, 21.1.

Reaction of Cyclopropylacetaldehyde with *t*-Butyl Peroxide.—This aldehyde (4.14 g., 0.049 mole) and peroxide (1.07 g., 0.0073 mole, n^{20}D 1.3893) were heated at 130° for 27 hr. Gasses evolved were led through a trap (−80°, containing 20 ml. of ether) into a Precision wet test meter. Carbon monoxide (0.88 l., S.C., 0.393 mole, 80% yield) was measured on the meter. The decarbonylation product, collected in the ether in the −80° trap, was found to be 1-butene (retention time, 8 min.; Fisher–Gulf gas chromatograph; 10-ft. column, paraffin oil on Celite; isothermal, 35°; helium flow, 20 ml. per min.). Other possible products gave different retention times under the same column conditions (butane, 9 min.; *cis*-2-butene, 10 min.; *trans*-2-butene, 11 min.; methylcyclopropane, 10.5 min.; and cyclobutane, 18 min.), and their mixtures with 1-butene always gave the expected two peaks.

The ether solution of the 1-butene was treated with 2,4-dinitrobenzenesulfenylchloride in glacial acetic acid, and the reaction mixture was allowed to stand for 16 hr. 2-Chlorobutyl 2,4-dinitrophenyl sulfide (m.p. 77–78°, mixture melting point with authentic sample was undepressed) was obtained.[48]

The same reaction products were obtained when cyclopropyl acetaldehyde (2.01 g., 0.024 mole) and *t*-butyl peroxide (0.79 g., 0.0054 mole) in chlorobenzene (25.6 g., n^{20}D 1.5248) were held at 130–135° for 48 hr.

(41) F. C. Whitmore, H. I. Bernstein, and I. W. Mixon, *J. Am. Chem. Soc.*, **60**, 2539 (1938).

(42) W. H. Urry and N. Nicolaides, *ibid.*, **74**, 5163 (1952).

(43) A. F. Forziati, A. R. Glaszow, Jr., C. B. Willingham, and F. D. Rossini, *J. Res. Natl. Bur. Std.*, **36**, 129 (1946).

(44) C. M. McCloskey and G. H. Coleman, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 221.

(45) L. I. Smith and E. R. Rogier, *J. Am. Chem. Soc.*, **73**, 4047 (1951).

(46) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 165, 461.

(47) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(48) N. Kharasch and C. M. Buess, *ibid.*, **71**, 2724 (1949).

Electrolytic Reductive Coupling. IV.[1] Mixed Couplings among Derivatives of α,β-Unsaturated Acids

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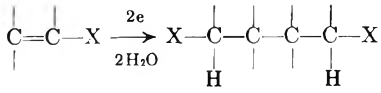
Electrolytic reductive coupling of derivatives of α,β-unsaturated acids, previously reported as a route to hydrodimers, has been broadened to include mixed reductive couplings among different species. The monomers are linked through their respective β-positions and there is thus provided a new synthesis of cyano esters, ester amides, etc. The factors which lead to the formation of either two or three products in this electrolytic coupling are discussed and illustrated. A novel preparation of lysine involving an electrolytic coupling step is presented. Appropriate derivatives of butadiene (*e.g.*, 1-cyano-1,3-butadiene) couple reductively with derivatives of monoolefinic acids to yield, after hydrogenation, 1,6-disubstituted hexanes. Under forcing conditions diethyl fumarate couples with *two* molecules of acrylonitrile to yield diethyl α,α'-bis(2-cyanoethyl)succinate.

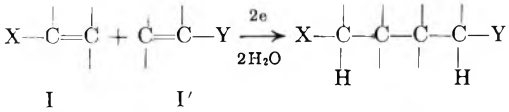
The discovery[2] that a variety of derivatives of α,β-unsaturated acids (I) may be individually hydrodimerized electrochemically in aqueous systems under mildly alkaline conditions provided a novel practical route to many difunctional compounds (II). It is



I II

X = –CN, –COOR, –$CONR_2$, etc.

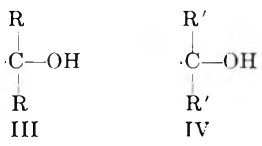
intrinsic in the hydrodimerization process, however, that products II are formed which are symmetrical and which have the functional groups X separated by four carbon atoms.[3] Greater versatility could be achieved if two *different* monomers (I and I′) could be reductively coupled since this would provide a means of obtaining valuable cyano esters, ester amides, etc.



I I′

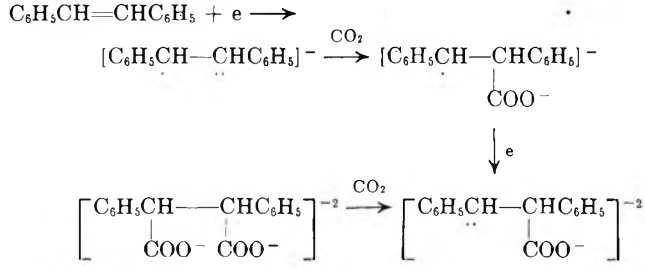
X, Y = –CN, –COOR, –$CONR_2$, etc.

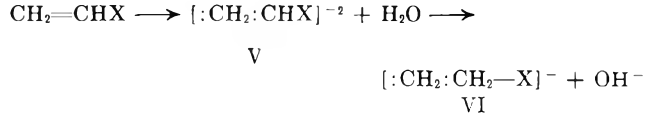
The literature on electrolytic mixed reductive coupling is restricted to the preparation of mixed pinacols in acid medium from a mixture of ketones[4] and the preparation of carboxylic acids by the electrolysis of conjugated olefins in the presence of carbon dioxide.[5] Since it is accepted that pinacol synthesis proceeds *via* a free-radical intermediate (III, IV), it is implicit that



III IV

in the formation of mixed pinacols one of the two participating ketones must accept an electron at the cathode at about the same cathode voltage as does the other. Three products are formed: two by self coupling and one by cross coupling. In the electrolytic reduction of stilbene in the presence of carbon dioxide, Wawzonek, *et al.*,[5] have proposed that the reaction probably proceeds *via* a stepwise addition of electrons and carbon dioxide, *i.e.*, through an anion free radical, to yield finally *m*-diphenylsuccinic acid. It has been suggested[6] that in hydrodimerization of derivatives of α,β-unsaturated acids (using acrylonitrile as an example), one molecule takes up *two* electrons at the cathode and forms a dicarbanion (V). The unshared electrons at the α-carbon atom are delocalized by resonance interaction with the activating group X or may displace OH^- from water to form a monocarbanion (VI).[7]





V VI

The β-position of V or VI then attaches to the β-position of another molecule of polarized (*but not reduced*) starting material to yield the coupled carbanion. On this basis, two types of mixed reductive couplings should be distinguishable: (a) when I and I′ are reduced at about the same cathode voltage,[8] the mixture will be reduced at some intermediate cathode voltage and *three* products should be formed; and (b) when I accepts electrons at a substantially more positive cathode voltage than does I′, controlled electrochemical reduction of the mixture at a cathode voltage close to that for reduction of I alone should produce only *two* products, one by hydrodimerization of I and by mixed

(1) Paper III: M. M. Baizer and J. D. Anderson, *J. Electrochem. Soc.*, **111**, 226 (1964).

(2) Paper II: M. M. Baizer and J. D. Anderson, *ibid.*, **111**, 223 (1964).

(3) When derivatives of butadiene, *e.g.*, 1-cyano-1,3-butadiene, are used, the functional groups in the hydrodimer may be separated by eight carbon atoms. See ref. 1.

(4) *E.g.*, M. J. Allen, J. A. Siragusa, and W. Pierson, *J. Chem. Soc.*, 1045 (1960).

(5) (a) S. Wawzonek, *et al.*, *J. Electrochem. Soc.*, **102**, 235 (1955); (b) J. W. Loveland, U. S. Patent 3,032,489 (May 1, 1962).

(6) (a) Paper I: M. M. Baizer, *J. Electrochem. Soc.*, **111**, 215 (1964); (b) I. G. Sevast'yanova and A. P. Tomilov, *Zh. Obshch. Khim.*, **33**, 2815 (1963); *Chem. Abstr.*, **60**, 1583*e* (1964).

(7) Evidence for the participation of a dicarbanion in a coupling reaction is presented below.

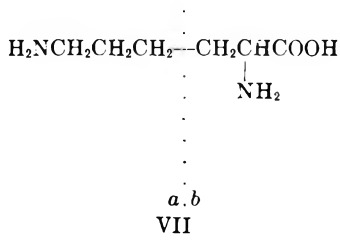
(8) Within *ca.* 0.20–0.25 v.

coupling. No hydrodimer of I′ should be found.[9] Improvement in the yield of mixed product should result from maintaining an excess of I′ in the reaction. These expectations were borne out.

Electrolysis at a mercury cathode of an equimolar mixture of ethyl acrylate (−1.8 v.)[12] and acrylonitrile (−1.9 v.) in aqueous methyltriethylammonium *p*-toluenesulfonate containing sufficient dimethylformamide to ensure homogeneity occurred at −1.83 to −1.85 v. Enough current was passed for only partial conversion[6] of the starting materials. The products isolated were diethyl adipate, ethyl δ-cyanovalerate, and adiponitrile.

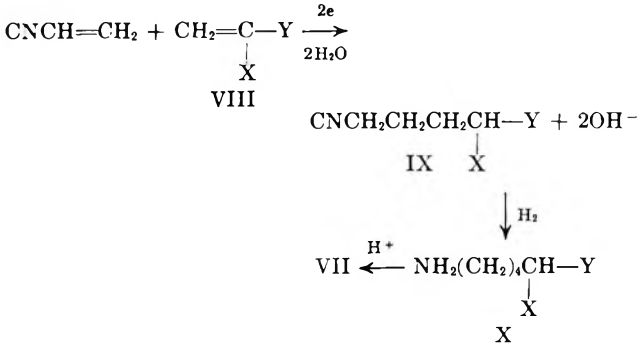
A similar electrolysis of diethyl maleate (−1.32 to −1.4 v.) with 2 moles of acrylonitrile (−1.9 v.) at −1.33 v. to −1.40 v. yielded tetraethyl butanetetracarboxylate and diethyl α-(2-cyanoethyl)succinate[13]; no adiponitrile was detectable by vapor phase chromatography.

Since moiety *a* of lysine (VII) can be regarded as being derived from acrylonitrile, and moiety *b* from a



VII

suitable derivative of acrylic acid, it appeared likely that VII could be synthesized in a minimum number of steps[14] by a sequence starting with electrolytic reductive coupling of acrylonitrile and an appropriate partner (VII). Since –X and –Y were to become ultimately



VIII IX X X

–NH_2 and –COOH, respectively, it was necessary that they survive the electrolysis intact or be reduced only in a manner favoring the synthesis (*e.g.*, $-NO_2 \rightarrow -NH_2$); for the sake of operating simplicity it was desirable that –X and –Y be converted to their respective end functions in one step.

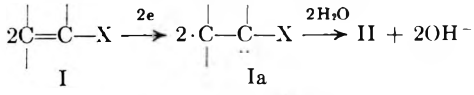
For illustrative purposes methyl α-acetamidoacrylate[15] (VIII, –X = $-NHCOCH_3$, –Y = $-COOCH_3$) was chosen as the coupling partner for acrylonitrile. A mixture of VIII and a tenfold molar excess of acrylonitrile was electrolyzed in aqueous tetraethylammonium *p*-toluenesulfonate at a mercury cathode. Reduction occurred at *ca.* −1.75 v. (*vs.* the saturated calomel electrode). The cyano ester IX (–X = $-NHCOCH_3$, –Y = $-COOCH_3$) was isolated by fractional distillation. Catalytic hydrogenation of IX in acetic anhydride containing a little sodium acetate using Adams' catalyst or, better, Raney nickel[14] followed by acid hydrolysis of the unisolated amino ester X (X = $-NHCOCH_3$, Y = $-COOCH_3$) yielded lysine dihydrochloride. Partial neutralization with pyridine[16] provided *dl*-lysine monohydrochloride whose infrared spectrum (Nujol mull) was superimposable upon that of a reference sample.[17] While no efforts were made to optimize the yields, it is apparent that the electrolytic coupling is the critical step in the sequence. In this connection, it is interesting that (a) the presence of an α-acetamido group in VIII has not blocked the coupling reaction; (b) the proximity of the cathode voltages for the reduction of methyl α-acetamidoacrylate (−1.75 v.) and acrylonitrile (*ca.* −1.9 v.) leads to the formation of some hydrodimer of the latter (adiponitrile); and (c) selection of a member of class VIII with a more positive reduction potential would therefore minimize by-product formation.

In contrast to the above electrolytic cyanoethylation which leads to a six-carbon chain, ordinary cyanoethylation of α-acylamidomalonates, as in Galat's synthesis of glutamic acid,[18] yields only a five-carbon chain.

A study of the electrolytic hydrodimerization of 1-cyano-1,3-butadiene had shown[1] that coupling of two molecules occurs mainly through the δ,δ-positions to yield (after catalytic hydrogenation of the intermediate products) sebaconitrile and only to a minor extent through the β,β- (→ 3,4-diethyladiponitrile) and the β,δ-positions (→ 3-ethylsuberonitrile). The preponderance of sebaconitrile indicates clearly that the δ-position of cyanobutadiene is most susceptible to attack by either electrons or carbanions.[19] Therefore, controlled mixed reductive coupling between cyanobutadiene and more difficultly reducible derivative of a monoolefinic acid (which can suffer carbanionic attack only at the β-position) should lead mainly to a straight-chain product.

A mixture of 6.0 moles of acrylonitrile (−1.9 v.) and 1.0 mole of cyanobutadiene (*ca.* −1.5 v.) in 80%

(9) Neglecting the polarographic data[10] which certainly point to a two-electron uptake in the reduction of acrylonitrile, one can visualize hydrodimerization as proceeding *via* coupling of ion-radical intermediates at the free-radical sites,[11] but one cannot apply this concept to the coupling of I



I Ia

and I′ when the cathode voltage is not sufficiently negative for I′ to accept electrons. Attack by the carbanionic end of Ia upon the β-position of I or I′ would lead to α-to-β coupling and not the observed β-to-β coupling. See, however, footnote 18, page 221 of ref. 1.

(10) M. N. Platonova, *J. Anal. Chem. USSR*, **11**, 317 (1956).

(11) M. Szwarc, *Nature*, **178**, 1168 (1956); see also ref. 5a.

(12) Figures in parentheses refer to the cathode potentials *vs.* the saturated calomel electrode for the hydrodimerization of the individual monomer during preparative runs.[3]

(13) P. C. Mitter and A. C. Roy, *J. Indian Chem. Soc.*, **5**, 47 (1928); *Chem. Abstr.*, **22**, 3882[8] (1928).

(14) An elegant short synthesis of lysine from cyclohexanone is described by A. F. Ferris, G. S. Johnson, F. E. Gould, and H. Stange, *J. Org. Chem.*, **25**, 1302 (1960).

(15) E. Rothstein, *J. Chem. Soc.*, 1968 (1949); H. Hellmann, K. Teichmann, and F. Lingens, *Chem. Ber.*, **91**, 2427 (1958).

(16) J. C. Eck and C. S. Marvel, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 374.

(17) Purchased from Nutritional Biochemicals.

(18) A. Galat, *J. Am. Chem. Soc.*, **69**, 965 (1947).

(19) One can conceive of other molecules which would present an intramolecular analog to the mixed coupling of diethyl maleate and acrylonitrile discussed above: molecule (or site) A may more readily accept electrons at the cathode than molecule (or site) B, but B is more subject to carbanionic attack.

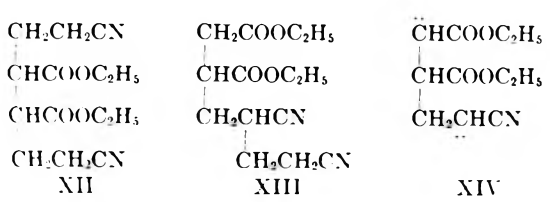
aqueous tetraethylammonium *p*-toluenesulfonate was electrolyzed; the cathode voltage was controlled so as not to become more negative than −1.71 v. After removal of the excess starting materials the residue was catalytically hydrogenated. The crude product contained 54.6% suberonitrile. The distilled fraction boiling in the range for suberonitrile and isomers contained 79.6% of the former. This experiment was complicated by (a) the inevitable presence of the hydrodimers of cyanobutadiene[1] and (b) the probable mixed reductive coupling products of cyanobutadiene dimer[1] and acrylonitrile or cyanobutadiene. The highest boiling material collected (222° at 0.47 mm.) had a molecular weight and N content approximating such a "higher" condensation product.

Electrolysis at −1.7 v. of a mixture of 1 mole of cyanobutadiene (*ca.* −1.5 v.) and 8 moles of ethyl acrylate (−1.85 v.) containing acetonitrile as co-solvent yield (after hydrogenation) a cyano ester, which on the basis of analogy we consider to be the straight-chain compound XI.

$$CN(CH_2)_6COOC_2H_5$$
XI

It has been pointed out above that the dicarbanion V formed upon acceptance of 2e at the β-position by an activated olefin may be the reactive species in coupling or that the dicarbanion may first be converted to a monocarbanion VI. A particularly favorable case for determining the viability of V presented itself in the mixed reductive coupling of diethyl fumarate (*ca.* −1.3 v.) and acrylonitrile (−1.9 v.): the ester dicarbanion has symmetry and acrylonitrile is exceptionally susceptible to carbanionic attack. In this electrolysis it was necessary to use a large excess of acrylonitrile and a limited amount of proton donor (in order not to present too great competition for the dicarbanion) but not so little proton donor as to allow anionic polymerization of acrylonitrile to occur.[20]

In the electrolysis diethyl fumarate was added dropwise from a buret to a solution of tetraethylammonium *p*-toluenesulfonate in acrylonitrile containing a small amount of water, and the rate of addition was regulated so as to maintain the cathode voltage at *ca.* −1.4 to −1.5 v. Slightly more current was passed than was necessary for a 2e uptake by the ester. Fractionation yielded, in order of increasing boiling point, diethyl succinate, diethyl succinate, diethyl α-(2-cyanoethyl)succinate, tetraethyl butanetetracarboxylate, and a product containing two cyanoethyl groups.[21] Of the two possible structures of the last product, XII and XIII, XII would *a priori* appear to be favored because in the precursor dianion XIV, the position α to CN might be expected to react with proton donors more readily than the position α to $COOC_2H_5$.[22] Proton magnetic resonance analysis favored XII or XIII.



Both the formation of diethyl α-(2-cyanoethyl)succinate and the formation of XII illustrate a point repeatedly demonstrated in mixed reductive coupling, namely that an activated olefin (*e.g.*, diethyl fumarate) may electrochemically form a carbanion capable of participating in Michael adduction even when the corresponding saturated compound (*e.g.*, diethyl succinate) cannot form the carbanion by proton abstraction under Michael conditions.

Experimental[23]

The apparatus and general procedure have been described previously.[6] The catholyte volume in the present experiments was *ca.* 150 ml. and the cathode area 55 cm.^{2} In all cases the acrylonitrile contained a trace of *p*-nitrosodimethylaniline as stabilizer.

Ethyl δ-Cyanovalerate.—The catholyte contained 80 g. (0.80 mole) of ethyl acrylate, 42.4 g. (0.80 mole) of acrylonitrile, 80 g. of 76.5% methyltriethylammonium *p*-toluenesulfonate, and 42 g. of dimethylformamide. Electrolysis at 3 amp. was carried out at 40° for 3 hr. A total of 4 ml. of acetic acid was added dropwise to the catholyte in this period to maintain the pH at *ca.* 8. The catholyte then was diluted with twice its volume of water, the mercury separated, and the solution was extracted with five 50-ml. portions of methylene chloride. The extracts were washed with water and dried over Drierite. Volatile materials were removed on a water bath with an aspirator. The residues from two similar runs (total 53.2 g.) were fractionated through a Todd column. Each fraction was analyzed by vapor phase chromatography for diethyl adipate (total 3.5 g.), ethyl δ-cyanovalerate (total 15.1 g.), and adiponitrile (total 17.0 g.). The infrared spectrum of the cyanovalerate was superimposable upon that of an authentic sample.

Diethyl α-(2-Cyanoethyl)succinate.—The catholyte consisted of 86.0 g. (0.50 mole) of diethyl maleate, 53.0 g. (1.0 mole) of acrylonitrile, 98.5 g. of 86.5% tetraethylammonium benzenesulfonate, and 10 g. of dimethylformamide. Electrolysis at 3 amp. proceeded for 3 hr. at 30°. A total of 2.5 ml. of acetic acid was used for pH control. The combined methylene chloride extracts from two identical runs were fractionated through a Todd column and yielded, after combination and redistillation of similar fractions, 70.9 g. of tetraethylbutanetetracarboxylate, b.p. 159–160° (0.85 mm.), $n^{25}D$ 1.4427, and 7.1 g. of slightly impure[24] diethyl α-(2-cyanoethyl)succinate, b.p. 126–130° (0.65 mm.), $n^{25}D$ 1.4408.

Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.17; mol. wt., 227. Found: C, 58.13; H, 7.53; N, 7.80; mol. wt., 212.

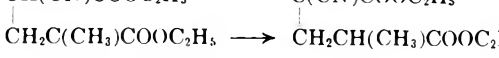
No adiponitrile was found by vapor phase chromatographic examination of the forerun boiling up to 143° (1 mm.).

Electrolytic Reductive Coupling of Acrylonitrile and Methyl α-Acetamidoacrylate.—A solution of 14.3 g. (0.1 mole) of the ester and 53.0 g. (1.0 mole) of acrylonitrile (containing a trace of *p*-nitrosodimethylaniline as stabilizer) in 70 g. of 69% aqueous tetraethylammonium *p*-toluenesulfonate was electrolyzed at 20°. An average of 2.0 amp. was passed through the cell. After 6.8 amp.-hr. the catholyte was diluted with twice its volume of water and treated in the usual manner in the presence of hydroquinone. After removal of solvent and excess acrylonitrile, the residual liquid (17.2 g., $n^{25}D$ 1.4564) was slowly distilled through a microapparatus equipped with a fraction cutter.

(20) This type of reaction will be discussed in a subsequent paper.

(21) The fractions were monitored by infrared analysis. The appearance, disappearance, and final reappearance of −CN absorption as the boiling points increased was a convenient means of locating the respective products.

(22) An example in which a carbanion with the charge α to an ester group rearranges to the isomer with the charge α to the cyano group is cited by E. D. Bergmann, D. Ginsburg, and R. Pappo, *Organic Reactions*, **10**, 186 (1959).



(23) Melting points and boiling points are uncorrected. The cathode used was mercury in all cases.

(24) A purer sample was obtained in the diethyl fumarate experiment described below.

After recovery of 2–3 g. of starting ester, there was obtained 4.4 g. of adiponitrile and 5.9 g. of crude product, b.p. 180–190° (0.24 mm.). Redistillation yielded **methyl α-acetamido-δ-cyanovalerate** (IX), b.p. 166–174° (0.20 mm.), $n^{25}D$ 1.4680.

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.14; mol. wt., 198. Found: C, 54.87; H, 6.87; N, 14.25; mol. wt., 197.

IX Conversion to *dl*-Lysine Monohydrochloride.—A suspension of 3.8 g. of IX, 0.75 g. of Raney nickel,[14] and 1.0 g. of anhydrous sodium acetate in 15 ml. of acetic anhydride was shaken at room temperature with hydrogen at 50-lb. initial pressure for 4 hr. in a Parr apparatus. The mixture was filtered. Volatile materials were removed *in vacuo*. The sirupy residue was heated under reflux with 20 ml. of concentrated HCl for 7 hr. Volatile products were again removed *in vacuo*. The residual sirup was dissolved in 20 ml. of hot absolute ethanol, treated with charcoal, and filtered. Addition of an excess of dry ether precipitated 5.5 g. of a gum which was dissolved in 30 ml. of hot absolute ethanol and treated with 1.0 ml. of pyridine. After refrigeration, a small quantity of pyridine hydrochloride was removed. Addition of 10 drops of pyridine precipitated crude *dl*-lysine monohydrochloride. Further crops were obtained from the filtrate by careful addition of pyridine. The crude product was dissolved in 3 ml. of water, treated with charcoal, and filtered. Addition of 25 ml. of absolute ethanol followed by refrigeration yielded pure white crystals, 0.37 g., m.p. 264°.

In another preparation in which Adams' catalyst was used instead of Raney nickel the purified product melted at 267°.

Suberonitrile.—The catholyte contained 98 g. (1.8 moles) of acrylonitrile and 18.3 g. (0.23 mole) of freshly distilled 1-cyano-1,3-butadiene dissolved in 115 g. of 80% tetraethylammonium *p*-toluenesulfonate. The cathode voltage was regulated manually at −1.69 to 1.71 v. (*vs.* the saturated calomel electrode). The initial amperage was 3.0 and this was gradually reduced to 0.25 toward the end of the run. A total of 10.6 amp.-hr. (coulometer) was used. The temperature was maintained at 25° and the pH at *ca.* 8. The residual liquid, after removal of materials volatile at 30 mm. on the water bath, weighed 25.9 g. It was dissolved in 90 ml. of absolute ethanol containing 1.00 g. of 5% palladium on carbon and hydrogenated at room temperature at an initial pressure of 36 lb. The uptake was 14.25 lb., 0.166 mole (calcd. for hydrogenation of 1,6-dicyano-2-hexene, 15.4 lb., 0.179 mole). The saturated product (25.3 g.) was distilled. The first cut, 16.5 g., b.p. 150 (2.9 mm.) to 162° (3.2 mm.), $n^{25}D$ 1.4428, was virtually pure suberonitrile.

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.54; H, 8.88; N, 20.57; mol. wt., 136. Found: C, 70.41; H, 9.09; N, 20.75; mol. wt., 138.

The final cut, b.p. 222 (0.47 mm.) to 226° (0.55 mm.), $n^{25}D$ 1.4732, had a molecular weight of 204–210 and 21.3% N, indicating a product with three nitrogen atoms.

Ethyl 7-Cyanoheptanoate.—The catholyte contained 88 g. (0.88 mole) of ethyl acrylate (stabilized by hydroquinone), 8.7 g. (0.11 mole) of cyanobutadiene, 43 g. of acetonitrile, and 99 g. of 80% tetraethylammonium *p*-toluenesulfonate. The cathode voltage was regulated at −1.67 to −1.70 v. which required gradually lowering the amperage from 2.7 to 0.25. A total of 5.0 amp.-hr. was passed. The operating temperature was 30–35°. The recovered crude product (12.4 g.) was hydrogenated as above and the saturated products were fractionated through a 2-ft. jacketed Vigreux column. The fractions (4.1 g.) containing the product of mixed coupling, b.p. 155–175° (18 mm.), were combined and refractionated to yield pure product boiling at 162–164° (18 mm.), $n^{25}D$ 1.4342.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.44; H, 9.74; N, 7.43.

Higher boiling fractions contained mixtures of the cyano ester and sebaconitrile.

Diethyl α,α′-Bis(2-cyanoethyl)succinate.—The catholyte contained 100 ml. of acrylonitrile, 1.5 ml. of diethyl fumarate, 1.0 ml. of water, and 50 g. of tetraethylammonium *p*-toluenesulfonate. The anolyte contained 20 g. of 60% quaternary salt. During the electrolysis the cathode voltage was maintained at −1.48 to −1.50 v. by dropwise addition of 14.9 ml. of diethyl fumarate over a period of 7 hr. The temperature was 25° for the first 90 min. and 40° thereafter. The amperage was in the range of 1.50–0.50, total 6.0 amp.-hr. The crude product (21.0 g.) was fractionated through a 2-ft. Vigreux column. The fraction boiling at 129° (0.45 mm.), $n^{25}D$ 1.4430, was pure diethyl α-(2-cyanoethyl)succinate.

Anal. Found: C, 58.11; H, 7.53; N, 6.28.

Intermediate fractions were shown by vapor phase chromatographic analysis to consist of mixtures of tetraethyl butanetetracarboxylate and diethyl α-(2-cyanoethyl)succinate. The highest boiling fraction was redistilled and the product collected at 176–178° (0.25 mm.), $n^{25}D$ 1.4565.

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 59.75; H, 7.18; N, 10.19.

The proton magnetic resonance spectrum was determined at room temperature on the Varian A-60 spectrometer operating at 60 Mc./sec. Spectro Grade chloroform and carbon tetrachloride were used as solvents and tetramethylsilane as internal standard. The spectrum of the sample was obtained in *ca.* 25% solution by volume. The proton magnetic resonance spectra of known model compounds [adiponitrile and diethyl α-(2-cyanoethyl)succinate] were obtained by the same technique. The τ-values and the intensities of the signals of the unknown were used to assign the nonequivalent nuclei in a direct comparison with the model compounds: 8.7 (for 6.2 H of CH_2 CH_3), 8.0 (for 4.1 H of $-CH_2-CN$), 7.4 (for 4.0 H of $-CH_2-C<$), 6.4 (for 1.9 H of $>CH-C$), and 5.8 (for 3.8 H of $-O-CH_2-$). These data indicated that structure XII was more probable than structure XIII.

Acknowledgment.—All instrumental analyses were performed by Donald Beasecker's group. The proton magnetic resonance spectra were obtained and interpreted by Louis Boros.

Photolysis of Nortricyclanone Tosylhydrazone Sodium Salt

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Photochemical decomposition of nortricyclanone tosylhydrazone sodium salt (1) pursues a course rather different from that of the pyrolysis. 3-Nortricyclyl *p*-tolyl sulfone (5) is formed in yields as high as 50% under *aprotic* conditions. Irradiation of 1 in the presence of free nortricyclanone tosylhydrazone gives nortricyclanone N-tosyl-3-nortricyclylhydrazone (6), identical with a sample prepared by an independent synthesis. Mechanistic implications of these observations are discussed briefly.

Thermal decomposition of *p*-toluenesulfonylhydrazone (tosylhydrazone) salts has become an important method for the generation of carbenes.[1] Dauben's observation that irradiation of camphor tosylhydrazone sodium salt gave high yields of tricyclene, presumably *via* the carbene, suggested that photochemical decomposition of tosylhydrazone salts parallels closely the thermal process.[2] In a study of the behavior of nortricyclanone tosylhydrazone sodium salt (1) we have

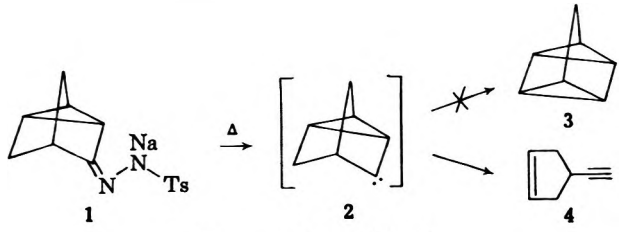
(1) See, for example, E. Chinoporos, *Chem. Rev.*, **63**, 235 (1963).

(2) W. G. Dauben and F. G. Willey, *J. Am. Chem. Soc.*, **84**, 1497 (1962).

found major differences between the pyro- and photolytic reaction pathways.

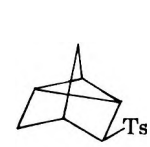
Nortricyclanone was synthesized by bromination of norbornene with N-bromosuccinimide (54% yield)[3] and oxidation of the resulting 3-bromonortricyclene by a modification of Kornblum's[4] alkaline dimethyl sulfoxide procedure.[5] When dissolved at room temperature in dimethyl sulfoxide containing an equivalent of silver fluoborate, the bromo compound was smoothly transformed into the dimethyl-3-nortricyclyloxysulfonium salt. Triethylamine was introduced and the mixture was heated for a short time on the steam bath to complete the oxidation to nortricyclanone (69% yield). Finally, the tosylhydrazone was prepared (87%) from the ketone and tosylhydrazine in hot pyridine.[6]

Near the completion of our work with the tosylhydrazone sodium salt **1**, Cristol[7] reported that thermal decomposition of this substance, which presumably led to nortricyclylidene (**2**), resulted not in ring closure of the carbene to quadricyclene (**3**),[8] but in twofold ring scission to 4-ethynylcyclopentene (**4**, 42% yield).[9] By pyrolyzing **1** at 160° in tetraglyme we had obtained this acetylene in comparable yield and had completely characterized it on the basis of chemical, microanalytical,[10] and spectral evidence. Our data are fully in accord with those of Cristol.[11]



Ts = *p*-toluenesulfonyl

A stirred suspension of **1** in purified tetrahydrofuran or diglyme was irradiated several hours with a Hanovia 450-w. Type L mercury lamp equipped with a Pyrex filter. Although some hydrocarbon **4** was found by g.l.c. (gas–liquid chromatography) in the resulting pale yellow suspension,[12] adsorption chromatography on alumina of the nonvolatile, ether-soluble fraction of the product led to the isolation in as high as 50% yield of a crystalline compound, m.p. 72–74°. The infrared spectrum (chloroform) showed prominent maxima at 7.65 and 8.75 μ characteristic of sulfones and at 12.0 μ, suggestive of a nortricyclyl residue.[3] Presence of a *p*-tolyl group was indicated by the n.m.r. spectrum (carbon tetrachloride) which featured an AB quartet (doublets at τ 2.31 and 2.72, J = 8.0 c.p.s.) attributable to aryl protons and a singlet at τ 7.56 corresponding to the methyl. The photolysis product was identified as 3-nortricyclyl *p*-tolyl sulfone (**5**) by spectral and mixture melting point comparison with an authentic sample, which was synthesized by addition of *p*-toluenethiol to norbornadiene followed by hydrogen peroxide oxidation.[13]



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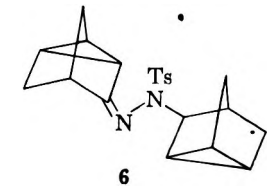
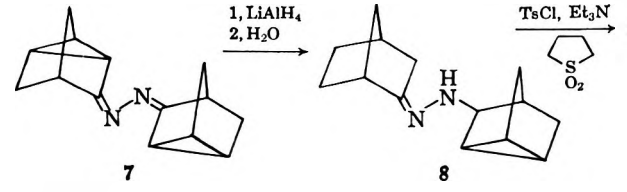


6

In certain of the photolysis runs the sulfone was accompanied by a higher melting (162–163°) substance, $C_{21}H_{24}N_2O_2S$, produced in yields as high as 52%. This compound was neutral, lacked N–H stretching absorption in the infrared spectrum, and exhibited an ultraviolet spectrum virtually identical with that of nortricyclanone tosylhydrazone. Since structure **6**, nortricyclanone N-tosyl-3-nortricyclylhydrazone, fits these data, authentic **6** was synthesized in the following fashion. Nortricyclanone azine (**7**) was prepared from the ketone and anhydrous hydrazine in refluxing ethanol.[14] Reduction of **7** with lithium aluminum hydride in boiling ether proceeded in near-quantitative yield to the nicely crystalline but air-sensitive hydrazone **8** ($\lambda_{max}^{CHCl_3}$ 3.04, 5.95 μ), which was transformed without purification into **6** through the action of tosyl chloride and triethylamine in hot sulfolane.[15] Infrared spectral, melting point, and mixture melting point comparison of **6** with the higher melting photolysis product demonstrated that the two were identical.



7 **8**

Formation of **6** in the photolysis was traced to the presence of free tosylhydrazone, *i.e.*, incomplete conversion to the salt **1**. When a small excess of dry, gran-

(3) J. D. Roberts, E. R. Trumbull, W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

(4) N. Kornblum, W. J. Jones, and G. J. Anderson, *ibid.*, **81**, 4113 (1959).

(5) Preparation of the tricyclic ketone from norbornadiene by the method of H. K. Hall, Jr. [*ibid.*, **82**, 1209 (1960), addition of formic acid, methanolysis, and oxidation] resulted in comparable over-all yields.

(6) Attempts to make the tosylhydrazone with HCl catalysis [the general procedure of C. H. De Puy and D. H. Froemsdorf, *ibid.*, **82**, 634 (1960)] led only to 5(?)-chloro-2-norbornanone tosylhydrazone. Thermal decomposition of this compound as its sodium salt gave 3-chloronortricyclene (60%).[9,11]

(7) S. J. Cristol and J. K. Harrington, *J. Org. Chem.*, **28**, 1413 (1963).

(8) The tetracyclic substance **3** might have been anticipated on the basis that tricyclenes are formed, often in excellent yield, in reactions proceeding *via* the norbornylidene **i** and its derivatives. See, for example, D. C. Kleinfelter and P. von R. Schleyer, *J. Am. Chem. Soc.*, **83**, 2329 (1961), and references contained therein.

i

(9) This event was foreshadowed by observations of L. Friedman and H. Shechter [*ibid.*, **82**, 1002 (1960)]. Pyrolysis of cyclopropanecarboxaldehyde tosylhydrazone sodium salt gave *inter alia* small quantities of ethylene and acetylene, the products of a cleavage entirely analogous with that of **2**. Similarly, ethylene and methylacetylene were minor decomposition products of the sodium salt of methyl cyclopropyl ketone tosylhydrazone.

(10) Satisfactory microanalyses were obtained on all new compounds with the exception of **8**, which was used without purification, as noted.

(11) A. J. Fry, Ph.D. dissertation, University of Wisconsin, 1963.

(12) Cristol[7] found that photochemical decomposition of **1** gave low yields of **4**, but he did not further investigate the reaction mixture.

(13) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Am. Chem. Soc.*, **80**, 635 (1958).

(14) The azine was also found (4% yield) among the photolysis products of the tosylhydrazone salt **1**.

(15) Sulfolane appears to be an excellent solvent for sulfonylations on nitrogen. Dimethylformamide, also strongly dipolar and aprotic, has been used effectively by Carpino, but, with certain weakly basic amines, formylation (by a modified Vilsmeier reaction) rather than sulfonylation may occur in dimethylformamide.

ular sodium hydride was used to form the salt in tetrahydrofuran or diglyme, **6** was isolated in considerable quantity, but use of excess fresh sodium hydride–mineral oil dispersion gave none. Apparently in the former case coating of the hydride particles with the salt **1** had prevented much of the base from reacting. Deliberate use of insufficient sodium hydride dispersion had the same effect on product composition. The most likely pathway to **6** is alkylation of the weakly acidic sulfonamide function of nortricyclanone tosylhydrazone by diazonortricyclene. Hence isolation of **6** supports the view that diazo compounds are intermediates in the photolysis of sulfonylhydrazone salts.[16]

To our knowledge 3-nortricyclyl *p*-tolyl sulfone (**5**) is the first sulfone prepared by decomposition of a sulfonylhydrazone salt in aprotic media.[17] The compound arises in the thermal as well as the photochemical destruction of **1**, but the yield (10%) is dramatically lower in the pyrolysis. Photolysis runs which give substantial quantities of **6** yield very little sulfone. This is most easily interpreted by assuming that diazonortricyclene is an intermediate on the pathway to sulfone as well as to **6**. Sulfinate ions may react with diazonortricyclene directly; perhaps more likely, the carbene **2** (from the diazo compound) may attack sulfinate ion, giving the reasonably stable sulfone anion which is later protonated. The latter process would be analogous to the trapping of methylene[18] and halocarbenes[19] by triphenylphosphine, since sulfinate ion is "divalent" in the same sense as is a phosphine.[20]

Experimental[21]

Nortricyclyl Bromide.[3]—Norbornene (100 g., 1.065 moles) was dissolved in 650 ml. of carbon tetrachloride, and N-bromosuccinimide (200 g., 1.123 moles) was added, followed by 20 mg. of *p*-toluenesulfonic acid. The initially white suspension was boiled under reflux and stirred vigorously for 5 hr., during which time it became a deep red-brown. After the flask had been cooled for some time in an ice bath, succinimide was separated by filtration and carbon tetrachloride removed by distillation through a Vigreux column. The residual dark brown oil was distilled to afford nortricyclyl bromide, 98.5 g. (0.57 mole, 53.5%), b.p. 60–65° at 12 mm.

Nortricyclanone. Method A. Oxidation of Nortricyclyl Bromide by Dimethylsulfoxide, Catalyzed by Silver Fluoborate.—To a solution of silver fluoborate[22] (50 g., 0.285 mole) in 1600 ml. of dry dimethyl sulfoxide was added nortricyclyl bromide (50 g., 0.289 mole), whereupon silver bromide quickly began to precipitate. After 1 hr. at room temperature, precipitation appeared complete. Triethylamine (35 g., 0.347 mole) was added with vigorous swirling, and the mixture quickly darkened. It was allowed to stand, with occasional swirling, for 2 hr., after which it was dark brown. The mixture then was heated on a steam bath for 20 min., allowed to cool, and filtered. The filtrate was diluted with 6 l. of water and extracted with ether until the extracts were colorless. The combined light yellow ether extracts were washed with water and dried over magnesium sulfate. When the ether had been taken off through a Vigreux column, distillation of the residual orange oil afforded nortricyclanone, 21.5 g. (0.199 mole, 68.8%), b.p. 63–65° at 14 mm.

Method B. *Via* **Nortricyclanol.**—This alcohol was prepared by addition of formic acid to norbornadiene followed by methanolysis,[5] and also by silver oxide catalyzed hydrolysis of nortricyclyl bromide, described below.

Nortricyclyl bromide (80.5 g., 0.465 mole) and water (22 ml., 1.22 moles) were dissolved in sufficient tetrahydrofuran (350 ml.) to produce a homogeneous solution. Silver oxide (70 g., 0.299 mole) was added all at once; the suspension was boiled under reflux with stirring. Silver bromide began to precipitate almost immediately. After 7 hr., the flask was cooled; a small amount of metallic silver coated its walls. The inorganic residue was removed by filtration and washed with ether. The filtrate was diluted with 1 l. of water and 200 ml. of ether, and the two phases were separated. After the aqueous phase had been extracted several times with ether, the combined organic extracts were washed with water and dried over sodium sulfate. This ether solution of nortricyclanol was used directly in the next step.

Nortricyclanol was oxidized by the method of Brown and Garg.[23] Vigorous stirring was found to be necessary to effect complete oxidation. Yields of nortricyclanone ranged from 55–75%.

Nortricyclanone Tosylhydrazone.—Tosylhydrazine (Aldrich Chemical Company, 44.72 g., 0.240 mole) was dissolved in 125 ml. of pyridine, and nortricyclanone (26.00 g., 0.240 mole) was added. The pale yellow solution was heated on the steam bath for 90 min. and then quenched in 800 ml. of cold water. A pale yellow oil separated, but when vigorously scratched with a glass rod it quickly crystallized. After an hour's standing, the off-white crumbly solid was isolated by filtration, washed with water, and dried on a porous plate. Recrystallization from methanol gave 57.5 g. (0.208 mole, 86.5%) of nortricyclanone tosylhydrazone, m.p. 165–165.5° dec. Three additional recrystallizations from methanol afforded an analytical sample, m.p. 165.5–166.0° dec.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.84; H, 5.84; N, 10.14; S, 11.61. Found: C, 60.88; H, 5.92; N, 10.19; S, 11.85.

Photolysis of Nortricyclanone Tosylhydrazone Sodium Salt (1) under Aprotic Conditions.—Nortricyclanone tosylhydrazone (1.00 g., 3.62 mmoles) was dissolved in 75 ml. of freshly distilled tetrahydrofuran.[24] Sodium hydride (0.10 g., 0.19 g. of a 52% dispersion in mineral oil, 4.2 mmoles) was added and the air above the mixture was replaced by dry nitrogen. The mixture was stirred for several hours to ensure complete conversion of the tosylhydrazone to its sodium salt. The resulting white suspension was stirred magnetically and irradiated for 4 hr., by the end of which time evolution of nitrogen apparently had ceased. The tan suspension was diluted with 600 ml. of water and extracted with ten 100-ml. portions of ether. The combined ether extracts were washed ten times with water, and then dried over magnesium sulfate. The solvent was distilled through a helix-packed column[25a]; the residual light brown oil was chromatographed over 10 g. of Fisher alumina in a 10 × 0.5 in. column. Elution with

(16) It is well known that diazo compounds are intermediates in the *thermal* decomposition of sulfonylhydrazone salts [see, for example, J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959); L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959); D. G. Farnum, *J. Org. Chem.*, **28**, 870 (1963)]. In the photolysis of camphor tosylhydrazone sodium salt Dauben[2] observed a transient red color which he attributed to the diazo compound.

(17) W. R. Bamford and T. S. Stevens [*J. Chem. Soc.*, 4735 (1952)] obtained phenyl *p*-tolyl sulfone in 14% yield when benzaldehyde tosylhydrazone sodium salt decomposed in hot ethylene glycol. Powell and Whiting[15] and also Friedman and Shechter[16] have shown that this hydroxylic solvent favors carbonium ion formation *via* protonation of the intermediate diazo compound; thus the sulfone probably arises by combination of sulfinate ion with benzyl cation. The nortricyclyldiazonium ion cannot be an intermediate in our reaction since sulfone yields are best when the medium is rigorously aprotic.

(18) V. Franzen and G. Wittig, *Angew. Chem.*, **72**, 417 (1960).

(19) A. J. Speziale, G. J. Marco, and K. W. Ratts, *J. Am. Chem. Soc.*, **82**, 1260 (1960); D. Seyferth, S. O. Grim, and T. O. Read, *ibid.*, **82**, 1510 (1960).

(20) A variety of other "potentially divalent" species such as cyanide ion may prove effective at intercepting carbenes in aprotic media.

(21) Except where noted, melting points were determined on a Kofler micro hot stage and are corrected. N.m.r. spectra were measured at 60 Mc./sec. on a Varian Associates A-60 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as internal standard. Photochemical experiments were performed with a Hanovia 450-w. Type L mercury lamp with a water-cooled quartz jacket and Pyrex filter. Microanalyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich.

(22) K. Heyns and H. Paulsen, *Angew. Chem.*, **72**, 349 (1960); G. A. Olah and H. W. Quinn, *J. Inorg. Nucl. Chem.*, **14**, 295 (1960). Silver fluoborate is also available from Chemicals Procurement Laboratories, Inc., 18-17 130th Street, College Point, N. Y.

(23) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(24) Tetrahydrofuran and diglyme (dimethyl ether of diethylene glycol) were used interchangeably with no significant effect on the reaction course. They were purified by distillation from lithium aluminum hydride.

(25) (a) G.l.c. analysis of the solution after concentration to a volume of 10 ml. revealed the presence of 4-ethynylcyclopentene (**4**) in 6–8% yield. This should not be taken as an accurate measure of the yield of **4**, as some codistillation of the volatile hydrocarbon with the large volume of solvent may have occurred. (b) In chloroform.

20% benzene in pentane afforded nortricyclanone azine (*vide infra*), m.p. 129–133° (uncor., Hershberg apparatus), 15 mg., 3.9%. Further elution with benzene afforded 3-nortricyclyl *p*-tolyl sulfone, m.p. 72–74°, 0.351 g., 39%. A mixture of this material and an authentic sample of 3-nortricyclyl *p*-tolyl sulfone, m.p. 76–77°, prepared by the method of Cristol, *et al.*,[13] melted at 73–76°, and their infrared spectra were identical. Yields of the sulfone ranged from 34 to 50% in other runs.

3-Nortricyclyl *p*-Tolyl Sulfone (5) by Thermal Decomposition of 1.—Nortricyclanone tosylhydrazone (0.240 g., 0.869 mmole) was dissolved in 15 ml. of diglyme, and excess sodium hydride (0.058 g. of 54% dispersion) was added. The mixture was refluxed for 0.5 hr., cooled, and thrown into 50 ml. of cold water. The resulting oily suspension was extracted several times with pentane; the combined extracts were washed with 10% sodium hydroxide and then with several portions of water, and dried over sodium sulfate. Removal of the solvent at reduced pressure gave 0.096 g. of viscous brown residue, which was chromatographed on 7 g. of Fisher alumina. Elution with benzene afforded 0.023 g. (10%) of crude sulfone. This was recrystallized from ligroin (b.p. 60–68°), yielding 14 mg. of tan crystals whose infrared spectrum was identical with that of authentic material.

Nortricyclanone N-Tosyl-3-nortricyclylhydrazone (6) by Photolysis.—Nortricyclanone tosylhydrazone (1.00 g., 3.62 mmoles) was dissolved in 100 ml. of dry diglyme.[24] Dry sodium hydride (0.18 g., 7.5 mmoles) was added; the mixture was magnetically stirred for 15 min. and then irradiated with continued stirring for 3 hr. The resulting white suspension was diluted with 750 ml. of water and extracted with ten 100-ml. portions of pentane. The pentane extracts were washed several times with water and dried over sodium sulfate. Solvent was distilled through a Vigreux column until the residue had been concentrated to a volume of 40 ml. When this residue was chilled to −78°, a white solid, m.p. 137–142°, separated. This was shown (*vide infra*) to be nortricyclanone N-tosyl-3-nortricyclylhydrazone (0.34 g., 0.925 mmole, 51.5%). Four recrystallizations from heptane afforded an analytical sample, m.p. 162–163°.

Anal. Calcd. for $C_{21}H_{24}N_2O_2S$: C, 68.44; H, 6.56; S, 8.70. Found; C, 68.12; H, 6.32; S, 8.58.

The n.m.r. spectrum consisted of an AB quartet at τ 2.45 and 2.76 (J = 8 c.p.s.), singlets at 7.43 and 7.62, and complex absorption from 7.78 to 9.17, relative areas 4:1:3:16, respectively. Presence of nitrogen in this neutral compound was indicated by sodium fusion. The infrared spectrum[25b] exhibited absorption at 5.97 (C=N), 8.60 (sulfonamide), and 12.4 μ (tricyclene).[3] No N–H stretching absorption was evident. The ultraviolet spectrum was measured in acetonitrile: λ_{max} 222 mμ (ϵ 11,500), 262 sh (2540), and 274 (1400). That of nortricyclanone tosylhydrazone in the same solvent displayed these features: λ_{max} 225 mμ (ϵ 14,500), 263 sh (1370), and 274 (675).

Nortricyclanone Azine (7).—Nortricyclanone (5.4 g., 0.050 mole) was placed in a 50-ml. three-necked flask fitted with a dropping funnel and condenser; the flask was heated to 80–100° under nitrogen. A solution of hydrazine hydrate (1.25 g., 0.025 mole) in 15 ml. of absolute ethanol containing 3 drops of glacial acetic acid was added to the flask dropwise with stirring. Boiling under reflux was continued for 2 hr. after addition was complete; the solution then was allowed to stand overnight. The solvent was taken off at reduced pressure, and the yellow crystalline residue recrystallized from ligroin (b.p. 60–68°). Nortricyclanone azine was obtained in 66% yield (3.50 g., 0.016 mole). A second recrystallization from ether gave white crystals, m.p. 142–145°. An analytical sample, m.p. 143–143.5° (uncor., Hershberg apparatus) was obtained after four recrystallizations from heptane.

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60; N, 13.20. Found: C, 79.50; H, 7.57; N, 13.14.

Nortricyclanone 3-Nortricyclylhydrazone (8).—A slurry of lithium aluminum hydride (0.190 g., 5.0 mmoles) in 10 ml. of ether was boiled under reflux with stirring in a nitrogen atmosphere. To this was added dropwise a solution of nortricyclanone azine (1.06 g., 5.0 mmoles) in ether. The mixture was refluxed for 8 hr. after addition was complete. Water (1 ml.) was added and the mixture was filtered through a Filter Cel–magnesium sulfate pad. The ether was taken off under reduced pressure, affording 1.03 g. of nearly white solid (m.p. 131–132°, uncor., Hershberg apparatus). Recrystallization from ligroin resulted in white rosettes. Presence in the infrared spectrum[25b] of N–H stretching (3.04 μ) and C=N stretching (5.95 μ) absorption bands indicated that this substance was the hydrazone 8. The rosettes, which were quite susceptible to air oxidation, were used directly in the following experiment.

Nortricyclanone N-Tosyl-3-nortricyclylhydrazone (6) by Tosylation of (8).—Triethylamine (0.048 g., 0.47 mmole) was dissolved in 2 ml. of sulfolane[26] and tosyl chloride (0.090 g., 0.47 mmole) was added. Nortricyclanone 3-nortricyclylhydrazone (0.101 g., 0.47 mmole) then was introduced. As the temperature was raised, the hydrazone gradually dissolved; solution was complete by the time the temperature had reached 140–150°. After about 3 hr. at this temperature, the dark brown solution was quenched in cold water, whereupon a brown oil separated. The oil was extracted into ether and washed successively with dilute hydrochloric acid, dilute sodium hydroxide, and water. The ether solution was dried over sodium sulfate and stripped under reduced pressure. The heavy brown oil which remained was dissolved in 1:4 benzene–pentane and chromatographed on 5 g. of Fisher alumina. Elution with 1:1 benzene–pentane afforded 0.018 g. of colorless oil, which soon crystallized. After one recrystallization from hexane, nortricyclanone N-tosyl-3-nortricyclylhydrazone was obtained as small white prisms, m.p. 158.5–160°. A mixture of this material with that obtained in the photolytic experiment (*vide supra*), m.p. 155.5–157°, melted at 155–156°, and their infrared spectra were identical.

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(26) The sulfolane (tetramethylene sulfone) was obtained from the Phillips Petroleum Co. and was vacuum distilled before use.

Norsteroids. V. The Application of the Benzilic Acid Rearrangement to the Synthesis of A-Norpregnanes[1,2]

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5α-Pregn-1-en-2-ol-3,20-dione (a diosphenol) was prepared by (a) conversion of 2α-bromo-5α-pregnane-3,20-dione to the pyridinium salt, treatment of this with *p*-nitroso-N,N-diethylaniline, and hydrolysis of the resulting nitrone; (b) hydrolysis of the bromo ketone to the ketol, followed by oxidation with cupric acetate or bismuth trioxide; and (c) oxygenation of 20,20-ethylenedioxy-5α-pregnan-3-one, followed by hydrolysis of the ketal group. The diosphenol underwent the benzilic acid rearrangement to give a single product, A-nor-5α-pregnan-2-ol-20-one-2-carboxylic acid, in high yield. This compound was converted to other A-norpregnane derivatives.

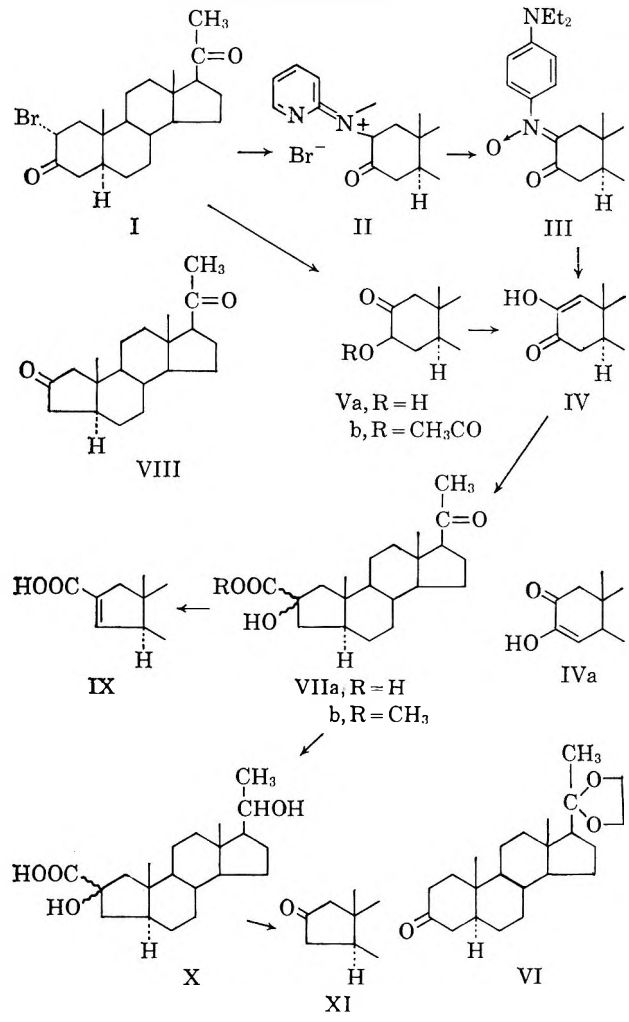
In a previous paper[1] the synthesis of A-norcholestane derivatives by the benzilic acid rearrangement of cholestane-2,3-diosphenols was reported. The yields were practically quantitative and the rearrangement was stereospecific. This method has now been applied to the preparation of A-norpregnane derivatives, interesting compounds because one has recently been shown to possess biological activity.[4]

Since no A-ring 2,3-diketones in the pregnane series could be found in the literature, it was first necessary to find a practical route to such compounds. The classical route to α-diketones (diosphenols) involves the selenium dioxide oxidation of a methylene group adjacent to a carbonyl group. However, in view of the low yields obtained with this method in the cholestane series[5] and the presence of the C-20 carbonyl group, this procedure was not investigated.[6] Because of the ready availability of 2α-bromo-5α-pregnane-3,20-dione (I), several routes using this compound were investigated. The first (and most successful) involved the application to the above bromo ketone of the method developed by Ruzicka, Plattner, and Furrer[7] for the preparation of the diosphenols of cholestane-2,3-dione (see Scheme I). The bromo ketone was treated with pyridine to give 5α-pregnane-3,20-dione-2-pyridinium bromide[8] (II) in 85% yield. The salt was then treated with *p*-nitroso-N,N-diethylaniline to give 5α-pregnane-3,20-dione-2-(*p*-N,N-diethylaminophenyl)nitrone (III) in 78% yield. When the nitrone was hydrolyzed with dilute hydrochloric acid a 93% yield of 5α-pregn-1-en-2-ol-3,20-dione (IV) was obtained. The over-all yield of diosphenol, based on bromo ketone, by this route was 62%, and the method can be used on a relatively large scale.

An alternate path to the diosphenol involves the oxidation of an A-ring ketol. Wendler, Taub, and Graber reported[9] that α-bromo ketones could be hydrolyzed conveniently with aqueous potassium hydroxide to ketols. Using their procedure, the bromo ketone was hydrolyzed to a ketol in 41% yield. An acid fraction, presumably a Favorskiĭ rearrangement product, and an unsaturated ketone were obtained also, but were not investigated further. The crude ketol was purified by chromatography, and its structure tentatively was assigned as 3β-hydroxy-5α-pregnane-2,20-dione (Va) on the following basis. Gallagher and Hollander[10] showed that mild alkaline hydrolysis

SCHEME I

SYNTHESIS OF A-NORPREGNANES



(1) The previous paper in this series: H. R. Nace and M. Inaba, *J. Org. Chem.*, **27**, 4024 (1962).

(2) The major portion of this research was sponsored by the U. S. Public Health Service, National Institutes of Health, Grant AM 05249-02. A preliminary report has been published: H. R. Nace, M. Inaba, and D. H. Nelander, *Trans. N. Y. Acad. Sci.*, **25**, 23 (1962).

(3) Abstracted from the Ph.D. thesis of D. H. Nelander, Brown University, 1963; Jesse Metcalf Fellow, 1960–1961.

(4) (a) F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959); L. J. Lerner, A. Bianchi, and A. Borman, *Proc. Soc. Exptl. Biol. Med.*, **103**, 172 (1960). (b) After completion of this work, a report appeared describing the benzilic acid rearrangement of a 3,4-diketopregnane [B. Camerino and U. Valeavi, *Gazz. chim. ital.*, **93**, 735 (1963)].

(5) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938).

(6) One attempt was made to oxidize 20,20-ethylenedioxy-5α-pregnan-3-one in 90% ethanol. Only 5α-pregnane-3,20-dione was recovered.

(7) L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 524 (1944).

(8) A. Butenandt, L. Mamoli, H. Dannenberg, L.-W. Mash, and J. Paland, *Ber.*, **72**, 1617 (1939).

(9) N. L. Wendler, D. Taub, and R. P. Graber, *Tetrahedron*, **7**, 173 (1959).

(10) T. F. Gallagher and V. P. Hollander, *J. Biol. Chem.*, **162**, 533 (1946); T. F. Gallagher, *ibid.*, **162**, 539 (1946).

of isomeric α-bromo ketones proceeded with inversion, but that the ketols could then isomerize in the basic medium through the enediol to give a mixture in which the most stable isomer predominated. Since ketols in which the hydroxyl group is equatorial are the most stable, the one in question here must be either 3β-hydroxy-5α-pregnane-2,20-dione (Va) or 2α-hydroxy-5α-pregnane-3,20-dione. This is supported by the infrared spectrum which had a single O–H stretching band at 2.81 μ. An axial hydroxyl group adjacent to a carbonyl group shows two bands at 2.78 and 2.85–2.9 μ.[11]

The choice between the two equatorial isomers was made on the basis of the molecular rotations of the ketol acetate and the parent ketone. Williamson and Johnson[12] showed that acetylation of ketols with acetic anhydride and pyridine proceeds with retention of configuration and no isomerization. As shown in Table I, the 2β-acetoxy and the 3β-acetoxy cholestanone derivatives have large positive molecular rotation differences.

TABLE I

MOLECULAR ROTATIONS OF CHOLESTANE-2,3-KETOL ACETATES

	Ref. 12		ΔMD
	$[\alpha]_D$	MD	(ketol acetate–ketone)
Cholestan-3-one	+41°	+159	
2α-Acetoxy-3-one	+52°	+231	+72
2β-Acetoxy-3-one	+87°	+387	+228
3β-Acetoxy-2-one	+76°	+338	+179
3α-Acetoxy-2-one	+54°	+240	+81

The ketol acetate Vb in question here had $[\alpha]_D$ +157°, MD +588, ΔMD +205 (ketol acetate Vb − 5α-pregnane-3,20-dione); thus it is assigned the structure of 3β-hydroxy-5α-pregnane-2,20-dione (Va). The crude ketol was probably a mixture of isomers with ketol Va predominating. Since the hydrolysis was carried out under basic conditions, the formation of some 17-iso compound was expected. However, the acetate prepared from the pure ketol showed only a single peak on v.p.c. analysis, and no attempt was made to isolate isomers from the mother liquors of the pure ketol.

The ketol then was oxidized to the diosphenol by two methods. The first employed cupric acetate in methanol[13] and gave a 25% yield of what appeared to be a mixture of diosphenols, which yielded diosphenol IV on recrystallization. The second method was based on Rigby's[14] qualitative test for ketols which involves the oxidation of them with bismuth trioxide, precipitating bismuth metal. The ketol was oxidized in this manner in acetic acid and the diosphenol was obtained in 40% yield.

Recently a direct method for the conversion of ketones to diosphenols by air or oxygen oxidation in the presence of potassium *t*-butoxide was reported by Bailey, Barton, Elks, and Templeton.[15] They found, however, that in the case of 5α-pregnane-3,20-dione attack also took place at the 17-position to give a mixture of products. This was confirmed in the present work, a gummy intractable mixture being obtained. However, when the 20-carbonyl group was protected by conversion to the ethylene ketal VI the oxidation was successful, and the diosphenol was obtained in 33% yield after hydrolysis of the protective group. This method was only tried on a small scale and with further study it is possible that the yields could be improved.

The diosphenol obtained from the above reactions is assigned the structure of 5α-pregn-1-en-2-ol-3,20-dione (IV) on the basis of its n.m.r. spectrum, which showed a singlet peak at −382 c.p.s. (tetramethylsilane[16b]) owing to a vinyl proton. The vinyl proton at C-1 in this compound has no adjacent protons available for spin–spin coupling and thus should show no splitting. The n.m.r. spectrum of 5α-cholest-3-en-3-ol-2-one[16] had a doublet at −344 c.p.s., J = 12 c.p.s., showing that the C-4 vinyl proton is split by the C-5 proton. When the diosphenol IV was treated under the conditions used by Stiller and Rosenheim[5] to obtain the isomeric diosphenol in the cholestane series, a mixture of the two diosphenols, still rich in IV (*ca.* 75%), was obtained. The n.m.r. spectrum of the mixture still showed a singlet peak at −382 c.p.s. for the C-1 vinyl proton and a doublet peak at −348.5 c.p.s., J = 9 c.p.s., for the vinyl proton at C-4. The two diosphenols could not be separated by t.l.c. and they could not be eluted from a v.p.c. column.

The diosphenol IV was rearranged by treatment with potassium hydroxide in propanol or ethanol to give A-nor-5α-pregnan-2-ol-20-one-2-carboxylic acid (VIIa) in 90% yield. Column chromatography and t.l.c. indicated the presence of only one of the two possible isomers from the rearrangement, showing that the benzilic acid rearrangement again was stereospecific.[1] The hydroxy acid was converted to its methyl ester VIIb, and v.p.c., t.l.c., and column chromatography of this also indicated only a single isomer. In one rearrangement experiment, however, isomers were observed. The hydroxy acid isolated had a lower melting point and a lower optical rotation than the pure acid. Recrystallization of the mixture from acetone–dilute hydrochloric acid converted it to the single hydroxy acid VIIa. The mixture of hydroxy acids was esterified with methanol and v.p.c. analysis of the mixed esters indicated a 3:1 mixture of isomers, one of which had a retention time identical with that of the pure methyl ester VIIb. Presumably the isomerization involves the formation of some 17-iso compound, which is converted back to the 17β compound on treatment with acid (see below for further examples of this behavior). In all but the one experiment this isomerization of the hydroxy acid by the basic reaction medium must have been reversed during the isolation under acidic conditions.

The position of the hydroxyl group and the carboxyl group was established by treating the hydroxy acid with lead tetraacetate in acetic acid, which gave the

(11) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Am. Chem. Soc.*, **78**, 5027 (1956).

(12) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

(13) J. C. Sheehan and W. F. Erman, *J. Am. Chem. Soc.*, **79**, 6050 (1957); M. N. Huffman, *J. Biol. Chem.*, **167**, 273 (1947); B. G. Christensen, N. G. Steinberg, and R. Hirshmann, *Chem. Ind.* (London), 1259 (1958).

(14) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(15) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *ibid.*, 1578 (1962); see also B. Camerino, B. Patelli, and R. Sciaky, *Tetrahedron Letters*, **16**, 554 (1961), and D. H. R. Barton, S. K. Pradhan, S. Sternhell, and J. F. Templeton, *J. Chem. Soc.*, 255 (1961).

(16) (a) We are indebted to Dr. Robert Iacona of this laboratory for this sample. (b) Tetramethylsilane (TMS) was used as an internal reference.

known A-nor-5α-pregnane-2,20-dione[17-19] (VIII) in 90% yield. This material gave only a single peak on v.p.c., but, when a sample was chromatographed on alumina the benzene eluates showed two peaks on v.p.c. One fraction was shown to contain 35% of an isomer in this manner, and when this fraction was treated with methanolic hydrogen chloride the amount of isomer was reduced to 25%. However, recrystallization of this material from acetone–dilute hydrochloric acid gave complete reconversion to the 17β-A-nor-2 20-dione. This behavior demonstrates that alumina is basic enough to cause isomerization at C-17 and that acetone–dilute hydrochloric acid is superior to methanolic hydrogen chloride for the conversion of 17-isopregnanes to the 17β compounds. Rull and Ourisson[18] prepared the A-nor-2,20-dione by Marker's procedure,[17] which involves only acidic conditions, and obtained a mixture of the 17α and 17β isomers, which must have been formed during purification of the product by alumina chromatography.

The configuration of the substituents at C-2 in the hydroxy acid VIIa is tentatively assigned as 2β-hydroxy-2α-carboxy on the basis of reasoning described previously,[1] but no direct evidence is available to support this assignment.

The hydroxy acid VIIa and its methyl ester proved to be very resistant to dehydration, in agreement with the behavior of the analogous compounds in the cholestane series.[1] The acid was dehydrated by heating at 300° and 0.05 mm. to give A-nor-5α-pregn-2-en-20-one (IX) in 69% yield. The position of the double bond is assigned on the basis of the n.m.r. spectrum, which showed a doublet peak at −432.5 c.p.s., $J = 7$ c.p.s., due to the splitting of the C-3 vinyl proton by the C-5 proton. This splitting is consistent with the calculations made by Dauben, Boswell, and Templeton[20] for the behavior of a 5α-A-nor-2-ene system, and opposite to the result obtained in the cholestane series.[1] There the structure of the olefin obtained by pyrolysis of the hydroxy acid was assigned as the 1-ene on the basis of a single vinyl proton peak at −428 c.p.s. When the n.m.r. spectrum of the same sample was determined with a newer instrument capable of better resolution, it showed a doublet peak at −431 c.p.s., $J = 6$ c.p.s., and accordingly, the unsaturated acid in the cholestane series is also the 2-ene-2-carboxylic acid.

The A-nor-5α-pregnan-2-ol-20-one-2-carboxylic acid was reduced with sodium borohydride to A-nor-5α-pregnane-2,20-β-diol-2-carboxylic acid (X) in 26% yield. The 20β-configuration is assigned on the basis of an analogous reduction of 2,3-seco-5α-pregnan-20-one-2,3-dioic acid by Weisenborn[21] which was shown to give the 20β isomer. The A-nor diol acid X was then cleaved with lead tetraacetate to give A-nor-5α-pregnan-20β-ol-2-one (XI) in 94% yield. This was readily oxidized with Jones' chrominum trioxide reagent[22] to give the known A-nor-5α-pregnane-2,20-dione (VIII) in 80% yield.

Experimental[23]

5α-Pregnane-3,20-dione.—A solution of 1.00 g. (3.16 mmoles) of 5α-pregnane-3β-ol-20-one in 150 ml. of acetone was cooled to 15°, 0.92 ml. of Jones' chromium trioxide reagent[22] was added, and the solution was stirred for 5 min. Then 1 l. of cold water was added; the precipitate was collected, air-dried, and recrystallized from acetone to give 0.94 g. (95%) of 5α-pregnane-3,20-dione, m.p. 198–201°, $[\alpha]^{24}D$ +119° (*c* 1.08, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.85 μ, R_f 1.00 (3:1 benzene–ether or 30:10:1 benzene–ether–acetic acid), T_r 1.16 (225°); lit.[19] m.p. 200–201°, $[\alpha]D$ +121° (*c* 1, $CHCl_3$), $\lambda_{max}^{CCl_4}$ 5.84 μ.

2α-Bromo-5α-pregnane-3,20-dione (I).—This compound was prepared as described previously[24] and had m.p. 200–200.5°, $[\alpha]^{24}D$ +116° (*c* 1, $CHCl_3$), λ_{max}^{KBr} 5.76 and 5.85 μ, R_f 1.29 (3:1 benzene–ether); lit. m.p. 199–202°, $\lambda_{max}^{CCl_4}$ 5.77 and 5.86 μ,[19] $[\alpha]^{24}D$ +104°.[24]

5α-Pregnane-3,20-dione-2-pyridinium Bromide (II).—A solution of 6.3 g. (15.9 mmoles) of 2α-bromo-5α-pregnane-3,20-dione in 40 ml. of dry pyridine was boiled under reflux until a pale yellow precipitate formed. Boiling was continued for 4 hr. and then the solvent was distilled under reduced pressure until a slurry remained. It was cooled to 10°; the precipitate was collected and washed with petroleum ether (b.p. 30–60°) to give 6.4 g. (85%) of the pyridinium bromide II, m.p. 275–276°. T.l.c. (3:1 benzene–ether) indicated that only the immobile salt was present. An analytical sample was prepared by recrystallization from ethanol and had m.p. 276–277°, $[\alpha]^{24}D$ +41° (*c* 1.07, $CHCl_3$), λ_{max}^{KBr} 5.85 and 6.12 μ, lit.[8] m.p. 285°.

Anal. Calcd. for $C_{26}H_{36}BrNO_2$: C, 65.81; H, 7.65. Found: C, 65.25; H, 7.32.

5α-Pregnane-3,20-dione-2-(*p*-N,N-diethylaminophenyl)nitrone (III).—A solution of 5.00 g. (10.2 mmoles) of the pyridinium bromide II in 113 ml. of 1:1 (v./v.) chloroform–ethanol was cooled to 0° and a slurry of 1.87 g. (10.5 mmoles) of *p*-nitroso-N,N-diethylaniline and 11 ml. of 1 *N* sodium hydroxide was added. The mixture was stirred for 4 hr. at room temperature, the organic solvents were evaporated under reduced pressure, and the solid was collected. It was recrystallized from acetone to give 3.34 g. (63%) of the nitrone III, m.p. 183–185°. A second crop of 0.78 g. (15%) had m.p. 177–179°. Further recrystallization from acetone gave an analytical sample, m.p. 184.5–185°; λ_{max}^{KBr} 5.86, 5.96, and 6.24 μ; R_f 0.48 (3:1 benzene–ether) and 0.37 (30:10:1 benzene–ether–acetic acid).

Anal. Calcd. for $C_{31}H_{44}N_2O_3$: C, 75.57; H, 9.00. Found: C, 75.11; H, 8.67.

5α-Pregn-1-en-2-ol-3,20-dione (IV).—To a solution of 7.65 g. (15.6 mmoles) of the nitrone III in 300 ml. of benzene was added 500 ml. of 2 *N* hydrochloric acid, whereupon the deep-red benzene solution immediately turned green. The resulting mixture was stirred for 12 hr. and then the layers were separated. The aqueous layer was extracted with three 300-ml. portions of benzene; the combined benzene layers were washed with 2 *N* hydrochloric acid and with water, and then dried over sodium sulfate: the benzene was evaporated under reduced pressure to give 4.8 g. (93%) of the diosphenol IV. A sample gave a red-brown color with aqueous ferric chloride. Recrystallization from glacial acetic acid gave 4.6 g. (90%), m.p. 225–227°. The analytical sample had m.p. 227–228°; $[\alpha]^{26}D$ +134° (*c* 0.98, $CHCl_3$); λ_{max}^{KBr} 2.90, 5.88, and 6.00 μ; λ_{max}^{EtOH} 270 mμ (ε 7800); R_f 0.34 (3:1 benzene–ether) and 0.98 (30:10:1 benzene–ether–acetic acid).

(17) R. E. Marker, O. Kamm, and D. M. Jones, *J. Am. Chem. Soc.*, **59**, 1595 (1937).

(18) T. Rull and G. Ourisson, *Bull. soc. chim. France*, 1573 (1958).

(19) N. Pappas and H. R. Nace, *J. Am. Chem. Soc.*, **81**, 4556 (1959).

(20) W. G. Dauben, G. A. Boswell, and W. H. Templeton, *ibid.*, **83**, 5006 (1961).

(21) F. L. Weisenborn, U. S. Patent 3,040,091 (1962); *Chem. Abstr.*, **57**, 13,838 (1962).

(22) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(23) Melting points were determined with a Hershberg apparatus and Anschutz thermometers and are corrected. Microanalyses were by Dr. S. M. Nagy and associates, Microchemical Laboratory, Massachusetts Institute of Technology. Analytical samples were recrystallized to constant melting point. Column chromatographic separations were made using silica gel (J. T. Baker and Co., chromatographic grade) or alumina (Merck and Co., Inc., chromatographic grade). For thin layer chromatography (t.l.c.) R_f values are reported relative to the R_f value for 5α-pregnane-3,20-dione, and were determined on glass plates with a 500-μ coating of silica gel. The plates were developed by spraying with a solution of 2,4-dinitrophenylhydrazine and phosphoric acid in 95% ethanol. For vapor phase chromatography (v.p.c.), T_r values refer to relative retention times using a 4-ft. column containing a 1% QF-1 coating on Gas-Chrom Z support. A-Nor-5α-pregnane-2,20-dione was used as the standard.

(24) M. Rubin, H. Wishinsky, and F. Bompard, *J. Am. Chem. Soc.*, **73**, 2338 (1951).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.83; H, 8.94.

The n.m.r. spectrum of the analytical sample showed a single, vinyl proton peak at −382 c.p.s. (TMS). Under the conditions used by Stiller and Rosenheim[5] to obtain the base-stable 2,3-diosphenol in the cholestane series, a mixture still rich in the acid-stable form IV (*ca.* 75%) was obtained, m.p. 220–223°. The n.m.r. spectrum of the mixture showed a split vinyl proton at −348.5 c.p.s. (TMS), J = 9 c.p.s., and a hydroxyl proton at −435 c.p.s. for the base-stable form. The single vinyl proton peak for the acid-stable form at −382 c.p.s. was still present, but less intense.

For comparison, the n.m.r. spectrum of 5α-cholest-3-en-3-ol-2-one (diosphenol A)[1,5,16] was determined and it showed a doublet peak at −344 c.p.s., J = 12 c.p.s., assigned to the vinyl proton, and a singlet peak at −435 c.p.s. for the hydroxyl proton.

3β-Hydroxy-5α-pregnane-2,20-dione (Va).—A solution of 4.00 g. (10.1 mmoles) of 2α-bromo-5α-pregnane-3,20-dione (I) in 200 ml. of tetrahydrofuran was added to 4.0 g. of potassium hydroxide in 200 ml. of water and the mixture was boiled under reflux for 30 min. The tetrahydrofuran was distilled under reduced pressure, the residual slurry was cooled, and the white solid was collected and air-dried. (An oily acidic fraction was recovered from the aqueous filtrate by acidification, but was not investigated.)

The white solid was chromatographed on silica gel and the various fractions were examined by t.l.c., using 3:1 benzene–ether. The benzene eluates gave spots of R_f 0.28 and 0.49 (yellow), 0.91 and 1.29 (brown), and 1.48 and 1.70 (pink, unsaturated ketone). The benzene–ether (9:1) eluates gave spots of R_f 0.31 and 0.46 (yellow), and the residues from these eluates were combined to give 1.37 g. (41%) of the ketol Va. (When the reflux time for the hydrolysis was extended to 2 hr., the yield of the ketol was 35%.) Recrystallization from benzene gave material of m.p. 181–185°, $[\alpha]^{24}D$ +120° (*c* 0.99, $CHCl_3$), λ_{max}^{Nujol} 2.81 and 5.87 μ, R_f 0.48 (3:1 benzene–ether) and 0.65 (30:10:1 benzene–ether–acetic acid). An analytical sample was obtained by recrystallization from ether–cyclohexane and had m.p. 181–182°, $[\alpha]^{24}D$ +130° (*c* 0.89, $CHCl_3$), λ_{max}^{KBr} 2.81 and 5.87 μ.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.01; H, 9.95.

The 3-acetate derivative Vb was prepared by allowing a solution of 100 mg. (0.31 mmole) of pure ketol in 2 ml. of pyridine and 2 ml. of acetic anhydride to stand at room temperature for 2 days. Then 50 ml. of water and 100 ml. of ether were added; the ether layer was removed, washed twice with water, and dried; the ether was evaporated to give 70 mg. (60%) of acetate. T.l.c. showed the absence of any ketol. The product was recrystallized from ether–cyclohexane and then had m.p. 181–182°; $[\alpha]^{24}D$ +157° (*c* 0.77, $CHCl_3$); λ_{max}^{Nujol} 5.72, 5.81, 5.89, and 8.10 μ; R_f 0.90 (3:1 benzene–ether); T, 3.90 (225°).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.58; H, 9.15.

Oxidation of 3β-Hydroxy-5α-pregnane-2,20-dione (Va). A. By Cupric Acetate.—A mixture of 300 mg. (0.905 mmole) of the ketol Va, 450 mg. of cupric acetate, and 24 ml. of methanol was boiled under reflux for 1 hr. Then 3 ml. of water was added, the solution was boiled for 15 min., and then it was cooled and acidified with dilute hydrochloric acid. The resulting mixture was extracted with ether; the ether extract was washed with water, and cooled to 0°; 50 ml. of 20% aqueous potassium hydroxide was added. The insoluble potassium salt of the diosphenol was collected and then shaken with ether and 2 *N* hydrochloric acid. The ether layer was washed with 5% sodium bicarbonate solution and with water, and then dried; the ether was evaporated to give 75 mg. (25%) of diosphenol IV, m.p. 209–216°. Recrystallization from methanol gave material, m.p. 223–225°, m.m.p. (with authentic material) 221–224°. A sample gave a red-brown color with aqueous ferric chloride solution.

B. Bismuth Trioxide.—To a boiling solution of 100 mg. (0.30 mmole) of the ketol Va in 10 ml. of acetic acid was added 56 mg. of bismuth trioxide. The resulting mixture was boiled under reflux for 2 hr., then cooled, diluted with 50 ml. of water, and extracted with three 100-ml. portions of benzene. The benzene extract was dried over anhydrous sodium sulfate, the benzene was evaporated, and the 110 mg. of crude diosphenol was taken up in ether, converted to the potassium salt, and back to the diosphenol as in A above. Recrystallization from acetic acid and water gave 40 mg. (40%), m.p. 225–226°, m.m.p. (with authentic diosphenol) 225–227°.

20,20-Ethylenedioxy-5α-pregnan-3β-ol.—A solution of 10.0 g. (31.4 mmoles) of 5α-pregnan-3β-ol-20-one, 0.67 g. of *p*-toluenesulfonic acid, and 125 ml. of ethylene glycol in 400 ml. of dry benzene was boiled under reflux with a Dean–Stark water separator. After 40 hr., as no additional amount of water could be detected in the water separator, the solution was cooled, made alkaline with alcoholic potassium hydroxide, washed with water until the washings were neutral, and dried over sodium sulfate. The solvent was removed and the residue was recrystallized from 1:1 acetone–methanol to give 10.24 g. (90%) of the ketal, m.p. 170–171°, $[\alpha]^{26}D$ +16° (*c* 1.32, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.85 μ, R_f 0.50 (3:1 benzene–ether), T, 0.33 (225°) and 0.28 (210°).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56. Found: C, 75.90, H, 10.57.

20,20-Ethylenedioxy-5α-pregnan-3-one (VI).—A slurry of 8.1 g. of chromium trioxide and 80 ml. of dry pyridine was added to a solution of 10.0 g. (27.6 mmoles) of the ketal in 100 ml. of dry pyridine, and the resulting mixture was stirred for 10 hr. Then 180 ml. of water was added, the mixture was filtered, and the precipitate was washed thoroughly with ether. The filtrate and washings were combined; the organic layer was removed, washed with water, dried over sodium sulfate, and evaporated. The residue was recrystallized from methanol to give 6.65 g. of the keto ketal VI, m.p. 187–188°, $[\alpha]^{26}D$ +35° (*c* 1.15 $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.87 μ. A second crop of 0.52 g. had m.p. 185–188° (72% total yield).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.74; H, 10.00.

A 100-mg. sample of the oxo ketol was dissolved in 2.5 ml. of tetrahydrofuran and 1.5 ml. of 3 *N* perchloric acid, and the solution was allowed to stand at room temperature for 8 hr. Then it was diluted with 8 ml. of water and the resulting precipitate was collected. It was recrystallized from acetone and had m.p. 199–201°; lit.[25] m.p. 200.5° for 5α-pregnane-3,20-dione.

Oxygenation of 20,20-Ethylenedioxy-5α-pregnan-3-one (VI).—To a solution of sodium *t*-butoxide in *t*-butyl alcohol (prepared by adding 100 mg. of sodium to 20 ml. of *t*-butyl alcohol) was added a solution of 100 mg. (0.28 mmole) of the keto ketal VI in 10 ml. of *t*-butyl alcohol and the resulting solution was stirred under an atmosphere of oxygen. After 2 hr. the reaction was stopped after an oxygen uptake of 87% of the theoretical value. The mixture was acidified with 4 *N* hydrochloric acid, allowed to stand overnight, and then extracted successively with 200-, 100-, and 50-ml. portions of ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated, to give 80 mg. of crude material. This was dissolved in ether and the potassium salt was precipitated by the addition of 50% potassium hydroxide solution. The salt was collected and acidified to give 30 mg. (33%) of the diosphenol, which was recrystallized from an acetic acid–water mixture and then had m.p. 224–226°; λ_{max}^{KBr} 2.90, 5.87, and 5.98 μ; R_f 0.34 (3:1 benzene–ether) and 0.98 (30:10:1 benzene–ether–acetic acid).

A-Nor-5α-pregnan-2-ol-20-one-2-carboxylic Acid (VIIa).—A solution containing 500 mg. (1.51 mmoles) of the diosphenol IV and 4.7 g. of potassium hydroxide in 130 ml. of 1-propanol and 10 ml. of water was boiled under reflux for 14 hr. The solution then was concentrated under reduced pressure to 50 ml., acidified, and extracted with three 100-ml. portions of ether. The ether extract then was washed with water and extracted with three 100-ml. portions of half-saturated sodium bicarbonate solution. The bicarbonate extract was acidified and extracted with three 100-ml. portions of ether. This ether extract was washed with water, dried over sodium sulfate, and evaporated to give 559 mg. of crude acid. Recrystallization from an ether–petroleum ether (b.p. 30–60°) mixture gave 475 mg. (90%) of the A-noracid VIIa, m.p. 240–241°; $[\alpha]^{26}D$ +98° (*c* 1.02, $CHCl_3$); λ_{max}^{KBr} 2.98 (broad), 5.79, and 5.88 μ; R_f 0.10 (3:1 benzene–ether) and 0.49 (30:10:1 benzene–ether–acetic acid). The analytical sample was prepared by recrystallization from an acetone–dilute hydrochloric acid mixture, and had m.p. 239–240°, $[\alpha]^{25}D$ +96° (*c* 0.99, $CHCl_3$).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.37; H, 9.26. Found: C, 72.12; H, 9.06.

When ethanol was used instead of 1-propanol, essentially the same yields were obtained, but there was less trouble with emulsions during the ether extractions.

Rearrangement of a mixture of the two diosphenols gave the same hydroxy acid VIIa.

(25) A. Butenandt and G. Fleischer, *Ber.*, **68**, 2094 (1935).

From one experiment, hydroxy acid was obtained which had m.p. 236–238°, $[\alpha]^{26}D$ +53° (c 1.04, $CHCl_3$). Recrystallization of a sample from a mixture of acetone and dilute hydrochloric acid gave a quantitative recovery of the hydroxy acid with m.p. 240–241°, $[\alpha]^{24}D$ +99° (c 0.84, $CHCl_3$).

A sample of the acid (m.p. 236–238°) was esterified with 5% methanolic hydrogen chloride (see below) to give an oil, $[\alpha]^{24}D$ +43° (c 1.05, $CHCl_3$), R_f 0.83 (3:1 benzene–ether). The oil was analyzed by v.p.c. and gave two peaks, T_r 0.88 and 1.13 (225°), ratio of the peak areas, 1:3. Assuming the oil to be a 3:1 mixture of the 17β and 17α isomer, the ΔMD value for 17β → 17α was determined, using the molecular rotation of the pure ester (MD +141), and was found to be −283. The agreement with the ΔMD value of −262 calculated from the molecular rotations of 5α-pregnan-3β-ol-20-one and 17-iso-5α-pregnan-3β-ol-20-one[26] strongly indicates that considerable amounts of the 17α isomer were formed under the basic conditions of the rearrangement.

Methyl A-Nor-5α-pregnan-2-ol-20-one-2-carboxylate (VIIb).—A solution of 50 mg. of the hydroxy acid in 25 ml. of 5% methanolic hydrogen chloride was boiled under reflux for 5 hr. The solvent was removed, the oily residue was taken up in ether, and the ether solution was washed successively with water, 5% sodium bicarbonate solution, and water. After drying the solution, the ether was distilled and the oily residue was recrystallized from ether–petroleum ether to give the methyl ester VIIb, m.p. 126–126.5°; $[\alpha]^{24}D$ +62° (c 0.34, $CHCl_3$); λ_{max}^{KBr} 2.82, 5.75, and 5.84 μ; R_f 0.82 (5:1 benzene–ether); T_r 1.15 (225°).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.95; H, 9.64.

A-Nor-5α-pregnane-2,20-dione (VIII).—A solution of 100 mg. (0.29 mmole) of the hydroxy acid VIIa and 190 mg. of lead tetraacetate in 10 ml. of glacial acetic acid was stirred at room temperature for 2 days and then heated on a steam bath for 1 hr. Then 25 ml. of water was added, the mixture was extracted with five 50-ml. portions of ether, and the ether extract was washed with water until the washings gave no precipitate or yellow color when 10% potassium iodide solution was added. The ether solution then was washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and the ether was distillled. The residue was recrystallized from ethanol–water to give 78 mg. (90%) of the 2,20-dione VIII, m.p. 177–179°, $[\alpha]^{26}D$ +257° (c 1.01, $CHCl_3$), λ_{max}^{KBr} 5.74 and 5.87 μ, R_f 1.04 (3:1 benzene–ether), T_r 1.00 (225°); lit. m.p. 180°,[17] 174–178°, $\lambda_{max}^{CCl_4}$ 5.75 and 5.85 μ, $[\alpha]D$ −134° (c 1, $CHCl_3$)[19], $[\alpha]D$ +255°.[18]

The bis-2,4-dinitrophenylhydrazone derivative was prepared by dissolving 27 mg. of the 2,20-dione in 10 ml. of ethanol and adding a filtered solution of 66 mg. of 2,4-dinitrophenylhydrazine in 5 ml. of ethanol containing 16 drops of concentrated hydrochloric acid. The resulting slurry was heated on a steam bath for 5 min. and then allowed to stand at room temperature for 3 days. Then the red precipitate was collected, washed thoroughly with ethanol containing concentrated hydrochloric acid, and recrystallized from chloroform–ethanol to give 31 mg. (55%), m.p. 281–282°, lit.[19] m.p. 261–263°.

A 640-mg. sample of pure 2,20-dione VIII was taken up in benzene and chromatographed on a column of 50 g. of alumina. V.p.c. analysis of each of the fifteen benzene eluates showed that a mixture of two components was present, T_r 0.73 and 1.00 (225°). The content of the minor component (T_r 0.73) increased until it reached a maximum of 35% in the tenth fraction. This fraction was evaporated to dryness, the residue was taken up in methanolic hydrogen chloride, boiled for 2 min., and then the methanol was evaporated. V.p.c. analysis of the residue showed, that the content of the minor component had been reduced to 25%. The 75:25 mixture was then recrystallized from acetone–dilute hydrochloric acid and the pure 17β-2,20-dione was recovered in quantitative yield, only one peak, T_r 1.00, on v.p.c.

A-Nor-5α-pregn-2-en-20-one-2-carboxylic Acid (IX).—A 9-mm. Pyrex test tube, containing 170 mg. (0.488 mmole) of the hydroxy acid VIIa, was evacuated to 0.05 mm., bathed with a yellow flame until the white solid darkened slightly, and then sealed. The tube was then kept in a Wood's metal bath at 300° until the bubbling ceased (15 min.). The crude product had R_f 1.08 with faint spots at 1.24 and 1.35 (30:10:1 benzene–ether–acetic acid). It was taken up in benzene and chromatographed on a column of 150 g. of silica gel. Benzene eluted 22 mg. of an oil; λ_{max}^{film} 3.40, 5.78, and 5.86 μ. Benzene–ether (9:1) eluted 111 mg. (69%) of A-nor-5α-pregn-2-en-20-one-2-carboxylic acid (IX), m.p. 258–260°. Recrystallization from ether–petroleum ether gave 101 mg. (63%), m.p. 259–260°; $[\alpha]D$ +118° (c 0.95, $CHCl_3$); λ_{max}^{KBr} 2.95, 5.87, and 6.21 μ; λ_{max}^{EtOH} 226 mμ (ε 10,100) at 1.1 × 10^{-4} mole per liter; R_f 1.00 (30:10:1 benzene–ether–acetic acid). A sample decolorized a basic potassium permanganate solution.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.12; H, 9.09.

The n.m.r. spectrum of the unsaturated acid showed a doublet at −432.5 c.p.s. (TMS), J = 7 c.p.s.

A-Nor-5α-pregnane-2,20β-diol-2-carboxylic Acid (X).—To an aqueous suspension of 500 mg. (1.44 mmoles) of the hydroxy acid in 40 ml. of water containing 60 mg. of sodium hydroxide was added a solution of 110 mg. (2.88 mmoles) of sodium borohydride and 30 mg. of sodium hydroxide in 10 ml. of water. The mixture was heated to 50° and the resulting solution was stirred for 24 hr. The mixture then was cooled in an ice bath, acidified with dilute hydrochloric acid, and extracted with four 300-ml. portions of ether. The ether extract was washed with water and dried over sodium sulfate; and the ether was evaporated to give 410 mg., m.p. 211–215°. This material was powdered and boiled in 100 ml. of chloroform for 5 min.; the undissolved solid was removed. This solid was recrystallized twice from acetone to give 130 mg. (26%) of A-nor-5α-pregnane-2,20β-diol-2-carboxylic acid (X), m.p. 251.5–252.5°; $[\alpha]^{26}D$ +20° (c 0.23, $CHCl_3$); λ_{max}^{KBr} 2.85, 2.94, and 5.90 μ; R_f 0.29 (30:10:1 benzene–ether–acetic acid).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.03; H, 9.68.

A-Nor-5α-pregnan-20β-ol-2-one (XI).—A mixture of 27 mg. (0.077 mmole) of A-nor-5α-pregnane-2,20-β-diol-2-carboxylic acid (X), 60 mg. of lead tetraacetate, and 15 ml. of glacial acetic acid was heated on a steam bath until solution occurred, and then the solution was allowed to stand at room temperature for 2 days. Ether (150 ml.) and water (150 ml.) were added, and the ether layer was removed and washed with water until the washings were colorless on treatment with 10% potassium iodide solution.

Then the ether layer was washed twice with 100-ml. portions of 5% sodium bicarbonate solution and once with 100 ml. of water, and dried over sodium sulfate. The ether was removed to give 22 mg. (94%) of A-nor-5α-pregnan-20β-ol-2-one (XI), m.p. 216–218°, R_f 0.48 (3:1 benzene–ether). Recrystallization from ether–petroleum ether gave 20 mg. (85%), m.p. 217–218°; $[\alpha]^{26}D$ +43° (c 0.57, $CHCl_3$); λ_{max}^{KBr} 2.81, 5.74, and 9.04 μ; T_r 0.35 (225°).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.84; H, 10.74.

A 10-mg. (0.033 mmole) sample in 5 ml. of acetone was treated with 1 ml. of Jones chromium trioxide reagent.[22] The solution was stirred for 5 min.; 50 ml. of water was added; the white solid was collected and recrystallized from ether–petroleum ether to give 8 mg. (80%) of A-nor-2,20-dione VIII, m.p. 177–180°, m.m.p. (with an authentic sample) 177–180°, λ_{max}^{KBr} 5.75 and 5.88 μ, R_f 1.07 (3:1 benzene–ether), T_r 0.99 (225°).

(26) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co. New York, N. Y., 1959, p. 566.

Factors Controlling the Reactions of Nortricyclyl and Dehydronorbornyl Chloride with Sodium and with Magnesium

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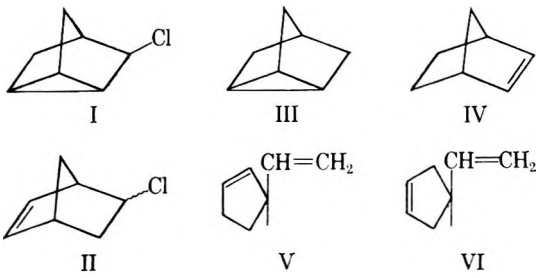
Three factors have been found which affect product composition in the reactions of nortricyclyl and dehydronorbornyl chloride with sodium and with magnesium: temperature, ionic character of the carbon–metal bond, and the presence of either a ring double bond or potential double bond. Evidence concerning these three factors is presented and a mechanism is suggested for the formation of 3- and 4-vinylcyclopentene in the reactions of nortricyclyl and dehydronorbornyl chloride with sodium.

Recently we have reported that treatment of either nortricyclyl chloride (I) or dehydronorbornyl chloride (II) with sodium in *n*-decane at 85–90° generates very nearly identical C_7 hydrocarbon fractions consisting of nortricyclene (III), norbornene (IV), 3-vinylcyclopentene (V), and 4-vinylcyclopentene (VI).[2] Further



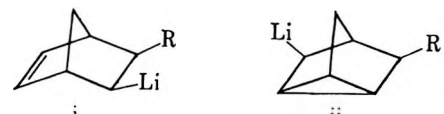
study of these and similar reactions has revealed three factors which control product composition: temperature, ionic character of the carbon–metal bond, and the presence of either a ring double bond (dehydronorbornyl chloride) or potential double bond (nortricyclyl chloride).

Investigation of the effect of temperature demonstrated that, as the maximum reaction temperature is reduced, the percentage of the C_7 hydrocarbon fraction representing the ring cleavage products V and VI decreases from a total of 55.8% at 154 to 1.0% at 0° (Table I).

Roberts and co-workers[3] have reported that hydrolysis of the Grignard reagent prepared from either dehydronorbornyl or nortricyclyl bromide produces nortricyclene. Grignard reagents in these two systems were reinvestigated at temperatures equivalent to those used in the sodium reaction by preparing the Grignard reagents from the alkyl chlorides in di-*n*-butyl ether, and then subjecting them to heating at 130°. After hydrolysis the Grignard reagent prepared from dehydronorbornyl chloride (54% *endo*, 46% *exo*) produced a 48.1% yield of C_7 hydrocarbons: 92.3% nortricyclene, 7.2% norbornene, and a trace (0.5%) of 3- and 4-vinylcyclopentene. Nortricyclyl chloride resulted in a 15.2% yield of nortricyclene and norbornene in a similar ratio of 87.4:12.6 with no detectable 3- and 4-vinylcyclopentene present.

To rule out the possible influence of the different solvents used in the Grignard and sodium reactions, reactions of the alkyl chlorides with sodium in di-*n*-butyl ether at 85–90° were carried out. Vinylcyclopentenes were formed, and the product ratios were similar to those obtained in the *n*-decane solvent. The reaction of dehydronorbornyl chloride (II, 54% *endo*, 46% *exo*) leads to a C_7 hydrocarbon composition of 65.6% III, 14.2% IV, and 20.2% V and VI, while I produces a corresponding composition of 57.7% III, 9.5% IV, and 32.8% V and VI. The more highly ionic bond of the alkyl sodium compound,[4] then, is apparently necessary in order for the ring cleavage reaction to make any significant contribution to product composition. The greater density of negative charge available for rearrangement at the carbon atom of the more highly ionic bond would seem to point to a carbanionic rearrangement. This dependence upon the ionic character of the carbon–metal bond is consistent with the carbanionic rearrangements in the 2,2-diphenylpropyl system studied by Zimmerman and Zweig.[5,6] A final argument in favor of a carbanionic cleavage mechanism is that several studies of dehydronorbornyl and nortricyclyl free radicals have not revealed similar ring cleavages to that reported here.[7]

The question of whether or not the ring double bond or potential double bond is necessary in the starting chloride for ring cleavage was answered by investigating the reaction of norbornyl chloride (VII) with sodium. Norbornyl chloride (50% *exo*, 50% *endo*) when treated with sodium produces a 27% yield of C_7 hydrocarbons composed of 32.2% nortricyclene (III), 30.0% norbornene (IV), and 37.8% norbornane. No ring cleavage products were found. The nortricyclene seems best explained by an intramolecular insertion reaction of carbene intermediate VIII, generated as the



R = *n*-C_4H_9, C_6H_5 | R = *n*-C_4H_9, C_6H_5, *i*-C_3H_7, *t*-C_4H_9

(1) National Defense Act Fellow, 1959–1962.

(2) P. K. Freeman, D. E. George, and V. N. M. Rao, *J. Org. Chem.*, **28**, 3234 (1963).

(3) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

(4) The sodium–carbon bond has an estimated 47% ionic character while the magnesium–carbon bond has only 27% and the lithium–carbon bond is intermediate with 43% (E. G. Rochow, D. R. Hurd, and R. N. Lewis, "The Chemistry of Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 65, 77).

(5) H. E. Zimmerman and A. Zweig, *J. Am. Chem. Soc.*, **83**, 1196 (1961).

(6) The absence of ring cleavage following generation of intermediate i and ii by addition of alkyl and aryl lithium to norbornadiene, investigated by G. Wittig and E. Hahn [*Angew. Chem.*, **72**, 781 (1960)] and G. Wittig and J. Otten, [*Tetrahedron Letters*, **10**, 601 (1963)], may be explained on the basis of the first two factors. The reactions were, in general, carried out at lower temperatures and the carbon–lithium bond would be expected to be less susceptible to carbanionic rearrangement.

(7) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Am. Chem. Soc.*, **80**, 635 (1958); P. J. Graham, E. L. Buhle, and N. Pappas, *J. Org. Chem.*, **26**, 4658 (1961); E. S. Huyser and G. Echegaray, *ibid.*, **27**, 429 (1962); J. W. Wilt and A. A. Levin, *ibid.*, **27**, 2319 (1962).

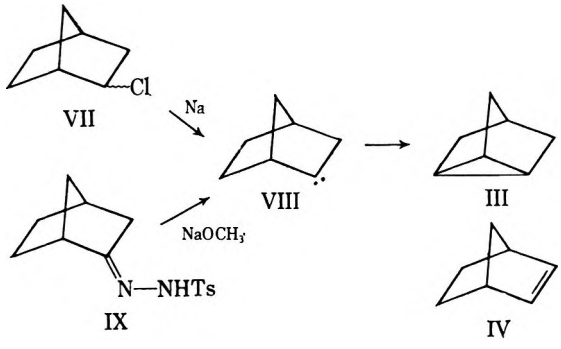
TABLE I

THE REACTIONS OF NORTRICYCLYL AND DEHYDRONORBORNYL CHLORIDE WITH SODIUM

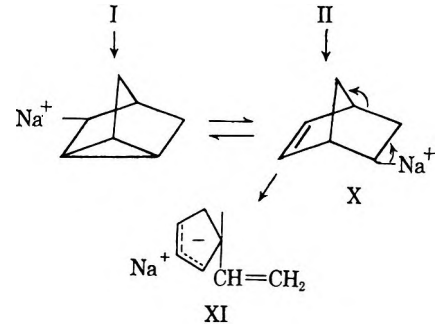
RCl	Oil-bath temp., °C.	Max. temp.,[a] °C.	Yield, %	III, %	IV, %	V, %	VI, %	Norbornadiene, %
I[b]	85–90	154	20.5	34.3	9.9	18.7	37.1	
I[c]	85–90	133	19.2	71.0	10.0	5.9	13.1	
II[c]	85–90	133	27.1	64.0	13.0	7.5	13.5	2.0
I[c]	25	108	21.8	85.6	8.5	1.7	4.2	
II[c]	25	108	29.5	80.2	11.7	2.3 (combined)		5.8
I[c]	0	0	8.3	93.0	6.0	1.3 (combined)		
II[c]	0	0	10.4	79.6	7.4	1.0 (combined)		12.0

[a] Maximum temperature reached inside the reaction flask. [b] No solvent used. [c] Alkyl chloride, 5.00 g.; *n*-decane, 12.5 ml.; 0.90 g. of sodium.

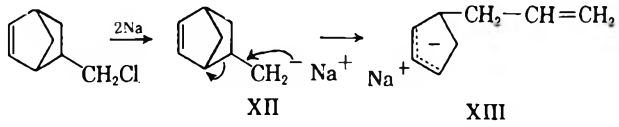
result of α-elimination induced by norbornylsodium, since carbenoid decomposition of the *p*-toluenesulfonylhydrazone of norcamphor results nearly exclusively in nortricyclene.[8] In spite of the fact that only trace amounts of norbornene are formed in basic decomposition of IX, α-elimination as well as β-elimination must be listed as a possible reaction pathway for the production of norbornene from VII. The different norbornene–nortricyclene ratios may be the result of different modes of formation of bivalent carbon intermediate VIII.[9]



The dependence of the ring cleavage on the presence of a double bond or potential double bond may be rationalized on the basis of two factors: stabilization of the carbanion by allylic resonance[10] and greater relief of strain in the more highly strained system.[11] Thus, the cleavage reaction may be viewed as the result of the electronic shifts pictured in X which produce mesomeric carbanion XI.[12]



Similar cleavage of a norbornyl carbanion would have produced a nonresonance-stabilized vinylcyclopentyl carbanion. Two additional examples of this type of ring cleavage are found in the generation of 3- and 4-allylcyclopentene upon treatment of dehydronorbornylmethyl chloride with sodium (XII → XIII),[13] and in the generation of Δ^3-cyclopentenylacetamide by cleavage of dehydronorcamphor with sodium amide.[14]



The ring cleavage reaction of norbornadiene recently reported by Finnegan and McNees[15] may also be classified with the above reactions. Treatment of norbornadiene with amylsodium results in the generation of cyclopentadiene and acetylene. The authors favor a cleavage mechanism involving proton abstraction at C-2 rather than C-7.[16] The cleavage of the C-3–C-4 bond, resulting from the shift of the pair of electrons at C-2 to form a C-2–C-3 triple bond (XIV) is analogous to those listed above. This bond cleavage is clearly dependent on the second double bond since 2-nor-

(8) L. Friedman and H. Schechter, *J. Am. Chem. Soc.*, **83**, 3159 (1961); this decomposition was repeated in our laboratories with nearly identical results [a trace (0.5%) of norbornene was detected in the C7 hydrocarbon fraction].

(9) While in some cases there is good agreement of product composition for reactions proceeding *via* a bivalent carbon intermediate formed by different routes [for example, see G. L. Closs, *ibid.*, **84**, 809 (1962)] in other instances significant differences in product composition are apparent [G. L. Closs and J. J. Coyle, *ibid.*, **84**, 4350 (1962); G. L. Closs, R. A. Moss, and J. J. Coyle, *ibid.*, **84**, 4984 (1962); G. L. Closs and L. E. Closs, *Angew. Chem.*, **74**, 431 (1962)].

(10) The usual order of stability of carbanions (allyl > vinyl > alkyl), as measured by preferential proton abstraction by alkyl sodium, is upset in the case of cyclopentene. A. A. Morton and R. A. Finnegan [*J. Polymer Sci.*, **38**, 19 (1959)] have found that cyclopentene undergoes vinyl rather than allylic proton abstraction. Nevertheless it seems reasonable to assume that an allylic cyclopentenyl carbanion will be more stable than a cyclopentyl carbanion either through resonance or inductive stabilization.

(11) R. B. Turner, W. R. Meador, and R. E. Winkler [*J. Am. Chem. Soc.*, **79**, 4116 (1957)] have found that, in spite of the nonbonded repulsions introduced as a result of the reduction of the norbornene double bond, the heat of hydrogenation of norbornene is 6 kcal. greater than that for cyclohexene, and 7.4 kcal. greater than that for cyclopentene.

(12) G. Wittig and G. Klumpp [*Tetrahedron Letters*, **10**, 607 (1963)] have recently reported a reaction which may be quite similar in mechanism to the dehydronorbornyl chloride–sodium reaction. Treatment of norbornadiene with lithium produced norbornene, nortricyclene, and 3-vinylcyclopentene.

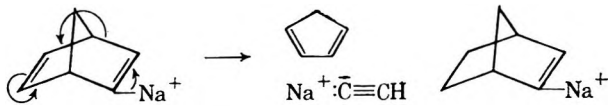
(13) P. K. Freeman, D. E. George, and V. N. M. Rao, preliminary experimental results concerning this reaction were presented at the Northwest Regional Meeting of the American Chemical Society, Bellingham, Wash., June, 1963, Abstracts, p. 25; complete details will be reported at a later date.

(14) S. J. Cristol and P. K. Freeman, *J. Am. Chem. Soc.*, **83**, 4427 (1961).

(15) R. A. Finnegan and R. S. McNees, *Tetrahedron Letters*, **17**, 755 (1962).

(16) This appears even more certain now, since A. Streitweiser, Jr., and R. A. Caldwell [*J. Org. Chem.*, **27**, 3360 (1962)] have found only C-2 proton abstraction when norbornadiene is treated with butyllithium with no evidence for C-7 proton abstraction.

bornenylsodium (XV), produced by treatment of norbornene with butylsodium in pentane[17] or as repeated in this laboratory in *n*-decane at 125–130°,[18] does not undergo ring cleavage.



XIV XV

Finally, it is interesting to note that the lack of a second carbon–carbon bond cleavage following the transformation of X to XI may be due to the fact that a vinyl carbanion would not be expected to be so good a leaving group as an ethynyl carbanion.[19]

Experimental[20]

Reactions of Nortricyclyl Chloride and Dehydronorbornyl Chloride with Sodium.—These reactions were carried out in *n*-decane as solvent as previously described, isolating the C_7 hydrocarbon fraction directly by vacuum distillation.[2] The results are summarized in Table I.

In order to test the effect of changing solvent upon the ring cleavage reaction, nortricyclyl chloride and dehydronorbornyl chloride (54% *endo*, 46% *exo*) were treated with sodium in di-*n*-butyl ether. The procedure was essentially the same as that used above with *n*-decane as solvent. Alkyl chloride (5.0 g.), 0.9 g. of sodium, 12.5 ml. of di-*n*-butyl ether, and an oil-bath temperature of 85–90° were employed. After the 1-hr. stirring period was complete, the reaction mixture was neutralized with methanol, washed with water, and dried. Vapor phase chromatographic analysis of the resulting di-*n*-butyl ether solution on a 3-m. Dow Corning QF-1 silicone oil column showed that the C_7 hydrocarbon fractions had the following compositions: 65.6% nortricyclene, 14.2% norbornene, and 20.2% 3- and 4-vinylcyclopentene from dehydronorbornyl chloride; 57.7% nortricyclene. 9.5% norbornene, and 32.8% 3- and 4-vinylcyclopentene from nortricyclyl chloride.

Nortricyclyl and Dehydronorbornyl Grignard Reagents.—To 2.0 g. (0.083 g.-atom) of magnesium and a crystal of iodine in a dry 100-ml. flask fitted with a mechanical stirrer, a pressure-equalized dropping funnel, and a condenser attached to a calcium chloride drying tube, was added 1 g. of nortricyclyl or dehydronorbornyl chloride in 1 ml. of absolute di-*n*-butyl ether. The mixture was stirred mechanically at 50–55°, oil-bath temperature, and the reaction began immediately. After an additional 10 ml. of di-*n*-butyl ether was added, 9.0 g. of the alkyl chloride in 9 ml. of di-*n*-butyl ether was added dropwise at 50–60°. The mixture was heated with stirring at 85–90° for 2 hr. in the first pair of experiments and at 125–130° for 75 min. in the second pair of experiments.

The mixture then was cooled to room temperature and poured into an ice-water mixture saturated with ammonium chloride. After shaking in a separatory funnel, the organic layer was washed with water and dried. Vapor phase chromatographic analysis of the di-*n*-butyl ether solution was accomplished on a 3-m. Dow Corning QF-1 column.

Nortricyclyl Grignard reagent heated at 85–90° gave a 68.3% yield of C_7 hydrocarbons composed of 96.8% nortricyclene, 3.2% norbornene, and a trace (0.1%) of 3- and 4-vinylcyclopentene. Dehydronorbornyl Grignard reagent (from dehydronorbornyl chloride, 44% *exo*, 56% *endo*) heated at 85–90° gave a 70.4% yield of C_7 hydrocarbons: 91.4% nortricyclene, 8.6% norbornene, and no detectable 3- and 4-vinylcyclopentene. Heated at 125–130°, nortricyclyl Grignard reagent produced a 15.2% yield of C_7 hydrocarbons: 87.4% nortricyclene, 12.6% norbornene, and no detectable 3- and 4-vinylcyclopentene. At this same temperature the dehydronorbornyl Grignard reagent (from dehydronorbornyl chloride, 46% *exo*, 54% *endo*) gave a 48.1% yield of C_7 hydrocarbons: 92.3% nortricyclene, 7.2% norbornene, and 0.5% 3- and 4-vinylcyclopentane.

Reaction of Norbornyl Chloride with Sodium.—Using the same procedure and apparatus described previously for nortricyclyl chloride,[2] 5.0 g. (0.037 mole) of norbornyl chloride (50% *endo*, 50% *exo*) was allowed to react with 0.85 g. (0.037 g.-atom) of sodium in *n*-decane at 85–90°. The C_7 hydrocarbon fraction (1.0 g.), isolated directly from the reaction mixture by vacuum distillation, had the following composition: 37.8% norbornane, 30.0% norbornene, and 32.2% nortricyclene.

The percentage composition was obtained by vapor phase chromatographic analysis of the product mixture on two different columns. A 2-m. Dow Corning 200 silicone oil column gave two peaks in the ratio of 70:30. The infrared spectrum of the isolated 30% peak, showed it to be norbornene, while infrared analysis of the 70% component proved that it was a mixture of norbornane and nortricyclene. A Carbowax 1500 column also gave two peaks in a 67.8:32.2 ratio. The 32.2% component corresponded to nortricyclene; the 67.8% component was a mixture of norbornene and norbornane.

Norcamphor *p*-Toluenesulfonylhydrazone.—Norcamphor *p*-toluenesulfonylhydrazone was prepared by a procedure modeled after that used by Cristol for nortricyclenone.[21] An analytical sample prepared by recrystallization from ethanol melted at 201.5–202.5° dec.

Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.47. Found: C, 60.55; H, 6.53.

Carbenoid Decomposition of Norcamphor *p*-Toluenesulfonylhydrazone.—This decomposition was carried out according to the procedure outlined for the sodium methoxide induced decomposition of nortricyclenone *p*-toluenesulfonylhydrazone.[21] The 28.7% yield of C_7 hydrocarbons obtained was principally nortricyclene (99.5%) with a trace of norbornene (0.5%).

Reaction of Norbornene with *n*-Butylsodium.—A solution of *n*-butylsodium in 70 ml. of *n*-decane was prepared from 7.3 g. of sodium (0.32 g.-atom) and 10.6 g. (0.115 mole) of *n*-butyl chloride using the procedure of Morton and co-workers.[22] A solution of 5.0 g. (0.053 mole) of norbornene in 10 ml. of *n*-decane was added dropwise to the *n*-butylsodium solution at 80–85°. After the addition was complete, the reaction flask was heated at an oil-bath temperature of 85–90° for 30 min. and then at 125–130° for 30 min. After washing the decane solution with water and drying, infrared analysis and vapor phase chromatographic analysis (on a 3-m. Dow Corning QF-1 silicone oil column and a 2-m. Dow Corning 200 silicone oil column) demonstrated that 3.74 g. of norbornene was present (a 75% recovery). There were no traces of any other C_7 hydrocarbons.

Acknowledgment.—The authors gratefully acknowledge the support of this research by the National Science Foundation (NSF-G13511).

(17) R. A. Finnegan and R. S. McNees, *Chem. Ind.* (London), 1450 (1961).

(18) The result in *n*-decane rules out the possibility, perhaps somewhat unlikely, that XV is a precursor of the 3- and 4-vinylcyclopentenes in the dehydronorbornyl chloride–sodium or nortricyclyl chloride–sodium reaction.

(19) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt Rinehart and Winston, New York, N. Y., 1959, p. 258.

(20) Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(21) S. J. Cristol and J. K. Harrington, *J. Org. Chem.*, **28**, 1413 (1963).

(22) A. A. Morton, G. M. Richardson, and A. T. Hallowell, *J. Am. Chem. Soc.*, **63**, 327 (1941).

Stereochemistry of Reactions of 7-Norbornenyl Anions

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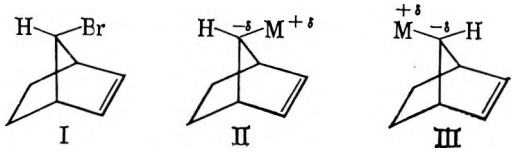
The action of magnesium and lithium on *syn*-7-bromonorbornene has been investigated. Carbonation of the organometallic reagents led to a 2:1 mixture of the corresponding *anti*-*syn* carboxylic acids. Oxidation of the Grignard reagent led to a 2:1 mixture of *anti*-*syn*-7-norbornenol.

In view of the striking differences in the products and rates of solvolysis of 7-*syn*- and -*anti*-norbornenyl derivatives,[1] in which partial positive charges are developed at the 7-position, it was of interest to devise experiments which would develop partial negative charge at this position in the norbornene skeleton. Of particular interest were the possibilities of rearrangements or cyclizations and the effects of the double bond on the relative stability of the two isomeric carbanions at C-7.

To this end, it was decided to investigate the action of magnesium and lithium on *syn*-7-bromonorbornene[2] (I). This halide should serve as a potential source of both possible anions, II and III, in view of the well-known racemization of optically active halides by these metals.[3] Information on the structure of the organometallic reagents could be gained by determination of the structure of the products formed on carbonation and oxidation reactions.

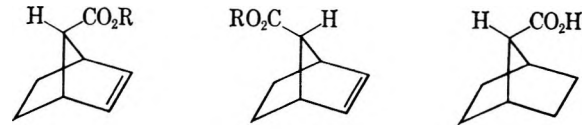


I II III

Results and Discussion

Treatment of *syn*-7-bromonorbornene with magnesium in diethyl ether followed by carbonation gave a 40% yield of a mixture of carboxylic acids. The mixture was converted to methyl esters and found (g.l.c.) to contain two components in a ratio of 2:1. Careful fractional distillation gave two isomeric esters, both of which showed strong infrared absorption at *ca.* 14 μ, indicating the presence of *cis* olefins.[4] The nuclear magnetic resonance spectra of both isomers strongly suggested that they were the *syn*- and *anti*-7-carbomethoxynorbornenes, IV and V.

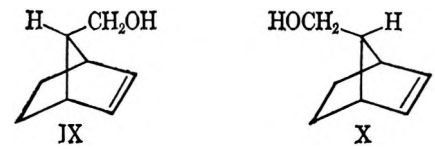
Verification of the presence of the norbornene skeleton in both isomers was accomplished by conversion of both isomers to a known norbornane derivative. Basic hydrolysis of the two esters gave two carboxylic acids, VI and VII, both of which absorbed 1 mole of hydrogen to produce the known[2] 7-carboxynorbornane (VIII). The only remaining problem was to determine which pair of isomers was *syn* and which pair was *anti*.



IV, R = CH_3 V, R = CH_3 VIII

VI, R = H VII, R = H

Several approaches to the problem of assigning the stereochemistry were investigated. The recent interest[5] in the use of infrared spectroscopy to detect intramolecular hydrogen bonding with π-electrons[6] offered the possibility of a relatively simple and unambiguous solution. It would only be necessary to convert the two esters to the corresponding unsaturated alcohols IX and X and determine which of them exhibited intramolecular hydrogen bonding. Only the *syn* isomer (IX) would be expected to show an interaction between the hydroxyl group and the double bond. Unfortunately, both isomers showed only a single hydroxyl absorption and no bonded hydroxyl



IX X

absorption[7] (see Experimental). Apparently, in the *syn* isomer the conformation of the hydroxyl group in which the hydrogen is close enough to interact with the double bond is sterically unfavorable and the O–H bond is directed away from the double bond.

Gas chromatography has also been used recently[8] to assign configurations to isomeric unsaturated alcohols. In the case at hand, it was found that one of the isomers had a retention time of 62 min. and the other a retention time of 83 min. It is tempting to assign structure IX to the more rapidly eluted isomer and structure X to the isomer which has the freer hydroxyl group and thus is bound more strongly to the column. In view of the results of the infrared measurements, however, it did not seem prudent to rely solely on these results for a structure proof.

A more convincing demonstration of the identity of the two series of isomers was provided by some data on

(1) S. Winstein, A. H. Lewin, and K. C. Pande, *J. Am. Chem. Soc.*, **85**, 2324 (1963); H. C. Brown and H. M. Bell, *ibid.* **85**, 2324 (1963); S. Winstein, M. Shatavsky, C. J. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955).

(2) H. Kwart and L. Kaplan, *ibid.*, **76**, 4072 (1954).

(3) See D. Y. Curtin and W. J. Koehl, Jr., *ibid.*, **84**, 1967 (1962), for a discussion and references.

(4) H. B. Henbest, G. D. Meakins, B. Nicholls, and R. A. L. Wilson, *J. Chem. Soc.*, 997 (1957); E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *ibid.*, 4073 (1956).

(5) I. M. Goldman and R. O. Crisler, *J. Org. Chem.*, **23**, 751 (1958); D. S. Trifan, J. L. Weinmann, and L. P. Kuhn, *J. Am. Chem. Soc.*, **79**, 6566 (1957); A. W. Baker and A. T. Shulgin, *ibid.*, **80**, 5358 (1958); P. von R. Schleyer, D. S. Trifan, and R. Bacskai, *ibid.*, **80**, 6691 (1958); R. West, *ibid.*, **81**, 1614 (1959); *cf.* R. Picolini and S. Winstein, *Tetrahedron Letters*, **13**, 4 (1959).

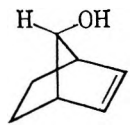
(6) A. M. Buswell, W. H. Rodebush, and R. M. Whitney, *J. Am. Chem. Soc.*, **69**, 770 (1947).

(7) We are indebted to Professor P. von R. Schleyer, Princeton University, for these measurements. Interestingly, the 8,8-dimethyl analog does show internal bonding in the *syn* form (see ref. 9).

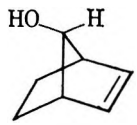
(8) C. H. DePuy and P. R. Story, *Tetrahedron Letters*, **6**, 20 (1959); *cf.* K. Mislow and J. C. Berger, *J. Am. Chem. Soc.*, **84**, 1956 (1962).

the retention times of the esters on a silver nitrate column. The two isomers were cleanly separated on a 2-ft. column of diethylene glycol on Celite. The lower boiling ester had a retention time of 25 min. compared with 59 min. for the higher boiling isomer. Under identical conditions of flow rate and temperature the retention times then were determined on a 2-ft. column packed with Celite which was impregnated with a saturated solution of silver nitrate in diethylene glycol. On the silver nitrate–glycol column the higher boiling ester had about the same retention time as before (50 min.), but the lower boiling ester now had a retention time of 71 min. This striking reversal in the order of retention times allows a definite assignment of configuration to be made. The silver ion would be expected to affect the retention time of only the isomer with the unhindered double bond (*i.e.*, *anti*); therefore the low-boiling ester is V. The fact that the *syn* isomer (IV) has nearly the same retention time on either column serves as a double check on the conclusions, since it excludes the possibility of any specific interaction between the ester functions and silver nitrate.[9]

Oxidation of the Grignard reagent was also investigated. A 33% yield of alcohols was obtained which was shown to contain *syn*-7-norbornenol (XI) and *anti*-7-norbornenol (XII) in a ratio of 28:72.



XI



XII

Preparation of the lithium reagent from *syn*-7-bromonorbornene proved to be erratic. The best results, which could not be duplicated, gave a 54% yield of acids on carbonation. Coincidentally, the *syn*–*anti* ratio of the acids was also about 1:2.

Rationalization of these results is difficult in view of the uncertainties in the structure of these reagents and the stereochemistry of their reactions.[10] A simple but not completely rigorous explanation of the results would be to assume that the organometallic reagent is produced in a thermodynamically controlled step. Assuming that carbonation proceeds with retention of configuration,[3,10d] two explanations are possible depending on the rates of the carbonation steps *vs.* the rates of interconversion of the *syn* and *anti* isomers. If the carbonation steps are very fast, the product ratio reflects differences in stability of the two anions. If rates of inversion are very fast, the product ratio reflects differences in transition state energies. In either case it appears that the *anti* form is more stable than the *syn* form of the organometallic derivatives. Presumably, this would be a result of the repulsion of the negative charge on the anion by the π-electrons of the double bond.[9] Steric effects do not appear to be responsible for the predominant formation of the *anti* isomer since it was shown that, in the case of the esters, the *syn* ester (IV) is slightly more stable than the *anti* ester (V).

In any case, it is clear that the 7-norbornenyl anion behaves differently from other allylcarbinyl anions. The Grignard reagent from allylcarbinyl chloride, for example, gives products which indicate scrambling of the methylene carbons, presumably *via* the cyclopropylcarbinyl system.[11] Similarly, 5-bromonorbornene yields only nortricyclyl products from Grignard reactions.[12] In the case of the cholesteryl Grignard reagent, no cyclization was observed, the carbonation product being 3β-carboxycholestene.[13] The effect of the double bond on the stereochemistry of this reaction is not known since the Grignard reagent from 3-chlorocholestanes also leads to 3β acid on carbonation.

It was of considerable interest to investigate the solvolytic behavior of *p*-toluenesulfonate derivatives of alcohols IX and X. It was anticipated that products and rates of reaction would be markedly different for the two. In actuality, the *syn* isomer did solvolyze somewhat faster than the *anti* isomer in glacial acetic acid. Of even greater interest is the lack of rearrangement of both systems.[14]

The n.m.r. spectral data of the compounds used in this study are summarized in Table I.

TABLE I

N.M.R. SPECTRAL DATA

Compound (no.)	Proton assignment,[a] τ-values 2,3	1,4	7	Other
anti-CO_2CH_3 (V)	4.0 (t, 2.0)	7.0	7.7 (m, 1.5)	6.4 (OCH_3)
anti-CO_2H (VII)	4.0 (t, 2.0)	6.9	7.6	
anti-CH_2OH (X)	4.0 (t, 2.0)	7.3		6.8 (CH_2O;
anti-OH (XII)	4.1 (t, 2.3)	7.5	6.5	d, 8.0)
syn-Br(I)	4.05 (s, 0.9)	7.0	6.2	
syn-CO_2CH_3 (IV)	4.05 (t, 1.9)	6.9	7.7 (t, 1.5)	6.5 (OCH_3)
syn-CH_2OH (IX)	4.0 (t, 1.9)	7.3		6.8 (CH_2O;
syn-CO_2H (VI)	4.0 (t, 2.0)	6.8	7.6	d, 7.0)
syn-OH (XI)	4.1 (m)	7.3	6.4	

[a] The multiplicity appears in parentheses followed by the coupling constants, c.p.s. (d = doublet, t = triplet, s = sextet, m = multiplet). In addition, all of these compounds exhibited two sets of multiplets centered at *ca.* τ 8.2 and 9.0, respectively.

There appears to be some long-range coupling between the 7-proton of ester V and the *endo*-5,6 protons. A comparison of the spectra of the *syn* and *anti* esters shows that the 7-proton of the *anti* isomer is coupled to protons in addition to those of the bridgeheads. The olefinic protons cannot be responsible since they appear as triplets in both cases. The doubling of the high-field peaks at *ca.* τ 9.0 strongly suggests that it is the *endo* protons[15] of the ethylene bridge which are responsible.[16]

(9) The configurations reported herein and in our preliminary communication of this work [R. R. Sauers, *Chem. Ind.* (London), 176 (1960)] have recently been confirmed by E. K. Bly and R. S. Bly [*J. Org. Chem.*, **28**, 3165 (1963)].

(10) (a) R. R. Sauers and G. T. Kwiatkowski, *ibid.*, **27**, 4049 (1962); (b) G. M. Whitesides, F. Kaplan, and J. D. Roberts, *J. Am. Chem. Soc.*, **85**, 2167 (1963); (c) G. Fraenkel, D. G. Adams, and J. Williams, *Tetrahedron Letters*, **12**, 767 (1963); (c) H. M. Walborsky and A. E. Young, *J. Am. Chem. Soc.*, **83**, 2595 (1961).

(11) M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Ruchardt, and J. D. Roberts, *ibid.*, **82**, 2646 (1960).

(12) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *ibid.*, **72**, 3116 (1950).

(13) E. J. Corey and R. A. Sneen, *ibid.*, **75**, 6234 (1953); G. Roberts, C. W. Shoppee, and R. J. Stephenson, *J. Chem. Soc.*, 2705 (1954).

(14) These results have been substantiated recently by R. S. Bly, R. K. Bly, and J. E. Goldberg, Abstracts of Papers, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan., 1964, p. 6C.

(15) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(16) Similar couplings have been observed; see J. Meinwald and Y. C. Meinwald, *J. Am. Chem. Soc.*, **85**, 2514 (1963).

Experimental[17]

syn- and *anti*-**7-Carbomethoxynorbornene (IV and V).**—A solution of 43 g. (0.25 mole) of *syn*-7-bromonorbornene[2] in 300 ml. of dry ether was added over 28 hr. to 20 g. (0.82 g.-atom) of magnesium under 200 ml. of ether an an atmosphere of nitrogen. The temperature was maintained at *ca.* 28° throughout the addition. Dry carbon dioxide was bubbled into the resulting mixture for 30 min. The reaction mixture was poured onto saturated ammonium chloride solution and acidified with cold, concentrated hydrochloric acid. The aqueous layer was extracted three times with ether and the combined ether layers were extracted with potassium hydroxide solution. Nine grams of neutral material remained in the ether phase (probably coupling products). Acidification of the basic extract followed by ether extraction, drying, and evaporation of the ether gave 13.6 g. (40%) of a mixture of the acids VI and VII. Treatment of the mixture with ethereal diazomethane gave a mixture of the esters (12 g.) which was analyzed directly on a 2-ft. column of silicone (SF-96) on Celite at 165°. The ratio of areas under the peaks was approximately 2:1. This mixture of esters was combined with 11.6 g. of esters from another run; the total was fractionated on a 460 × 10 mm. column of glass helices. There was obtained 11.7 g. of the *anti* isomer (b.p. up to 92.5° at 25 mm.) which was contaminated with a small amount of the *syn* isomer, 7.2 g. of the *syn* isomer (b.p. up to 95.5° at 25 mm.) which was contaminated with a small amount of the *anti* isomer, and 1.25 g. of a mixture containing nearly equal amounts of the two isomers. The pure isomers were obtained by redistillation of the first two fractions.

anti-**7-Carbomethoxynorbornene** (7.5 g.) had b.p. 93–93.5° (30 mm.) and $n^{25}D$ 1.4705.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.44; H, 8.03.

syn-**7-Carbomethoxynorbornene** (6.2 g.) had b.p. 95.5° (25 mm.) and $n^{25}D$ 1.4688.

Anal. Found: C, 70.86; H, 7.86.

The gas chromatography measurements were carried out at 97° and a flow rate of 138 ml. of helium/min. Retention times on a 2-ft. column of 40% diethylene glycol–Celite were for IV, 59 min., and V, 25 min. Retention times on a 2-ft. column of 40% diethylene glycol saturated with silver nitrate–Celite were for IV, 50 min., and V, 71 min.

Equilibration of the esters was carried out by refluxing 1.75 g. of a mixture of esters rich in *anti* isomer for 136 hr. in 12 ml. of methanol in which a small piece of sodium had been dissolved. The recovered esters (1.3 g.) were analyzed on a 5-ft. silicone–Celite column at 165°: *syn*, 55%, and *anti*, 45%. Equilibration of a mixture containing 80% *anti* isomer gave the same mixture of isomers.

syn-**7-Carboxynorbornene** (VI).—Hydrolysis of 2.0 g. of the *syn* ester in 15 ml. of methanol with 1 g. of potassium hydroxide gave 1.35 g. (74%) of acid VI after purification by sublimation, m.p. 91–96°.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.45; H, 7.59.

The benzylisothiouronium salt crystallized as plates from aqueous ethanol and had m.p. 170.5–171.5°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.14; H, 6.62; N, 9.21. Found: C, 62.84; H, 6.76; N, 9.35.

anti-**7-Carboxynorbornene** (VII).—Hydrolysis of 2.0 g. of ester V gave 1.2 g. (66%) of acid VII after sublimation, m.p. 70–73°.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.63; H, 7.37.

The benzylisothiouronium salt crystallized as plates from aqueous ethanol and had m.p. 168.5–169.5°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.25; H, 6.84; N, 9.06.

7-Carboxynorbornane (VIII).—Reduction of 0.138 g. (0.0010 mole) of either VI or VII with hydrogen in 10 ml. of methanol in the presence of 20 mg. of 10% palladium–charcoal resulted in quantitative uptake of 0.0010 mole of hydrogen in both cases. The product (0.109 g., 78%) from the *syn* acid melted at 74–75.5° (lit.[2] m.p. 77.5–78.5°) after sublimation. The product from the *anti* acid (0.102 g., 73%) melted at 76–77° after sublimation. A melting point of a mixture of the two products was 74–76.5°. The infrared spectra of the two were identical and corresponded closely with the published data for this compound.[2]

syn-**7-Methylolnorbornene** (IX).—Reduction of 2.0 g. of ester IV with 0.5 g. of lithium aluminum hydride in 30 ml. of ether gave 1.5 g. (92%) of alcohol IX, b.p. 52° (0.06 mm.), $n^{27}D$ 1.4935, O–H absorption at 3633 cm.$^{-1}$.[7]

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.62; H, 9.95.

The tosylate was prepared from tosyl chloride and pyridine, m.p. 38.5°–39.5° (needles from pentane).

Anal. Calcd. for $C_{15}H_{18}O_3S$: C, 64.73; H, 6.52. Found: C, 64.64; H, 6.50.

anti-**7-Methylolnorbornene** (X).—Reduction of 2.0 g. of ester V as above gave 1.6 g. (98%) of alcohol X, b.p. 61° (0.25 mm.), $n^{27}D$ 1.4970, O–H absorption at 3630 cm.$^{-1}$.[7]

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.12; H, 9.78.

The tosylate was prepared from tosyl chloride and pyridine, m.p. 60–61° (needles from pentane).

Anal. Calcd. for $C_{15}H_{18}O_3S$: C, 64.73; H, 6.52. Found: C, 64.51; H, 6.39.

The alcohols were analyzed on a 2-ft. column of polyethylene glycol (300) on Celite at 165° and a flow rate of 82 ml./min. Alcohol IX had a retention time of 62 min. and alcohol X had a retention time of 83 min.

Solvolysis of *p*-Toluenesulfonates of Alcohols IX and X.—The tosylates (0.56 g.) were dissolved in 25 ml. of glacial acetic acid which contained 0.20 g. of anhydrous sodium acetate and 1 ml. of acetic anhydride. The mixtures were heated to reflux for 4 days. Addition of ice was followed by ether extraction. Inspection of the infrared spectra of the crude products indicated that the *syn* isomer had solvolyzed completely while the *anti* isomer still showed strong bands associated with the tosylate. The crude acetates were reduced with lithium aluminum hydride in ether and the resulting alcohols were analyzed by gas chromatography (6-ft. Carbowax 20M, 148°). The products in both cases were essentially unrearranged alcohols as shown by retention times and comparative infrared spectra.

Oxidation of the Grignard Reagent.—The reagent was prepared as above from 2.30 g. (0.095 g.-atom) of magnesium and 5.60 g. (0.032 mole) of *syn*-7-bromonorbornene in 75 ml. of ether. The solution was cooled to 0–5° and oxygen was passed through the solution for 1 hr. Addition of saturated ammonium chloride solution was followed by ether extraction. The alcohols (1.16 g., 33%) were separated from the other neutral material (1.9 g.) by chromatography on alumina. The ratio of *syn*–*anti*-norbornenols was shown to be unaffected by this treatment. The *syn* isomer (28%) was identified by preparation of the phenylurethan derivative, m.p. 125–126° (lit.[18] m.p. 125–126°). The *anti* isomer (72%) was identified by its melting point, 117.5–118.5° (lit.[19] m.p. 118–119°). Infrared absorption at 13.9 (*syn*) and 14.1 μ (*anti*) and the n.m.r. spectra (Table I) also support these structures.

Carbonation of the Lithium Reagent of *syn*-7-Bromonorbornene.—Lithium metal (0.50 g., 0.072 g.-atom) was cut into small pieces and dropped into a flask containing 50 ml. of dry tetrahydrofuran under nitrogen. A few drops of a solution of 5.00 g. (0.029 mole) of *syn*-7-bromonorbornene in 45 ml. of tetrahydrofuran was added to the reaction mixture at room temperature. The reaction flask was then cooled to *ca.* −80° and the remainder of the bromide solution was added slowly over 3 hr. The resulting solution was stirred at −80° for 15 hr. and then poured over Dry Ice to effect carbonation. Addition of saturated ammonium chloride solution destroyed the complexes and was followed by ether extraction. The acidic product was separated by washing the combined ether extracts with potassium hydroxide solution. Acidification yielded 2.15 g. (54%) of a mixture of the *syn* and *anti* acids. Gas chromatographic analysis (see above) indicated a *syn* to *anti* ratio of 33:67.

(17) Melting points are corrected. Analyses were by G. Robertson, Florham Park, N. J. N.m.r. spectra were run in carbon tetrachloride on a Varian A-60 spectrometer.

(18) S. Winstein and E. T. Stafford, *J. Am. Chem. Soc.*, **79**, 505 (1957).

(19) S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956).

The Cycloaddition Reaction of N-Sulfinylaniline with Norbornene

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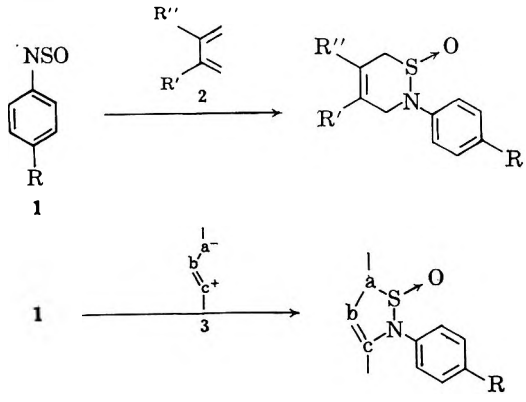
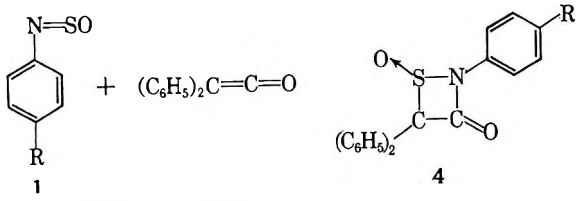
N-Sulfinylaniline reacts with norbornene in a novel manner to yield 1,2,3,4,4a,10b-hexahydro-1,4-methano-6H-dibenzo[*c,e*](1,2)thiazine 5-oxide (**6**, R = H). In analogous reaction with dicyclopentadiene, 5,6a,7,7a,10,-10a,11,11a-octahydro-7,11-methanobenzo[*c*]indeno[5,6-*e*](1,2)thiazine 6-oxide (**15**) is obtained.

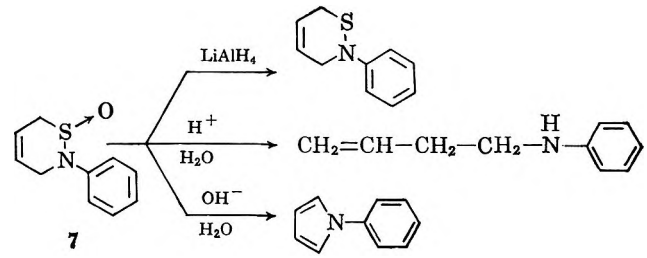
The cycloaddition reactions of N-sulfinylaniline (**1**, R = H) with 1,3-dienes (**2**) and 1,3-dipolar systems (**3**)



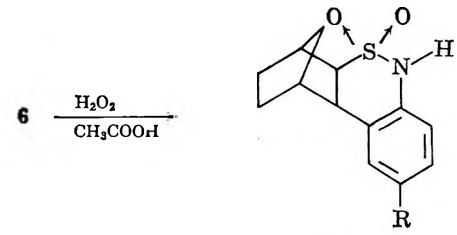
have been well documented in recent literature.[1-5] Further, Beecken and Korte[6] have reported that N-sulfinylanilines undergo 1,2-cycloaddition with diphenylketene to give thiazetidinone 1-oxides (**4**). In all cases, the reaction with **1** takes place across the —N=S— bond.

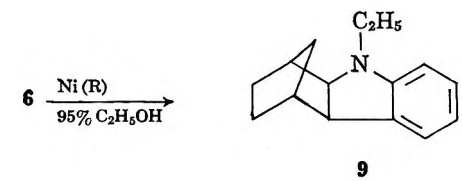


We have now found that, when **1** is treated with norbornene (**5**) in refluxing toluene, a 1:1 adduct (**6**) is obtained in which the N-sulfinylaniline participates as a "diene." The structure of **6** has been established on the basis of its degradation products and derivatives, as well as its infrared and nuclear magnetic resonance (n.m.r.) spectra (Table I). The reaction of **6** with dimethyl sulfate in aqueous, alkaline tetrahydrofuran gave the N-methyl derivative. This structure assignment was confirmed on the basis of its elemental analysis and infrared spectrum. Compound **6** was found to be stable in the presence of hot **6** *N* sodium hydroxide and **6** *N* hydrochloric acid, and to be unattacked by $LiAlH_4$ in refluxing tetrahydrofuran. The stability of this system is surprising in view of the reactions of 2-phenyl-3,6-dihydro-1,2-thiazine 1-oxide (**7**) with the same reagents under much milder conditions.[1]



Upon reaction of **6** with 30% hydrogen peroxide in glacial acetic acid, **8** is readily obtained. Desulfurization of **6** using degassed Raney nickel in refluxing ethanol afforded predominately the N-substituted hexahydrocarbazole (**9**), characterized by infrared, n.m.r. and elemental analysis.



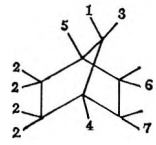


The desulfurization of **6** was repeated employing freshly prepared Raney nickel in refluxing methanol. The reaction mixture was separated into its three major volatile components, which were characterized as **10**, **11**, and **12**. These three components accounted for 60, 24, and 14%, respectively, of the volatile fraction, as determined by planimeter integration of the g.l.c. spectrum.

(1) G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, *Angew. Chem., Intern. Ed. Engl.*, **1**, 94 (1962).
(2) G. Kresze and R. Albrecht, *Angew. Chem.*, **74**, 781 (1962).
(3) E. G. Kataev and V. V. Plemenkov, *Zh. Obshch. Khim.*, **32**, 3817 (1962).
(4) P. Rajagopalan and H. U. Daeniker, *Angew. Chem., Intern. Ed. Engl.*, **2**, 46 (1963).
(5) R. Huisgen, R. Grashey, M. Seidel, H. Knupfer, and R. Schmidt, *Ann.*, **658**, 169 (1962).
(6) H. Beecken and F. Korte, *Tetrahedron*, **18**, 1527 (1962).

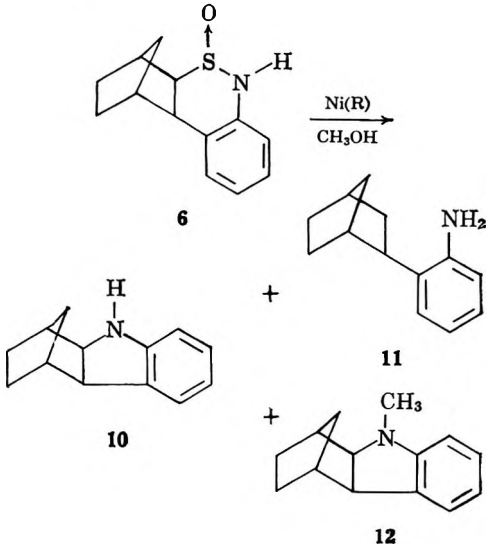
TABLE I

N.M.R. ASSIGNMENTS[a]

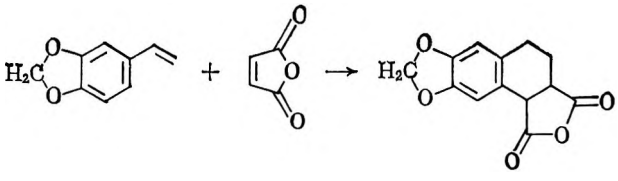


Compounds	Solvent	Aromatic protons[b]	Exchangeable protons[c]	Position 1	2	3	4	5	6	7
6	CF_3COOH	−7.8,[b] −8.15		−2.02	−2.02	−2.29	−2.82	−3.12	−3.97	−3.97
8	CF_3COOH	−7.59,[b] −7.98		−1.42	−1.83	−2.28	−2.8	−3.32	−3.98	−3.98
11	$CDCl_3$	−6.67	−3.42	−1.57	−1.57	−1.57	−2.5	−2.5	−1.57[d]	−2.5
10	$CDCl_3$	−6.75,[b] −7.22	−3.57	−1.57	−1.57	−1.57	−2.49	−2.47	−2.9	−2.9
12	$CDCl_3$	−7.09		−1.17	−1.47	−1.83	−2.35	−2.22	−3.2	−3.64
										−2.53[e]

[a] Proton assignments are in parts per million (p.p.m.) with tetramethylsilane at 0. The values given are, in most cases, the centers of complex multiplets. [b] Denotes aromatic proton *ortho* to the nitrogen atom. All examples noted have four aromatic protons. [c] Denotes protons on nitrogen which are readily exchanged when the $CDCl_3$ solution of the sample is agitated with D_2O. [d] Two protons. [e] $>N-CH_3$ protons.

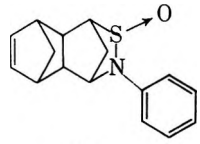


The reaction of **1** with norbornene resembles, in many ways, the reaction of *p*-alkoxy or 3,4-methylenedioxy styrenes with maleic anhydride,[7] in that an adjacent "double bond" of the phenyl ring is conjugated



with the vinyl side chain to form a reactive 1,3-diene. A fundamental difference is that, while *p*-alkoxy groups promote the reaction of styrene with maleic anhydride, these same groups in the *para* position of N-sulfinylanilines inhibit the reaction with norbornene. Thus far, norbornene and substituted norbornenes are unique in that no other cyclic or acyclic olefins tried would react with N-sulfinylanilines. The norbornene moiety would not be expected to rearrange during the reaction, because no Lewis acids are present at any time to promote the formation of carbonium ions. Also, as Huisgen[8] has found, norbornene can function as a 1,3-dipolarophile under similar reaction conditions with no evidence of rearrangement.

Kataev and Plemenkov have reported[3] a reaction between 1 mole of N-sulfinylaniline and 2 moles of cyclopentadiene which yielded a solid product, m.p. 190° dec. Their proposed structure (**13**) is based on the assumption that two cyclopentadiene molecules add to N-



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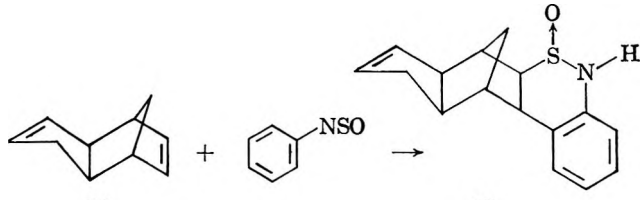
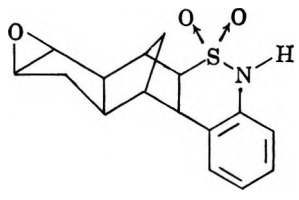
sulfinylaniline, sequentially. A repetition of this reaction, following the precise published directions, was found to yield a product which melted, after numerous recrystallizations from ethanol, at 246–248° dec. This compound is identical (infrared spectrum and mixture melting point) with the product (**15**) obtained from the reaction of 1 mole of dicyclopentadiene (**14**) with 1 mole of N-sulfinylaniline in toluene. This latter structure (which is in complete agreement with both the n.m.r. and infrared observations) requires that, in the reaction as described by Kataev and Plemenkov, dimerization had preceded the addition to N-sulfinylaniline. Hydrogen peroxide in acetic acid converts **15** to the corresponding epoxy sulfonamide **16**.



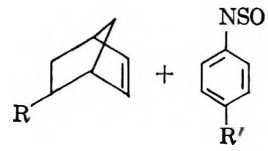
14 15



16

(7) M. C. Kloetzel, *Org. Reactions*, **4**, 32 (1948).
(8) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963).

TABLE II



		Carbon, %		Hydrogen, %		Nitrogen, %			
E	R'	Calcd.	Found	Calcd.	Found	Calcd.	Found	% yield	M.p. dec., °C.
H	NO_2	56.10	56.24	5.08	5.17	10.07	10.02	71.5	260.5
H	CH_3	67.98	67.77	6.92	6.49	5.66	5.86	20.2[a]	211–214
H	OCH_3	63.86	63.90	6.52	6.38	5.33	5.21	10.2	188–190
H	Cl	58.08	58.14	5.27	5.16	5.23	5.20	73	196–196.5
CN	H	65.10	65.37	5.47	5.25	10.85	10.79	7.7	259–260

[a] Yield was increased to 60%, based on *p*-methyl-N-sulfinylaniline, upon changing the mole ratio of norbornene–*p*-methyl-N-sulfinylaniline from 1:1 to 10:1.

Experimental

The melting points are uncorrected. All gas chromatograms were determined using a Wilkens Instrument Company Autoprep Model A-700 with helium as the carrier gas. N.m.r. spectra were obtained with the Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard. The N-sulfinylanilines are all known compounds and were prepared from the analogous amines according to the procedure of Michaelis and Herz.[9]

1,2,3,4,4a,10b-Hexahydro-1,4-methano-6H-dibenzo[*c,e*](1,2)thiazine 5-Oxide (6).—A 500-ml. three-necked flask was equipped with a mechanical stirrer reflux condenser, $CaCl_2$ drying tube, and nitrogen inlet tube. To the flask was added 13.9 g. (0.1 mole) of N-sulfinylaniline, 9.4 g. (0.1 mole) of norbornene, and 300 ml. of anhydrous toluene. The reaction mixture was blanketed with an atmosphere of dry nitrogen while being stirred and refluxed for a period of 72 hr. During this time the reaction mixture became quite dark and the formation of solid particles was noted on the walls of the flask. The reaction mixture was cooled in an ice bath, then filtered, and the filter cake was recrystallized from aqueous ethanol to afford 19.2 g. (81.5%) of the product as colorless needles, m.p. 230–232°, ν_{NH} 3154 and ν_{S-O} 1053 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{13}H_{15}NOS$: C, 67.01; H, 6.49; N, 6.01. Found: C, 67.00; H, 6.54; N, 5.98.

1,2,3,4,4a-10b-Hexahydro-1,4-methano-6H-dibenzo[*c,e*](1,2)thiazine 5,5-Dioxide (8).—A mixture of 5 ml. of 30% hydrogen peroxide, 5 ml. of glacial acetic acid, and 2.33 g. (0.01 mole) of 6 was placed in a 50-ml. erlenmeyer flask and allowed to stand overnight at room temperature. Upon pouring the reaction mixture over ice, there was obtained 1.92 g. (77.7%) of a colorless, crystalline compound, m.p 202–203°; ν_{SO_2} 1151 and 1130, ν_{N-H} 3311 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.07; N, 5.61. Found: C, 62.56; H, 6.14; N, 5.28.

5,6a,7,7a,10,10a,11,11a-Octahydro-7,11-methanobenzo[*c*]indeno[5,6-*e*](1,2)thiazine 6-Oxide (15).—By causing (0.1 mole) of N-sulfinylaniline to react with (0.1 mole) of dicyclopentadiene (14) under the same conditions as those employed in the preparation of 6, a dark brown solid was obtained. Crystallization from ethanol afforded 8.75 g. (32.3%) of light tan crystals, m.p. 247°; ν_{N-H} 3234 and ν_{S-O} 1052 cm.$^{-1}$ in Nujol; n.m.r. (CF_3CO_2H): three aromatic protons centered at −7.05 p.p.m., one aromatic proton in a multiplet at −6.78 p.p.m., and two olefinic protons—one at −5.55 and one at −5.75 p.p.m.

Anal. Calcd. for $C_{16}H_{17}NOS$: C, 70.91; H, 6.32; N, 5.17. Found: C, 71.27; H, 6.51; N, 5.26.

5,6a,7,7a,8,9,10,10a,11,11a-Decahydro-7,11-methano-8,9-oxirenobenzo[*c*]indeno[5,6-*e*](1,2)thiazine 6,6-Dioxide (16).—When 5 g. of 15 was oxidized by treating it with hydrogen peroxide in glacial acetic acid, as in the preparation of 8, there was obtained 4.5 g. (82.5%) of a colorless crystalline product. This compound decomposed without melting, beginning at 232°.

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.33; H, 5.66; N, 4.62. Found: C, 63.20; H, 5.64; N, 4.37.

1,2,3,4,4a,10b-Hexahydro-1,4-methano-6-methyldibenzo[*c,e*](1,2)thiazine 5-Oxide.—A mixture of 2.33 g. (10.0 mmoles) of 6 and 0.6 g. (15.0 mmoles) of sodium hydroxide was dissolved in 100 ml. of hot water and enough tetrahydrofuran to form a homogeneous solution. To this stirred mixture was added 1.8 g. (15.6 mmoles) of dimethyl sulfate and the solution was heated and stirred for 1 hr. To the solution was added 100 ml. of water and the resulting mixture was chilled, filtered, and the solids were washed with cold water. The filter cake was recrystallized from ethyl acetate to afford 1.2 g. of colorless needles, m.p. 230–231°, identified as starting material (6). The filtrate was evaporated to dryness under reduced pressure and a residue was obtained which, upon recrystallization from methylcyclohexane, gave colorless needles, m.p. 140–142°. The infrared spectrum (Nujol) confirmed the structural assignment.

Anal. Calcd. for $C_{13}H_{17}NOS$: C, 68.00; H, 6.93; N, 5.67. Found: C, 68.17; H, 6.98; N, 5.51.

Table II outlines the reactions of some substituted N-sulfinylanilines with norbornene and of N-sulfinylaniline with 5-cyanonorbornene.

1,2,3,4,4a,10b-Hexahydro-6H-9-amino-1,4-methanodibenzo[*c,e*](1,2)thiazine 5-Oxide.—Following the procedure for the reduction of aromatic nitro compounds to the corresponding amines, outlined by Surrey and Cutler,[10] a 3-l., three-necked flask was equipped with a reflux condenser and a stirrer. To the flask was added 15.5. g. (55 mmoles) of 1,2,3,4,4a,10b-hexahydro-6H-9-nitro-1,4-methanodibenzo[c,e](1,2)thiazine 5-oxide, 62 g. (1.06 g.-atoms) of iron filings, 1.55 g. (25.8 mmoles) of glacial acetic acid, 186 g. (2.48 moles) of ethanol, and 93 ml. of water. The mixture was stirred at reflux temperatures for 6 hr. The reaction mixture was filtered while still hot, then made alkaline with 3.4 g. (60 mmoles) of solid potassium carbonate, and filtered again. Evaporation of the solvent afforded 11 g. (80.4%) of a light brown solid. This product was recrystallized from ethyl acetate to yield 9.8 g. (73.0%) of cream-colored needles of 1,2,3,4,4a,-10b-hexahydro-6*H*-9-amino-1,4-methanodibenzo[c,e](1,2)thiazine 5-oxide, m.p. 198–200° dec.; infrared (split mull) ν_{NH_2} asymmetrical and symmetrical 3432 and 3340, S–O stretching frequency 1050, and out-of-plane hydrogen deformation for 1,2,4-trisubstituted benzene near 830 and 860 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.24; H, 6.64; N, 10.68.

Reaction of Cyclopentadiene with N-Sulfinylaniline.—Following the work of Kataev and Plemenkov,[3] 36.9 g. (0.6 mole) of 1,3-cyclopentadiene (98+% pure) and 27.8 g. (0.2 mole) of N-sulfinylaniline were sealed in a Pyrex Carius tube and heated in an oven at 105° for 21 hr. At the end of that time the tube was chilled, opened, and the solid product, which had formed as dark brown crystals, was removed. There was obtained 44.2 g. (81.8%) of material, the infrared spectrum of which was identical with 15, prepared from the reaction of 14 with N-sulfinylaniline. A portion of this material was recrystallized from ethanol to afford a light brown solid, m.p. 213–218° dec. Two more recrystallizations raised the melting point to 246–248° dec.

Raney Nickel Desulfurization of 1,2,3,4,4a,10b-Hexahydro-1,4-methano-6H-dibenzo[*c,e*](1,2)thiazine 5-Oxide.—To a 1-l. three-necked flask, equipped with a stirrer and reflux condenser, was added 27 g. (0.115 mole) of 6, 520 g. of wet, degassed Raney nickel (65% by weight of Ni) and 500 ml. of 95% ethanol. The reactants were stirred and heated at reflux temperature for a period of 26 hr. At the end of this time, the nickel was separated

(9) A. Michaelis and R. Herz, *Ber. deut. chem. Ges.*, **23**, 3480 (1890).

(10) A. R. Surrey and R. A. Cutler, *J. Am. Chem. Soc.*, **73**, 2413 (1951).

by filtration and the ethanol was evaporated under reduced pressure. Fractionation of the residue, utilizing a semimicro Vigreux column, afforded 17.3 g. (70.2%) of a water-white, rather viscous liquid, which was identified by infrared and n.m.r. as 9-ethyl-1,2,3,4,4a,9a-hexahydro-1,4-methanocarbazole (**9**), b.p. 166–170° (14–15 mm.). Using a standard technique,[11] the methiodide salt was prepared as colorless crystals from ethanol, m.p. 165–166°.

Anal. Calcd. for $C_{16}H_{22}IN$: C, 54.09; H, 6.25; N, 3.95. Found: C, 54.31; H, 6.74; N, 3.98.

The desulfurization reaction was then repeated utilizing 2.5 g. (0.01 mole) of **6**, 40 g. of freshly prepared Raney nickel (wet), and 300 ml. of methanol. Upon evaporation of the methanol, 1.82 g. of a water-white, viscous liquid was obtained. A portion of this liquid mixture was separated into its individual components by g.l.c. at 170°, employing a 5 ft. × 0.375 in. column packed with 20 M Carbowax 60–80 on acid-washed Chromosorb W. These major volatile components were thus isolated and characterized by n.m.r. and infrared as 1,2,3,4,4a,9a-hexahydro-9H-1,4-methanocarbazole (**10**), infrared ν_{N-H} 3360, ν_{C-N} 1285, and C–H out-of-plane deformation at 739 cm.$^{-1}$; *o*-(2-norbornyl)-aniline (**11**), infrared ν_{NH_2} asymmetrical and symmetrical 3380 and 3300, ν_{C-N} 1283, and C–H out-of-plane deformation at 740 cm.$^{-1}$. The third major volatile component was identified as 9-methyl-1,2,3,4,4a,9a-hexahydro-1,4-methanocarbazole (**12**), infrared C–H out-of-plane deformation at 740, and >N–CH_3 stretching frequency at 2732 cm.$^{-1}$. Based upon measurement of their respective peak areas, gas–liquid chromatography indicated that the mixture of amines was 60% **10**, 24% **11**, and 14% **12**, with the remaining 2% unidentified.

Acknowledgment.—The author wishes to thank Mr. R. A. Nyquist, Dr. A. W. Baker, and Dr. W. J. Potts for interpretation of the infrared spectra; also Mr. M. D. Yeaman and Dr. J. P. Heeschen for interpretation of the n.m.r. spectra. Thanks are due Dr. J. C. Little for helpful discussions during the course of the investigation.

(11) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 180.

Migratory Aptitudes of Unsaturated Groups[1]

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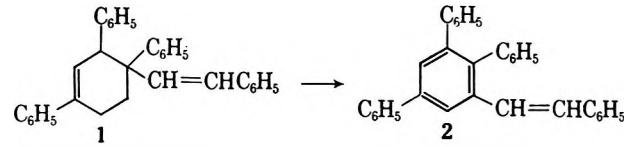
The quinone-induced dehydrogenative rearrangement of 1,1-disubstituted 1,2-dihydronaphthalenes containing phenyl, vinyl, and styryl groups has been studied. The observed order of migratory aptitudes, methyl < phenyl < styryl = vinyl, is in accord with the hypothesis that the rearrangement involves electrophilic attack by a carbonium ion intermediate.

Some time ago we observed[3] that dehydrogenation of the dimer (**1**) of 1,3-diphenylbutadiene with *o*-chloranil resulted in the formation of 2,3,5-triphenylstilbene (**2**). Not only were all carbon atoms retained, but it was proved conclusively that the aromatization involved the migration of a styryl group, the latter exhibiting a higher migratory aptitude than phenyl. This paper describes our initial efforts to utilize this reaction for studying migration aptitudes of unsaturated groups in general.

Evidence has been presented[4] that dehydrogenations of hydroaromatic compounds by quinones are initiated by hydride abstraction which results in a positively charged carbon–negatively charged ion pair. Proton transfer from the carbonium ion to the hydroquinone anion then produces the stable aromatic structure. Recent work[4b,c] is interpreted as supporting a mechanism which initially involves charge-transfer complex formation followed by hydride abstraction in the rate-determining step.

If this mechanism holds, blocks to aromatization presented by *gem* substitution might be overcome by migration processes similar to Wagner–Meerwein shifts. In fact, dehydrogenation of *gem*-substituted hydroaromatic compounds resulted[3,4a,d] in rearrangements with retention of all carbon atoms present in the



substrate, a reaction which contrasts with the elimination of blocking groups generally observed during dehydrogenation by conventional methods.

To our knowledge the formation of 2,3,5-triphenylstilbene[3] was the first clear demonstration of a 1,2 carbon-to-carbon shift by an unsaturated group under Wagner–Meerwein conditions, since the presence of acids normally precludes any clear-cut investigation of olefinic residues in the Wagner–Meerwein rearrangement.[5]

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(2) Abstracted from a dissertation submitted in partial fulfillment of the requirements for the Ph.D. degree, Florida State University, April, 1963.

(3) W. Herz and E. Lewis, *J. Org. Chem.*, **23**, 1646 (1958).

(4) (a) R. P. Linstead, E. A. Braude, L. M. Jackman, and A. N. Beames, *Chem. Ind.* (London), 1174 (1954); (b) E. A. Braude, L. M. Jackman, and R. P. Linstead, *J. Chem. Soc.*, 3548, 3564 (1954); (c) J. P. Barnard and L. M. Jackman, *ibid.*, 3110 (1960); (d) E. A. Braude, L. M. Jackman, R. P. Linstead, and G. Lowe, *ibid.*, 3123, 3133 (1960); (e) E. A. Braude, L. M. Jackman, R. P. Linstead, and J. S. Shannon, *ibid.*, 4794 (1961).

(5) Styryl migrations have been reported in the Schmidt reaction (carbon → nitrogen)[6-8] which, however, may be controlled to a large extent by stereochemistry rather than by relative migratory aptitudes. Migration of unsaturated groups has been observed in the course of peracid oxidation (carbon → oxygen).[9-11] Recent work[12] on the homologation of α,β-unsaturated ketones with diazomethane might be considered as an analogy. More closely related examples are the pinacolic rearrangement of substances containing a propenyl group reported by Deux,[13] the acid-catalyzed rearrangement of nepenthol to flavanepenthone,[14] and the pinacolic rearrangement of an intermediate hydroxytosylate, in the synthesis of *dl*-longifolene.[15] The former suffers from uncertainty regarding stereochemistry of starting materials and lack of proof for structure of products; the last two deal with rigid systems where stereochemistry might well have been the controlling factor. The subject of rearrangement to electron-deficient atoms has been covered thoroughly in a recent review.[16] Noteworthy is the statement (p. 515, ref. 16) that the styryl group may have a low migration aptitude.

(6) L. H. Briggs, G. C. DeAth, and S. R. Ellis, *J. Chem. Soc.*, 61 (1942).

(7) P. A. Smith and J. P. Horwitz, *J. Am. Chem. Soc.*, **72**, 3718 (1950).

(8) S. C. Bunce and J. B. Cloke, *ibid.*, **76**, 2244 (1954).

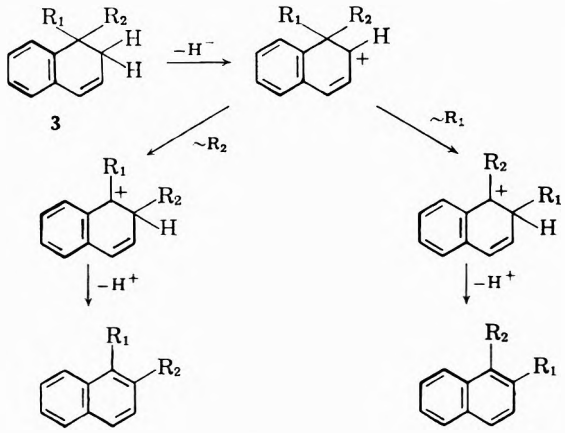
(9) J. Boeseken and A. L. Soesman, *Rec. trav. chim.*, **52**, 874 (1933).

(10) H. M. Walton, *J. Org. Chem.*, **22**, 1161 (1957).

(11) E. F. Smissman and F. B. Block, *J. Am. Pharm. Assoc. Sci. Ed.*, **48**, 526 (1959).

(12) W. S. Johnson, M. Neeman, and S. P. Birkeland, *Tetrahedron Letters*, **5**, 1 (1960); W. S. Johnson, M. Neeman, S. P. Birkeland, and N. A. Fedoruk, *J. Am. Chem. Soc.*, **84**, 989 (1962).

For example, in the system **3** (where R_1 and R_2 are different organic residues), if the dehydrogenation proceeds *via* a carbonium ion intermediate as already demonstrated[4] and if conformational factors do not intervene (*vide infra*), the composition of the product should be a measure of the migration aptitudes of R_1 and R_2. This is borne out by the dehydrogenative rearrangement of **3** (R_1 = methyl, R_2 = phenyl) which proceeded exclusively in the direction of phenyl rearrangement[4d] (see also Experimental). Introduction into **3** of residues containing double bonds should therefore permit the insertion of unsaturated groups into a scale of migratory aptitudes which, while specifically



applicable only to the rearrangement in question, might be capable of extension to other rearrangements involving migrations to electron-deficient carbon.[18]

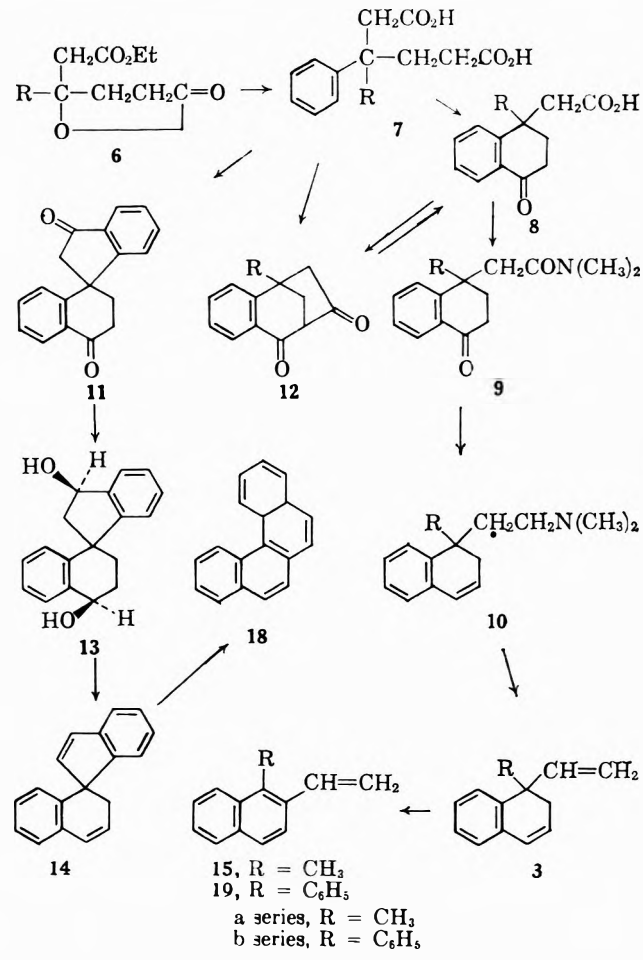
Results

As a direct consequence of our earlier work, we decided initially to study the synthesis and dehydrogenative rearrangement of the 1,1-disubstituted 1,2-dihydronaphthalenes **3a** and **3b**. The choice of compounds of type **3** instead of the much more readily available tetrahydronaphthalene analogs **4** was necessitated by the observation (see Experimental) that dehydrogenation of **4** (R_1 = methyl, R_2 = phenyl) was inconveniently slow and proceeded only in poor yield.

3a, R_1 = CH_3; R_2 = CH_2=CH—
b, R_1 = C_6H_5; R_2 = CH_2=CH— **4**

A number of approaches to **3a** and **3b** failed because steric compression in a 1,1-disubstituted 1,2-dihydronaphthalene bestows upon appropriately functionalized molecules an unusually high tendency toward cyclization, the peculiar geometry of the system bringing functional groups at C-3 or C-4 and the quaternary carbon atom into close proximity. These experiments will be

CHART I



detailed subsequently. The initial stages in the successful synthesis of **3a** have already been outlined in another communication.[19]

Friedel–Crafts condensation of 4-methyl-4-(carbethoxymethyl)butyrolactone (**6a**) with benzene gave a 78% yield of 3-methyl-3-phenyladipic acid (**7a**) which on cyclization with sulfuric acid on a steam bath afforded 1-methyl-1-carboxy-methyl-4-tetralone (**8a**), see Chart I). Reaction of **8a** with oxalyl chloride, benzene, and pyridine,[20] followed by treatment with dimethylamine resulted in the dimethylamide **9a**. Reduction of the latter with lithium aluminum hydride and dehydration of the basic fraction with 10% hydrochloric acid furnished 1-methyl-1-(2-dimethylaminoethyl)-1,2-dihydronaphthalene (**10a**) whose n.m.r. spectrum displayed the characteristic ABXY pattern of a 1,1-disubstituted 1,2-dihydronaphthalene.[21]

10a was converted to the amine oxide and the latter pyrolyzed by heating in dimethyl sulfoxide. It is note-

(13) M. Y. Deux, *Compt. rend.*, **213**, 209 (1941).
(14) K. W. Bentley and J. C. Ball, *J. Org. Chem.*, **23**, 1720 (1959).
(15) E. J. Corey, M. Chno, P. A. Vatakencherry, and R. B. Mitra, *J. Am. Chem. Soc.*, **83**, 1251 (1961).
(16) "Molecular Rearrangements," P. deMayo, Ed., Interscienee Publishers, Inc., New York, N. Y., 1963. See also ref. 17.
(17) C. J. Collins, *Quart. Rev.*, **14**, 357 (1960).
(18) For comments on this point as well as an example of isobutenyl group migration, see H. O. House, E. J. Grubbs, and Walter F. Gannon, *J. Am. Chem. Soc.*, **82**, 4099 (1960).

(19) W. Herz and G. Caple, *ibid.*, **84**, 3518 (1962).
(20) S. M. McElvain and G. R. McKay, Jr., *ibid.*, **78**, 6080 (1956).
(21) Values for chemical shifts and coupling constants given in this paper are approximate and were read directly from the spectra rather than calculated. The n.m.r. spectrum of 1-methyl-1-phenyl-1,2-dihydronaphthalene had nine aromatic protons at 7.15 and one methyl singlet at 1.68 p.p.m. The vinyl proton on C-4 appeared as two apparent sets of triplets at 6.51 and 6.34 p.p.m., $J_{3,4}$ = 10, the vinyl proton on C-3 at 5.84 p.p.m., $J_{2,3}$ = 13 c.p.s., in a pattern of six lines, none of which were of equal intensity. The two allylic protons on C-2 appeared as sixteen lines centered at 2.64 p.p.m., $J_{a,b}$ = 15, $J_{2,4}$ = 1.5 c.p.s. Hence H_{2a}, H_{2b}, H_3, and H_4 are an ABXY system which appeared in all compounds of type **3** synthesized and was very useful for identification purposes. Spectra were run on HR-60 or A-60 n.m.r. spectrometers in deuteriochloroform solution, with tetramethylsilane serving as internal standard. The A-60 spectrometer was purchased with the aid of a grant from the National Science Foundation.

worthy that the reaction required elevated temperatures rather than room temperature, in spite of the effectiveness of dimethyl sulfoxide in promoting eliminations.[22] This afforded a substance which had the properties to be expected of **3a** (infrared band at 1635 cm.$^{-1}$). The n.m.r. spectrum exhibited a complex signal at 7.17 p.p.m. (four aromatic protons), an approximate A_2B_2 doublet of triplets at 6.54 and 6.40 p.p.m. (H_4), and signals corresponding to two vinyl hydrogens in the region 6.10 to 5.66 p.p.m., one arising from the vinyl group and one from H_3. There was also a one-proton doublet of doublets at 4.87 p.p.m. (spacings 9, 2), apparently part of the ABC system of the vinyl group. The allylic protons at C-2 exhibited the usual pattern at 2.30 and the C-1 methyl singlet was found at 1.33 p.p.m.

1-Phenyl-1-vinyl-1,2-dihydronaphthalene (**3b**) was synthesized from 4-phenyl-4-(carbethoxymethyl)-butyrolactone[23] by an analogous series of reactions. However, cyclization of 3,3-diphenyladipic acid (**7b**) with concentrated sulfuric acid gave not **8b**, but a neutral product which because of the infrared bands at 1690 (α-tetralone) and 1710 cm.$^{-1}$ (cyclopentenone) was assigned structure **11**. This was confirmed by subsequent work (*vide infra*). Treatment of **7b** with 80% sulfuric acid gave the keto acid **8b** (infrared bands at 1705 and 1685 cm.$^{-1}$), but material prepared in this manner was difficult to purify. An improved method of preparation involved the reaction of **7b** with 1 mole equiv. of oxalyl chloride. This resulted in the formation of 3,3-diphenyladipic anhydride (infrared bands at 1800 and 1745 cm.$^{-1}$) which on treatment with stannic chloride in benzene at room temperature afforded **8b** in over 50% yield.

Polyphosphoric acid, which had converted **7a** to the bicyclo[3.2.1] octanedione **12a**,[19] when brought together with **7b** afforded a mixture of **11** and 1-phenyl-2,3-benzbicyclo[3.2.1]octane-4,6-dione (**12b**) in a 4:1 ratio. Authentic **12b**, infrared bands at 1750 and 1685 cm.$^{-1}$, was obtained from **8b** by treatment with excess oxalyl chloride in refluxing benzene. Cyclization of **8a** to **12a** with oxalyl chloride required a longer reaction time, presumably because of the smaller degree of steric compression.

The usual transformations of **8b** *via* **9b** and **10b** resulted in isolation of 1-phenyl-1-vinyl-1,2-dihydronaphthalene (**3b**) whose n.m.r. spectrum was in complete accord with the postulated structure. Signals corresponding to nine aromatic protons were centered at 7.07 p.p.m.; there was a doublet of triplets (H_4) at 6.42 and 6.29 p.p.m. ($J_{3,4} = 8$, $J_{2,4} = 1.5$ c.p.s.). The signal of the side-chain α-vinyl hydrogen was centered at 6.09 p.p.m. (four lines of equal intensity split 8, 6, and 8 c.p.s.) and superimposed on six lines due to H_3 which exhibited a fairly complicated pattern centered at 5.94 p.p.m. The methylene vinyl hydrogens betrayed their presence as four sets of doublets ($J = 1.5$ c.p.s.) in the ratio 2:1:2:1 at 5.21, 5.04, 4.81, and 4.52 p.p.m. Signals due to the two protons at C-2 were found at 2.72 p.p.m. (16 lines, AB portion of ABXY, apparent $J_{a,b} = 16$, $J_{2,4} = 1.5$).

Reduction of the spiro diketone **11** with lithium aluminum hydride proceeded stereoselectively in the direction of one of the possible isomeric diols, probably **13**. Dehydration of the diol with iodine in benzene furnished spiro[indene-1,1′(2′H)-naphthalene] (**14**), a substance which was of interest as incorporating both a phenyl and a styryl group at C-1. Its ultraviolet spectrum exhibited maxima at 263 and 221 mμ (ϵ 16,300 and 36,200), indicating some interaction between the chromophores. The n.m.r. spectrum was in accord with the postulated structure, the 16 lines of the allylic protons centered at 2.5 p.p.m. being in clear evidence. H_3 was centered at 6.1 p.p.m. (eight lines); signals due to H_4, $H_{3'}$, and $H_{4'}$ were superimposed on each other and could not be disentangled.

Dehydrogenation of **3a** with 10% excess *o*-chloranil in boiling toluene for 50 min. resulted in the recovery of 15% of starting material, the formation of much polymer, and the isolation, in 27% yield, of a substance (**15**) with an infrared band at 1630 cm.$^{-1}$ which was homogeneous by g.l.c. criteria and which on the basis of its n.m.r. spectrum was a methylvinylnaphthalene. It displayed a complex series of bands (six protons) from 8.45 to 7.30 p.p.m. due to the naphthalene ring, four lines (one proton) of equal intensity at 7.29, 7.25, 7.15, and 6.98 p.p.m. spaced 3, 6, and 11 c.p.s. apart, two additional vinyl protons appearing as four equally split doublets ($J = 1.5$ c.p.s.) at 5.79, 5.51, 5.44, and 5.25 p.p.m. (intensity 2:1:2:1, these and the preceding four lines are part of an ABC pattern), and a methyl singlet at 2.60 p.p.m.

Since oxidation of the dehydrogenation product (potassium permanganate–acetone) furnished 1-methyl-2-naphthoic acid (**16**), m.p. 176–178°, identical with authentic material, its structure was established as 1-methyl-2-vinylnaphthalene (**15**) which had resulted from migration of the vinyl group. This was confirmed by synthesis of **15** from **16** *via* the methyl ketone **17**. The synthetic material exhibited the same tendency to polymerize as the dehydrogenation product, thus accounting for the poor material balance of low molecular weight compounds during the dehydrogenation. A search for the isomeric 1-vinyl-2-methylnaphthalene which would have resulted from methyl migration was negative.

Dehydrogenation of **14** under the same conditions resulted in recovery of 15% of starting material and formation in 73% yield of an isomer, m.p. 64–66°, picrate m.p. 124–126°, which was identified as 3,4-benzphenanthrene (**18**), reported m.p. 68°, picrate m.p. 128°. Thus styryl migration had taken place exclusively; no evidence was found for the formation of chrysene which would have resulted from phenyl migration in spite of the greater steric hindrance in compound **18**.

The dehydrogenative rearrangement of **3b** in toluene was unsatisfactory. Use of refluxing xylene for 45 min. resulted in recovery of 40% of **3b**, 12% of polymer, and 31% of a phenylvinylnaphthalene [λ_{max} 242, 248, 278, 288, and 300 mμ (ϵ 37,200, 40,600, 9460, 11,600, and 8900)], whose n.m.r. spectrum showed eleven aromatic protons in the region 7.72–6.80 p.p.m.[24] and the

(22) D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.*, **84**, 1734 (1962).

(23) T. Kubota and T. Matsura, *J. Inst. Polytech Osaka City Univ. Ser. C*, **4**, 112 (1953).

(24) This included one sharp peak at 7.72 and four sharp peaks centered at 7.25 p.p.m.

usual ABC pattern of the vinyl group.[25] This was identified as 1-phenyl-2-vinylnaphthalene (**19**) by comparison with authentic samples of **19** and the isomeric 1-vinyl-2-phenylnaphthalene (**20**) which were synthesized from 1-phenyl-2-naphthoic acid and 2-phenyl-1-naphthoic acid, respectively. The characteristic ultraviolet [λ_{max} 218, 245 and 292 mμ (ε 34,400, 39,400, and 7500)] and n.m.r. spectra[26] of **20** permitted the conclusion, after careful scrutiny of the crude dehydrogenation products, that **20** had not been formed during the dehydrogenation of **3b** and that vinyl migration had taken place in preference to phenyl migration.

Discussion

The possibility that the course of the dehydrogenative rearrangements described earlier[3] and in the present communication is controlled stereochemically (migration of the group opposite the leaving hydride ion) may be discounted on the following grounds. If this effect were to exert a controlling influence on the migration, one would expect attack by the quinone from the least hindered side and subsequent migration of the bulkier group if the reaction were synchronous (which has been disputed[4]) or proceeded through an ion-pair intermediate instead of an open carbonium ion. This would explain the preference for phenyl over methyl migration, but fails to account for the observed migrations in **3b** and **14** where the less bulky group migrates.

It might next be argued that the greater migratory aptitude of styryl *vs.* phenyl in **1** and **14** is due to the greater dispersal of positive charge in a carbonium ion containing styryl as a bridging group. This difference in bridging ability rather than bulk by affecting the energies of the transition states leading to hydride abstraction would facilitate removal of hydride ion from the face opposite the styryl rather than opposite the phenyl group[27] and would result in a partially or completely bridged ion or ion-pair intermediate. However, anchimeric assistance by the migrating group in the rate-determining step has previously been ruled out[4d] because of the observation that the rates of dehydrogenation of **3** (R_1, R_2 = H; R_1, R_2 = phenyl; R_1, R_2 = methyl; and R_1 = methyl, R_2 = phenyl) are not significantly different after allowance has been made for inductive retardation by the phenyl group.[28] Moreover, the dispersal-of-charge argument offers some difficulties when applied to the vinyl group as a bridging entity (*vide infra*).

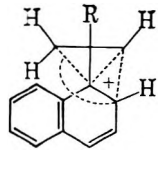
If participation is not a factor, there remains the possibility that bridging assumes importance in determining migratory aptitudes once an intermediate carbonium ion or ion pair has been formed. This could account for the observed order methyl < phenyl < styryl, but also requires that transition state A be of lower energy than transition state B. Such a result which at first glance seems surprising[29a,b] might perhaps be rationalized on the basis of semiempirical calculations for the stabilization energies imparted to homoallylic and homobenzylic cations,[30] although Simonetta and Winstein were careful to point out the importance of additional delocalization in the homobenzyl cation which their calculations did not take into account.

A B

If the dehydrogenative rearrangement is viewed, perhaps somewhat naively, as involving electrophilic attack by a carbonium ion formed through hydride ion abstraction, the observed order of migratory aptitudes falls clearly in line with the known order of reactivities of the unsaturated migrating groups toward electrophilic reagents. The experiments described in this paper and others to be undertaken in the future will thus allow an elaboration of the rule concerning migrations to electron-deficient carbon enunciated by House, Grubbs, and Gannon.[18]

Other Synthetic Approaches.—We record several schemes intended to lead to compounds of type **3** containing unsaturated groups at C-1 which, while unsuccessful, are of some interest in illustrating the steric compression present in this system.

Our first approach (Chart II) envisaged the preparation of 1-substituted 1-carboxy- or 1-cyano-4-tetralones from readily available starting materials for subsequent conversion to **3a** and **3b**. When 4,4-diphenyl-4-cyanobutyric acid (**21**) was cyclized with polyphosphoric, hydrofluoric, or 93% sulfuric acid, it was converted to 1-carboxamido-1-phenyl-4-tetratone (**22**) rather than the nitrile **23**. In 85% sulfuric acid the major product was 2,2-diphenylglutarimide; conversion of **21** to **23** was achieved through the acid



C

(25) Revealed as four equal peaks at 6.82, 6.62, 6.52, and 6.34 p.p.m., intensity one proton; and four doublets (J = 1.5 c.p.s.), total intensity two protons; intensity ratio 2:1:2:1 at 5.81, 5.50, 5.18 and 5.01 p.p.m.

(26) Aromatic proton signals from 8.15, deshielded *peri*-hydrogen, to 7.18 p.p.m.; ABC pattern of four equal peaks at 6.98, 6.79, 6.69, and 6.50, intensity one proton; and one doublet (J = 1.5 c.p.s.), one unbalanced triplet, and another doublet (J = 1.5 c.p.s.) at 5.49, 5.35, and 5.05 p.p.m.; intensity ratio 2:3:1; total intensity two protons.

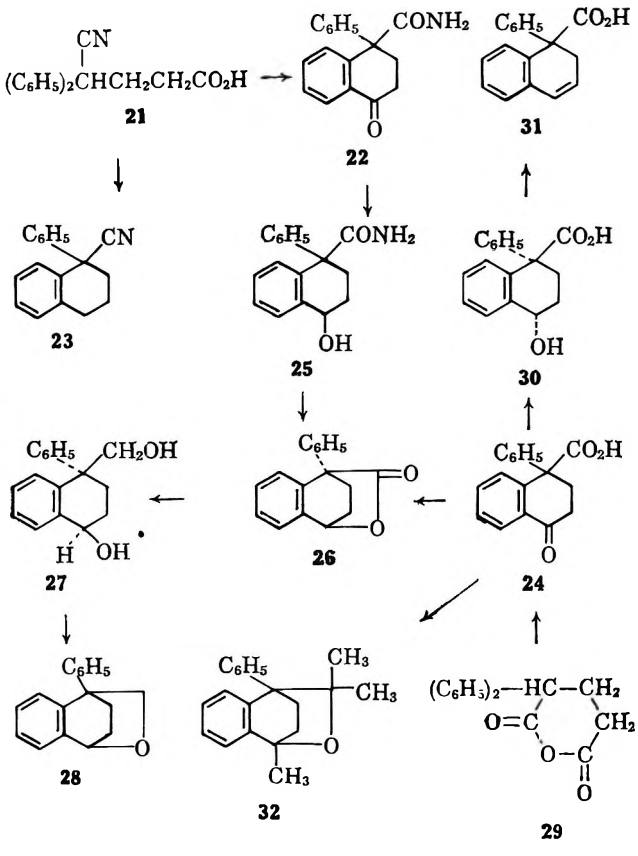
(27) Or, in **3a**, from the face opposite the phenyl rather than the methyl group.

(28) A referee has commented that the arguments of ref. 4d are not acceptable as proof against concertedness because the absence of significant rate enhancement does not necessarily exclude participation, and the allowance for the inductive effect of phenyl selected by the English workers is far from being generally accepted. We do not wish to become embroiled in controversy over this point, but feel, as has already been pointed out earlier that participation is perhaps less important in the system under study because the incipient positive charge generated during hydride abstraction can be delocalized effectively in another way (as in a 2-naphthalenium ion) and because models of 1,1-disubstituted 1,2-dihydronaphthalenes show that the migrating groups lie out of the plane necessary to achieve maximum participation. In any event, whether participation is or is not a factor, one is faced with the problem of accounting for the order methyl < phenyl < vinyl.

(29) (a) A similar statement could of course be made about the corresponding transition states for a concerted reaction involving preferred participation by the vinyl group. (b) More fanciful low-energy transition states resembling nonclassical ions can of course be invoked also, for example the symmetrical bicyclobutonium ion C. However, in the special case of **14**, steric requirements would probably inhibit its formation due to interaction between the phenyl group attached to C-1 and the phenyl attached to the migrating vinyl group, a factor which militates against the plausibility of this hypothesis.

(30) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954).

CHART II



chloride and treatment with aluminum chloride, but the low yields of pure product made this reaction unsuitable for synthetic work.

All attempts to hydrolyze the readily available **22** to the acid **24** failed. To circumvent this problem, **22** was reduced with sodium borohydride to **25** which upon hydrolysis and acidification or on treatment with alumina furnished the lactone **26**. The latter exhibited remarkable stability and was inevitably recovered on neutralization of a basic solution.

The ease with which **26** was obtained suggested further experimentation towards using it as an intermediate. However, several attempts to add Grignard reagents or methyllithium failed, the only identifiable compound being starting material. Reduction of **26** with lithium aluminum hydride to **27**, where the *cis* orientation of the hydroxymethyl and the C-4 hydroxyl is obvious, had as its objective selective dehydration of the secondary alcohol function which was to be followed by oxidation of the primary hydroxyl. However, when **27** was warmed with dilute acid, the product $C_{17}H_{16}O$ obviously was an ether, most likely **28**.

A successful route to **24** involved conversion of 2,2-diphenylglutaric acid to the cyclic anhydride **29** which on treatment with concentrated sulfuric acid furnished **24** in 56% yield. Reduction of **24** with sodium borohydride gave a mixture of epimeric alcohols which on treatment with 2 *N* hydrochloric acid furnished **26** (50%) as well as a small amount of *trans*-1-carboxy-1-phenyl-4-tetralol (**30**) whose stereochemistry is based on the following evidence. Heating above the melting point caused dehydration, the major product being the unsaturated acid **31** (60%) accompanied by the lactone **26** (20%). On the other hand, heating the mixture of epimeric alcohols gave **26** as the main product. Hence **26** is derived mainly from that epimer in which carboxyl and hydroxyl are *cis*. Because **30** was formed in relatively low yield only and was readily converted into **26**, it was not suitable for further work.

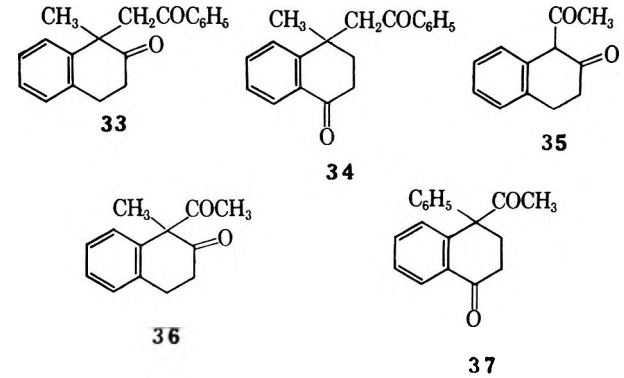
Reaction of **24** with methyllithium followed by dehydration with dilute acid led mainly to another cyclic ether (**32**) instead of the desired 1-isopropenyl-1-phenyl-4-methyl-1,2-dihydronaphthalene. Treatment of **24** with thionyl chloride and dimethylformamide furnished the acid chloride, since addition of methanol resulted in formation of the methyl ester, but further reaction with dimethylcadmium resulted in the recovery of 60% of **24**; the neutral residue could not be characterized satisfactorily.

The tendency toward cyclization exhibited in the above reactions is undoubtedly the result of steric compression abetted by the phenyl radical which as the bulkier group attached to C-1 would be expected to occupy a quasi-equatorial position. For example, no mention is made of lactone formation during acid treatment of the epimeric 1-carboxy-4-hydroxy-1,2,3,4-tetrahyronaphthalenes.[31]

A second route which promised hope of success in leading to some of the desired compounds involved 1-acyl-2-tetralones as starting materials. Reduction of 1-methyl-1-phenacyl-2-tetralone (**33**), from 1-methyl-2-tetralone and phenacyl bromide, with lithium aluminum hydride yielded a mixture of epimeric alcohols which was dehydrated with potassium acid sulfate, but only 25% of low molecular weight material was obtained whose properties indicated the presence of little diene and the formation of ethers. Ethers were also obtained when the isomeric 1-methyl-1-phenacyl-4-tetralone (**34**) was subjected to a similar series of transformations.

Treatment of the morpholine enamine of 2-tetralone with acetyl chloride in the presence of triethylamine[32] afforded **35** (64%) which was converted to **36** by alkylation with methyl iodide–sodium ethoxide–ethanol. Dehydration of the mixture of alcohols obtained by lithium aluminum hydride reduction again did not result in the isolation of identifiable products.

Lastly, Friedel–Crafts cyclization of 4,4-diphenyl-5-ketohexanoyl chloride[33] resulted in 1-acetyl-1-phenyl-4-tetralone (**37**). Lithium aluminum hydride reduction gave a diol mixture which afforded the usual noniden-



(31) K. Alder and K. Triebeneck, *Ber.*, **87**, 237 (1954); K. Kawazu, T. Fujita, and T. Mitsui, *J. Am. Chem. Soc.*, **81**, 932 (1959).

(32) S. Hönig and E. Löcke, *Ber.*, **92**, 652 (1959).

(33) E. J. Cragoe, Jr., and A. M. Pietruszkiewicz, *J. Org. Chem.*, **22**, 1338 (1957).

tifiable materials (mixture of ethers) on acid-catalyzed dehydration. Pyrolysis of the xanthate did not furnish a fraction containing **3b**.

Experimental[34]

1-Methyl-1-(2-N,N-dimethylaminoethyl)-1,2-dihydronaphthalene (10a).—To a solution of 9 g. of 1-methyl-1-carboxymethyl 4-tetralone (**8a**)[19] and several drops of pyridine in 200 ml. of benzene was added dropwise with stirring 10 ml. of oxalyl chloride in 50 ml. of benzene. Stirring was continued for 2 hr., the benzene was removed and replaced with ether, and excess dimethylamine was bubbled through. The solution was washed, dried, and concentrated. The gummy solid (**9a**), 8.5 g., infrared bands at 1685 and 1650 cm.$^{-1}$, was not analyzed but characterized as its dinitrophenylhydrazone, m.p. 198–200°.

Anal. Calcd. for $C_{11}H_{23}N_5O_5$: C, 59.28; H, 5.45. Found: C, 59.09; H, 5.28.

A solution of 8 g. of the gummy amide in ether was reduced with 4 g. of lithium aluminum hydride in the usual manner, hydrolyzed with water, and filtered. The ether filtrate was extracted with dilute hydrochloric acid; the acid extracts were warmed on the steam bath for 8 hr., cooled, made basic, and extracted with ether. The washed and dried ether extracts were distilled, yielding 6 g. of **10a**, b.p. 110–111° (0.3 mm.); the n.m.r. spectrum displayed the characteristic ABXY pattern of a 1,1-disubstituted 1,2-dihydronaphthalene as well as two N-methyl signals at 2.05, an $-N-CH_2-$ signal at 2.07, a $-CH_2C-$ signal at 1.72, and a methyl singlet at 1.22 p.p.m.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.81; H, 9.78; N, 6.51. Found: C, 83.86; H, 9.83; N, 6.44.

1-Methyl-1-vinyl-1,2-dihydronaphthalene (3a).—A solution of 11 g. of **10a**, 20 ml. of ethanol, and 10 ml. of 30% hydrogen peroxide was stirred for 17 hr., decomposed with manganese dioxide, and filtered; the solvents were removed *in vacuo*. The residual gum was dissolved in 25 ml. of ethanol and concentrated to dryness at reduced pressure. This was repeated and furnished the N-oxide as a white viscous gum which was heated with 75 ml. of dimethyl sulfoxide at 130° for 30 hr., cooled, and extracted with pentane. The pentane solution was extracted with dilute hydrochloric acid, washed, dried, and distilled, yielding 3 g. of **3a**, b.p. 84–86° (4 mm.). The substance was homogeneous on g.l.c. chromatography (diethylene glycol succinate column).

Anal. Calcd. for $C_{13}H_{14}$: C, 91.71; H, 8.52. Found: C, 91.66; H, 8.58.

3,3-Diphenyladipic Acid (7b).—To a mixture of 250 g. of anhydrous aluminum chloride in 1 l. of dry benzene was added at 3° 125 g. of 1-phenyl-1-(carbethoxymethyl)butyrolactone,[23] b.p. 165–172° (1.5 mm.), infrared bands at 1785 and 1735 cm.$^{-1}$, in 350 ml. of dry benzene in the course of 1 hr. with stirring. Stirring was continued overnight at room temperature, and the mixture was poured over ice–hydrochloric acid. Ether was added and the organic layer was extracted twice with 20% potassium hydroxide solution. The basic extracts were refluxed with 30 g. of potassium hydroxide and 100 ml. of ethanol, and acidified. The product was recrystallized from ethyl acetate, m.p. 187–189°, 65 g. (43%).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.27; H, 6.21.

Spiro[3-indanone-1,1′(4′)-tetralone] (11).—A mixture of 2 g. of **7b** and 20 ml. of concentrated sulfuric acid was heated at 85° for 25 min. and poured into ice. The gummy solid which separated was recrystallized from ethanol, yielding 1.5 g., m.p. 152–154°, infrared bands at 1710 and 1690 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.34; H, 5.78.

The red dinitrophenylhydrazone melted at 257–259°.

1-Phenyl-1-carboxymethyl-4-tetralone (8b).—A mixture of 4.4 g. of **7b**, 1.5 ml. of oxalyl chloride, several drops of pyridine, and 50 ml. of benzene was refluxed for 1 hr. and then concentrated *in vacuo*. The infrared spectrum of the residue indicated the presence of an anhydride. It was dissolved in 80 ml. of dry benzene and slowly added to a mixture of 8 m. of stannic chloride in 20 ml. of dry benzene with stirring. After 0.5 hr., the mixture was poured onto ice–hydrochloric acid. Ether was added and the organic layer was washed, dried, and evaporated. The residue was recrystallized from ethyl acetate–pentane, yielding 2.3 g. (56%), m.p. 175–177°; infrared bands at 3500–2600 (acid), 1710 (carboxyl), and 1690 cm.$^{-1}$ (tetralone).

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.42; H, 5.83.

1-Phenyl-2,3-benzbicyclo[3.2.1]octane-4,6-dione (12b).—A solution of 1.59 g. of **7b**, 2 ml. of oxalyl chloride 2 drops of pyridine, and 50 ml. of benzene was refluxed for 40 min., the solvent was removed *in vacuo*, and the residue was recrystallized from benzene–hexane, m.p. 183–185°, infrared bands at 1760 and 1695 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38; O, 12.20. Found: C, 82.25; H, 5.21; O, 12.06.

On treatment with base, **12b** was converted to **8b**. When 3 g. of **7b** was heated with 60 ml. of polyphosphoric acid for 1 hr. at 96° and then poured onto ice, the solid which precipitated exhibited bands at 1760, 1710, and 1685 cm.$^{-1}$. Extraction with base removed the component responsible for the band at 1760 cm.$^{-1}$ and left 2 g. of material identical with **11b**. Acidification of the basic extracts yielded **8b**. Since **8b** has no band at 1760 cm.$^{-1}$, it was formed by hydrolysis of the precursor **12b**.

1-Phenyl-1-(N,N-dimethylcarboxamidomethyl)-4-tetralone (9b).—A solution of 4 g. of **8b**, 4 ml. of oxalyl chloride, 40 ml. of dry benzene, and 4 drops of pyridine was stirred at room temperature for 1.5 hr., the benzene was removed *in vacuo* and replaced with 40 ml. of dry ether, and excess dimethylamine was bubbled through the solution. The mixture was concentrated at reduced pressure, diluted with 40 ml. of alcohol, enough water to cause cloudiness, and 0.5 g. of potassium hydroxide, and allowed to stand overnight. Further dilution with water was followed by extraction with ether, washing, and drying of the extracts. Concentration furnished a solid, 3.2 g. (73%), which was recrystallized from ethyl acetate, m.p. 142–143°, infrared bands at 1680 and 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.87; N, 4.56. Found: C, 78.10; H, 6.82; N, 4.94.

1-Phenyl-1-(2,N,N-dimethylaminoethyl)-1,2-dihydronaphthalene (10b).—Reduction of 25 g. of **9b** with 11 g. of lithium aluminum hydride and work-up in the manner described for **10a** furnished, on distillation, 15.5 g. (69%) of **10b**, b.p. 165–167° (0.7 mm.). The n.m.r. spectrum exhibited the following signals: 7.25 (nine aromatic protons), 6.66–5.85 (two protons, AB part of ABXY spectrum, H_3 and H_4), 2.68 (two protons, H_2), and 2.18 p.p.m. (ten protons, N-methyls, $-CH_2N$, and $-CH_2-$).

Anal. Calcd. for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.99; H, 8.00; N, 5.21.

1-Phenyl-1-vinyl-1,2-dihydronaphthalene (3b).—A solution of 15 g. of **10b**, 60 ml. of ethanol, and 11 ml. of 30% hydrogen peroxide was stirred for 14 hr., the peroxide was decomposed with manganese dioxide and filtered, the filtrate was concentrated *in vacuo*, and the residue repeatedly was dissolved in 25 ml. of absolute ethanol, and brought to dryness. The amine oxide, m.p. 124–126°, was heated with 100 ml. of dimethyl sulfoxide at 130° for 72 hr., cooled, extracted with pentane, the pentane layer was washed with dilute hydrochloric acid, water, dried, and distilled, yielding 3.9 g., b.p. 132–135° (1.5 mm.), infrared band at 1635 cm.$^{-1}$. The substance was homogeneous on g.l.c.

Anal. Calcd. for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.21; H, 6.86.

Spiro[indene-1,1′(2′H)-naphthalene] (14).—A solution of 10 g. of **11** in 200 ml. of absolute ethanol was reduced in the usual manner with 4 g. of sodium borohydride, mixed with 50 ml. of water, warmed for 20 min., diluted with 200 ml. of water, and extracted with ether. The ether solution was dried and concentrated, and the product was recrystallized from ethyl acetate, m.p. 145–146°, 8 g. (79% yield). The material (**13**) stubbornly retained water of hydration because several analyses gave values between $C_{18}H_{18}O_2$ and $C_{18}H_{20}O_3$, depending on the drying conditions.

A solution of 4 g. of **13**, 200 ml. of benzene, and 0.2 g. of iodine was refluxed for 12 hr., cooled, extracted with saturated sodium thiosulfate solution, dried, decolorized with charcoal, and concentrated to dryness *in vacuo*. The residue was recrystallized from ethanol, yielding 2 g., m.p. 99–101°.

(34) Melting and boiling points are uncorrected. Analyses were by Dr. F. Pascher, Bonn, Germany, and Drs. Weiler and Strauss, Oxford, England. Infrared spectra were taken in chloroform solution unless otherwise specified, ultraviolet spectra in 95% ethanol solution. Gas–liquid chromatograms were run on an F & M Model 500 instrument using 0.25 in. × 2 ft. copper tubing programmed from 85–220° at 11°/min. and held at the higher temperature, carrier gas helium at 60 ml./min.

Anal. Calcd. for $C_{18}H_{14}$: C, 93.87; H, 6.13. Found: C, 93.28; H, 6.44.

Dehydrogenation Studies.—The following dehydrogenations were carried out to establish conditions and necessary substrates. A solution of 5 g. of 1-methyl-1-phenyltetrahydronaphthalene[35] in 30 ml. of xylene was refluxed for 30 hr. with *p*-chloranil, cooled, diluted with petroleum ether (b.p. 35–60°), washed, dried, and concentrated. Distillation yielded 2.5 g. of starting material; chromatography of the nonvolatile residue did not furnish identifiable aromatic hydrocarbons. Substitution of *o*-chloranil resulted in the recovery of 50% of starting material; chromatography of the residue furnished 1-methyl-2-phenylnaphthalene in 7.5% yield. In a paper published after completion of this experiment, Braude and co-workers[4a] reported 56% dehydrogenation and the isolation of 1-methyl-2-phenylnaphthalene in unstated yield. These results suggested that 1,1-disubstituted 1,2-dihydronaphthalenes would be more satisfactory substrates.

At the beginning of this study, the preparation of 1-methyl-1-phenyl-1,2-dihydronaphthalene had not been recorded. It was prepared from 1,4-diphenylvaleric acid[36] *via* 1-methyl-1-phenyl-4-tetralone. Lithium aluminum hydride reduction of 28 g. of the tetralone followed by distillation of the crude alcohol from potassium acid sulfate furnished 15 g. of 1-methyl-1-phenyl-1,2-dihydronaphthalene, b.p. 131–134° (1 mm.), $n^{20}D$ 1.6133. Dehydrogenation of 2.75 g. of this substance with 4 g. of *o*-chloranil in 50 ml. of xylene for 20 min. followed by the usual work-up and chromatography over alumina (solvent and eluent pentane) resulted in isolation of 2.0 g. (73%) of 1-methyl-2-phenylnaphthalene, m.p. 83–85°, lit.[4d] m.p. 83–85°. Under approximately the same conditions, the English worker[4d] reported a 90% yield based on an infrared analysis of the crude product. Authentic 1-methyl-2-phenylnaphthalene, m.p. and m.m.p. 83–85°, was prepared from 1-methyl-2-phenyl-4-tetralone[37] by reduction with lithium aluminum hydride. The crude alcohol was dehydrated by distillation from potassium acid sulfate; the yield of 1-methyl-2-phenyl-1,2-dihydronaphthalene was 60%, b.p. 132–135° (1 mm.).

Anal. Calcd. for $C_{17}H_{16}$: C, 92.66; H, 7.34. Found: C, 92.47; H, 7.28.

Dehydrogenation of 2.65 g. of this substance with 3.5 g. of *o*-chloranil furnished 2 g. of 1-methyl-2-phenylnaphthalene.

Dehydrogenation of 3a.—A solution of 1.82 g. of **3a** and 3 g. of *o*-chloranil in 50 ml. of toluene was refluxed for 50 min., cooled, diluted with petroleum ether, extracted with 10% sodium hydroxide solution, washed with water, and dried. After solvent removal, a solid remained which was filtered and washed with petroleum ether. The washings were chromatographed over 40 g. of alumina (Alcoa F-20, solvent and eluent, petroleum ether). This resulted in recovery of 0.269 g. of **3a** which was eluted more rapidly and 0.5 g. of **15**, homogeneous on g.l.c., identical with synthetic **15** (infrared and n.m.r. spectrum) prepared as described below. The solid material, m.p. 200°, isolated from the reaction appeared to be polymeric **15**. Its infrared spectrum was similar to that of **15**, with the 1630-cm.$^{-1}$ band missing.

To a solution of 0.07 g. of **15** from the dehydrogenation in 20 ml. of acetone was added 2% aqueous permanganate solution until the color persisted. The mixture was filtered, the acetone was removed, 0.1 g. of potassium hydroxide was added then aqueous permanganate solution was added until the color persisted. Acidification of the filtrate afforded a solid which was recrystallized from benzene–petroleum ether, yielding 0.02 g., m.p. 176–178°; lit. (for 1-methyl-2-naphthoic acid) m.p. 175–177°,[38] 178°[39]; mixture melting point with authentic 1-methyl-2-naphthoic acid (**16**) prepared by the method of Nakazaki and Isoe[40] was 177–179°.

A mixture of 37 g. of **16**, 22 ml. of oxalyl chloride, several drops of pyridine, and 500 ml. of benzene was warmed for 30 min., concentrated *in vacuo*, diluted with dry ether, and cooled in a Dry Ice–acetone bath. A Grignard reagent prepared from 29 g. of methyl iodide in 500 ml. of dry ether was added. The mixture was stirred overnight and worked up in the usual fashion. The crude 1-methyl-2-acetylnaphthalene (**17**), 23 g., was recrystallized with severe losses from ligroin (b.p. 65–110°), m.p. 116–118°, infrared band at 1635 cm.$^{-1}$. The 2,4-dinitrophenylhydrazone melted at 183–185°.

Anal. Calcd. for $C_{19}H_{16}N_4O_4$: C, 62.63; H, 4.43. Found: C, 62.41; H, 4.24.

Reduction of 10 g. of **17** with 2.2 g. of lithium aluminum hydride in the usual manner resulted in a crystalline alcohol, m.p. 85–86°, which was not analyzed, but dehydrated by refluxing with benzene and iodine for 8 hr. The mixture was cooled, washed with a saturated solution of sodium thiosulfate, and dried. The infrared spectrum of the crude product, 9 g., indicated nearly 100% conversion to **15**, but, after chromatography over alumina (solvent and eluent, petroleum ether), only 1.5 g. of **15** was isolated, presumably because of polymerization on the column.

Anal. Calcd. for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.74; H, 7.26.

Dehydrogenation of 3b.—A solution of 1.445 g. of **3b**, 1.7 g. of *o*-chloranil, and 30 ml. of xylene was refluxed for 20 min., cooled, diluted with petroleum ether, extracted with 10% sodium hydroxide solution, washed with water, dried, and concentrated. The residue was chromatographed over alumina (solvent and eluent, petroleum ether). The initial fractions contained a mixture of **3b** and **19** whose composition was controlled by n.m.r. analysis; the middle fractions were pure **19** and the last fractions polymeric material (0.17 g.); total yield of recovered **3b**, 0.575 g.; of **19**, 0.45 g. When 2.21 g. of **3b** was dehydrogenated with 2.5 g. of *o*-chloranil in toluene, only 70% of starting material was accounted for; 40% was recovered **3b**, 18% was **19**, and the rest was polymer. The dehydrogenated material had an infrared band at 1625 cm.$^{-1}$ [n.m.r. signals from 7.72–6.80 (eleven aromatic protons, five sharp bands), 6.82, 6.62, 6.52, and 6.33 (four bands of equal intensity, α-vinyl proton), doublets (J = 1.5) at 5.81, 5.50, 5.18, and 5.01 p.p.m. (intensity ratio 2:1:2:1, two β-vinyl protons)] and was identical in all respects with synthetic 1-phenyl-2-vinylnaphthalene.

1-Phenyl-2-naphthoic and 2-Phenyl-1-naphthoic acid were prepared by the method of Huisgen and Rist.[41] To the acid chloride prepared from 18 g. of 2-phenyl-1-naphthoic acid and 12 ml. of oxalyl chloride in the usual fashion was added with cooling in a Dry Ice–acetone bath the Grignard reagent prepared from 10.2 g. of methyl iodide in 100 ml. of dry ether. The usual work-up furnished a gum which was chromatographed over alumina. The ketone fraction was eluted by benzene–petroleum ether (1:9) in a disappointingly small quantity, 1-g. yield, infrared band at 1710 cm.$^{-1}$ (inhibition of conjugation due to steric hindrance), positive iodoform and dinitrophenylhydrazone tests. It was not analyzed, but reduced immediately with 0.25 g. of lithium aluminum hydride in the usual manner. The crude alcohol was refluxed in xylene with iodine for 24 hr., cooled, and worked up as described previously. The crude product was chromatographed over alumina. Petroleum ether eluted 0.3 g. of viscous 1-vinyl-2-phenylnaphthalene (**20**), infrared band at 1640 cm.$^{-1}$, which differed in all respects from the dehydrogenation product. For analysis, the material was redistilled, b.p. 120° (1-mm. bath temperature), but, although the n.m.r. spectrum indicated a relatively high degree of purity, the results were unsatisfactory, perhaps owing to oxidation.

Anal. Calcd. for $C_{18}H_{14}$: C, 93.87; H, 6.13. Found: C, 91.62; H, 6.06.

To the acid chloride prepared from 6 g. of 1-phenyl-2-naphthoic acid, 4 ml. of oxalyl chloride, and 2 drops of pyridine was added at Dry Ice–acetone temperature a solution of 0.024 mole of methylmagnesium iodide in 50 ml. of dry ether. Stirring was continued overnight. The usual work-up furnished an oil which was chromatographed over alumina. Petroleum ether eluted 1.5 g. of 1-phenyl-2-acetylnaphthalene, m.p. 67–70°, infrared band at 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{14}O$: C, 87.78; H, 5.81. Found: C, 87.28; H, 5.81.

The above ketone, 1 g., was reduced with lithium aluminum hydride in the usual manner. The resulting crude alcohol was refluxed with iodine in benzene for 24 hr., worked up as usual, and the crude product was chromatographed over alumina. Petroleum ether eluted 0.5 g. of **19**, identical in all respects (in-

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(40) M. Nakazaki and S. Isoe, *Bull. Chem. Soc. Japan*, **32**, 1202 (1959).

(41) R. Huisgen and H. Rist, *Ann.* **594**, 137 (1955).

frared and n.m.r. spectra) with the material obtained by dehydrogenation of **3b**.

Anal. Calcd. for $C_{19}H_{14}$: C, 93.87; H, 6.13. Found: C, 94.03; H, 6.39.

Dehydrogenation of 14.—A solution of 1.8 g. of **14** and 2.1 g. of *o*-chloranil in 75 ml. of toluene was refluxed for 45 min., cooled, and worked up in the usual way. Chromatography of the neutral residue over alumina (solvent and eluent, petroleum ether) resulted in recovery of 0.27 g. of starting material. Benzene–petroleum ether (1:9) eluted 1.31 g. of a substance which was recrystallized from ethanol and melted at 64–66°. The picrate (red needles) melted at 124–126°. The ultraviolet spectrum [λ_{max} 216, 229, 272, 282, 302, 314, and 372 mμ (log ϵ_{max} 4.54, 4.34, 4.73, 4.89, 4.60, 4.02, and 3.72)] coincided with that reported[12] for 3,4-benzphenanthrene.

Evidence for chrysene in the mother liquors could not be obtained.

1-Carboxamido-1-phenyl-4-tetralone (22).—A mixture of 5 g. of 4,4-diphenyl-4-cyanobutyric acid (**21**)[43] in 50 ml. of polyphosphoric acid was heated on the steam bath for 2 hr.[14] and poured onto ice. The solid was filtered, washed, dissolved in ether, extracted with 10% sodium hydroxide solution, washed, dried, and concentrated. Recrystallization from ethyl acetate yielded 1.5 g. of **22**, m.p. 185–187°; infrared band at 3600, 3450 (amide), 1680, and 1670 cm.$^{-1}$ (amide and ketone).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.81; H, 5.75; N, 5.09.

The dinitrophenylhydrazone melted at 256–258°.

Anal. Calcd. for $C_{23}H_{19}N_5O_5$: C, 62.02; H, 4.30; N, 15.72. Found: C, 61.84; H, 4.56; N, 15.50.

Acidification of the basic extract from the above reaction gave 1.5 g. of 2,2-diphenylglutamic acid, m.p. 141–143°, lit.[43] m.p. 142–144°.

Compound **22** was also formed when 10 g. of **21** was allowed to stand overnight with 80 g. of hydrogen fluoride. Work-up in the usual way furnished 1 g. of **22**, m.p. 188°, and 8 g. of starting material. The best yield of **22** was obtained by heating 2 g. of **21**, 0.5 ml. of water, and 20 ml. of concentrated sulfuric acid on the steam bath for 20 min. The usual work-up resulted in 1.2 g. of **22**. When the concentration of sulfuric acid was reduced to 85%, the product was 2,2-diphenylglutarimide, m.p. 156°, lit.[42] m.p. 158–159°.

Hydrolysis of **22** with potassium hydroxide in ethylene glycol resulted in slow evolution of ammonia, but no well-characterized products were isolated from the acid fraction presumably because of self-condensation. When **22** was refluxed with nitrous acid in aqueous acetone, only starting material was recovered.

1-Cyano-1-phenyl-4-tetralone (23).—A mixture of 10 g. of **21**, 60 ml. of chlorobenzene, and 9 g. of phosphorus pentachloride was stirred for 30 min. Then 12 g. of anhydrous aluminum chloride was added in small portions. The stirring was continued for 20 min., and the mixture was hydrolyzed with cold 20% hydrochloric acid and extracted with ether, ether extracts were washed, dried, and distilled, the fraction with b.p. 190–195° (1 mm.) being collected. The ketonic material was purified *via* Girard's reagent and recrystallized from ethyl acetate, yielding 1 g., m.p. 108–110°, infrared bands at 2230 (–CN) and 1680 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{17}H_{13}N$: C, 82.65; H, 5.28; N, 5.67. Found: C, 82.28; H, 5.57; N, 5.85.

The dinitrophenylhydrazone melted at 235–237°.

Anal. Calcd. for $C_{23}H_{17}N_5O_4$: C, 64.70; H, 4.00; N, 16.44. Found: C, 64.69; H, 4.36; N, 16.75.

1-Carboxy-1-phenyl-4-tetralone (23).—2,2-Diphenylglutaric anhydride (**29**) was prepared from 2,2-diphenylglutaric acid by warming with acetic anhydride, m.p. 143–145°, lit.[43] m.p. 143°. Crude **29** from 30 g. of diphenylglutaric acid was heated on the steam bath with 150 ml. of concentrated sulfuric acid for 3 hr., allowed to stand at room temperature for 6 hr., poured onto ice, extracted with ether, washed, and dried; and the residue (**24**) was recrystallized from ethyl acetate–petroleum ether, m.p. 156–158°, 14 g. (56% yield), infrared bands at 1710 and 1690 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 77.15; H, 5.68.

The red dinitrophenylhydrazone melted at 225–227°.

Anal. Calcd. for $C_{23}H_{21}N_4O_6$: C, 61.88; H, 4.06. Found: C, 61.56; H, 4.37.

Cyclization of 6 g. of 2,2-diphenylglutaric acid with 60 g. of hydrofluoric acid and purification of the acid product *via* Girard's reagent furnished 1 g. of **24**, m.p. 156–158°.

A solution of 6 g. of **24**, 3 ml. of thionyl chloride, 3 ml. of dimethylformamide[45] and 150 ml. of dry chloroform was allowed to stand at room temperature for 20 hr. Removal of the solvent left the acid chloride as a yellow oil. A 0.15-g. portion was dissolved in 10 ml. of methanol, warmed and concentrated, and the residue was taken up in ether, washed, dried, and evaporated. The residue, 0.1 g., was the methyl ester of **24**, infrared bands at 1735 and 1685 cm.$^{-1}$, characterized as the 2,4-dinitrophenylhydrazone, m.p. 220–221°, from ethyl acetate.

Anal. Calcd. for $C_{24}H_{20}N_4O_6$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.60; H, 3.84; N, 12.38.

The remaining acid chloride was added to dimethylcadmium prepared from 3 g. of dry cadmium chloride in benzene. After 6 hr. at reflux, the mixture was cooled and hydrolyzed: the organic layer was extracted with base and dried, yielding 1.8 g. of crude 1-acetyl-1-phenyl-4-tetralone, infrared bands at 1710 and 1685 cm.$^{-1}$. The dinitrophenylhydrazone melted at 213–215°, but the analysis was poor, perhaps because of contamination by some dinitrophenylhydrazone.

Anal. Calcd. for $C_{24}H_{20}N_4O_5$: C, 64.86; H, 4.54; N, 12.60. Found: C, 63.43; H, 4.24; N, 12.05.

Acidification of the basic extract resulted in the recovery of 4 g. of **24**.

1-Carboxamido-1-phenyl-4-tetralol (25).—A solution of 0.5 g. of **22** in 50 ml. of absolute ethanol was reduced with 0.3 g. of sodium borohydride at room temperature for 3 hr. and at 60° for 1.5 hr. The solution was diluted with 50 ml. of water, refluxed for 10 min., cooled, and poured onto ice. The solid was recrystallized from ethanol–ethyl acetate, yielding 0.4 g., m.p. 200–202° (amide), infrared band at 1675 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.57; H, 6.23; N, 5.36.

Lactone of *cis*-1-Carboxy-1-phenyl-4-tetralol (26).—A mixture of 2 g. of **25**, 2 g. of potassium hydroxide, and 50 ml. of ethylene glycol was refluxed for 24 hr., cooled, and poured into ice–hydrochloric acid. The solid was recrystallized from benzene, yielding 1.3 g., m.p. 153–155°, infrared band at 1755 cm.$^{-1}$ (δ-lactone). The substance dissolved slowly on warming with base and was regenerated immediately upon acidification.

This substance was prepared also by heating a mixture of 1 g. of **25** and 4 g. of activated alumina at 220° for 40 min. (ammonia evolution), cooling, and extraction with hot alcohol. Concentration to small volume furnished 0.8 g. of **26**.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.65. Found: C, 81.01; H, 5.75.

Lactone **26**, as well as *cis*-1-carboxy-1-phenyl-4-tetralol (**30**), was also obtained by reduction of 10 g. of **24** in 50 ml. of methanol and 15 ml. of 2 *N* sodium hydroxide solution with 5.5 g. of sodium borohydride in 50 ml. of methanol and 2 ml. of sodium hydroxide. After 2.5 hr. at reflux, the mixture was acidified, concentrated *in vacuo*, and extracted with ether. Condensation of the ether extract furnished 3.3 g. of **26**. The aqueous layer was heated with 2 *N* hydrochloric acid for 2 hr., cooled, extracted with ether, and the ether layer was extracted with dilute base. Acidification of the basic extract and crystallization from ethanol yielded 1.5 g. of **30**, m.p. 234–236° dec.; infrared bands at 3600, 3430 (hydroxyl), bonded OH, and 1710 cm.$^{-1}$ (carboxyl).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.06; H, 5.51.

When alcohol **30** was heated above the melting point, there was obtained 1-carboxy-1-phenyl-1,2-dihydronaphthalene (**31**), m.p. 159–162° after recrystallization from benzene (60%), and lactone **26** (30%). As **31** was gradually converted to **26** on recrystallization (infrared spectrum), it was not analyzed. Acid **31** was isolated also by heating the mixture of epimeric alcohols from the sodium borohydride reduction of **24** until the evolution of water ceased, instead of refluxing with hydrochloric acid. The acidic fraction gave 12% of **31**, the neutral fraction, 68% of **26**.

***cis*-1-Hydroxymethyl-1-phenyl-4-tetralol (27).**—To a solution of 1.5 g. of lithium aluminum hydride in 25 ml. of ether was

(42) E. Clar, "Aromatische Kohlenwasserstoffe," Springer Verlag, Berlin, 1954, p. 161.

(43) F. Salmon-Legagneur, *Bull. soc. chim. France*, 994 (1952).

(44) A. D. Jarrett and J. D. Loudon, *J. Chem. Soc.*, 4052 (1955).

(45) J. Schmutz and H. Wittner, *Helv. Chim. Acta*, **43**, 793 (1960).

added dropwise 3 g. of **26** in 100 ml. of ether. The usual work-up and recrystallization from ethyl acetate afforded 2.8 g. (92%) of **27**, m.p. 132–134°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.34; H, 7.04.

4-Phenyl-5,6-benz-2-oxabicyclo[1.2.2]octane (28).—A mixture of 0.33 g. of **27** and 20 ml. of 10% hydrochloric acid was warmed on the steam bath for 30 min., cooled, and extracted with ether. The organic layer was dried and concentrated, and the residue was recrystallized from ethanol, yielding 0.28 g. of **28** (60%), m.p. 81–83°. The infrared spectrum indicated the absence of double bonds and hydroxyl groups.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.25; H, 6.98.

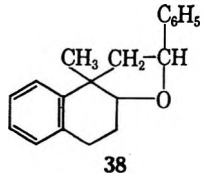
1,3,3-Trimethyl-4-phenyl-5,6-benz-2-oxabicyclo[2.2.2]octane (32).—To methyllithium prepared from 8.3 ml. of methyl iodide and 3 g. of lithium wire was slowly added 7 g. of **24** in 75 ml. of dry ether. Stirring was continued for 48 hr., the mixture was hydrolyzed with water, and the ether layer was washed, dried, and evaporated. The residue could not be induced to crystallize and was refluxed with 0.2 g. of iodine in 50 ml. of benzene for 20 hr., water being collected in a trap. The solution was washed with saturated sodium thiosulfate, dried, and distilled, the fraction with b.p. 130–133° (0.25 mm.) being collected. Chromatography of the distillate over alumina (solvent and eluent, hexane) yielded two fractions. The first, colorless oil, 0.75 g., absorbed bromine but was obviously a mixture (infrared analysis and n.m.r. spectrum). The second, colorless crystals from hexane, m.p. 111–113°, 0.6 g., exhibited no hydroxyl bands in the infrared and did not decolorize bromine. Since the n.m.r. spectrum exhibited no low-field signals characteristic of hydrogen on carbon carrying oxygen but had three methyl singlets, formula **32** was assigned.

Anal. Calcd. for $C_{20}H_{22}O$: C, 86.28; H, 7.79. Found: C, 85.75; H, 8.14.

1-Methyl-1-phenacyl-2-tetralone (33).—To a solution of 14 g. of 1-methyl-2-tetralone in 70 ml. of dry benzene was added, in a nitrogen atmosphere, 3.7 g. of sodium amide. After ammonia evolution had ceased, 17.5 g. of phenacyl bromide in 70 ml. of dry benzene was added dropwise with stirring. The mixture was refluxed for 18 hr., cooled, and hydrolyzed with water; the organic layer was washed, dried, and distilled, the fraction with b.p. 173–177° (1 mm.), 8 g. (33%), being collected. Redistillation and recrystallization from ethanol furnished the analytical sample, m.p. 113–114°, infrared bands at 1710 and 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 82.52; H, 6.54.

Lithium aluminum hydride reduction of **33** in the usual manner gave a mixture of alcohols (absence of carbonyl bands in the infrared) which was distilled from fused potassium acid sulfate, the fraction with b.p. 150–163° (0.5 mm.) being collected. Since microhydrogenation indicated the presence of only 0.74 double-bond equivalents, it was chromatographed over alumina (solvent and eluent, hexane). The first fraction, 0.25 g., absorbed bromine and had infrared bands at 1625 and 960 cm.$^{-1}$ (styryl group) but because of the low yield was not investigated further. The major fraction had an infrared spectrum similar to that of ethers **28** and **32**, and was perhaps **38**.



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1-Methyl-1-phenacetyl-4-tetralone (34).—A solution of acid chloride prepared from 26 g. of **8a** and 35 ml. of oxalyl chloride in 100 ml. of benzene was added to 80 g. of aluminum chloride in 100 ml. of benzene with stirring at 3°. Stirring was continued overnight; the mixture was decomposed by pouring over ice–hydrochloric acid, and the organic layer was extracted with dilute base, washed with water, dried, and concentrated. The residue was distilled, b.p. 191° (0.5 mm.), solidified on standing, and was recrystallized from hexane–ethyl acetate, m.p. 82–84°, yielding 23 g., infrared band at 1680 cm.$^{-1}$ (double strength).

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 82.14; H, 6.68.

Lithium aluminum hydride reduction of **34** gave a mixture of alcohols which was dehydrated with iodine in the usual fashion. Chromatography over alumina furnished material whose infrared and n.m.r. spectra indicated the absence of olefinic substances and the presence of an ether. Attempts to pyrolyze the alcohols *via* the acetates resulted in the same difficulties referred to earlier.[19]

1-Acetyl-2-tetralone (35).—A solution of 86 g. of 2-tetralone, 300 ml. of benzene, and 70 g. of morpholine was refluxed until the evolution of water stopped. Distillation furnished 105 g. (83%) of the morpholine enamine of 2-tetralone, b.p. 145–148° (0.3 mm.), m.p. 77°.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 78.83; H, 7.90. Found: C, 78.90; H, 7.69.

To a solution of 21.5 g. of the enamine and 16.7 ml. of triethylamine in 100 ml. of chloroform was added 7.8 ml. of acetyl chloride in 50 ml. of chloroform. The solution was stirred overnight, mixed with 50 ml. of 20% hydrochloric acid, refluxed for 5 hr., cooled, and diluted with water; the organic layer was washed, dried, and distilled. The fraction boiling at 100–110° (0.3 mm.) solidified and was recrystallized from ethanol, m.p. 72–73°, 12 g. (64%), infrared bands at 1700 and 1600 cm.$^{-1}$, positive ferric chloride test.

Anal. Calcd. for $C_{12}H_{11}O_2$: C, 76.55; H, 6.38. Found: C, 76.37; H, 6.45.

1-Acetyl-1-methyl-2-tetralone (36).—To sodium ethoxide prepared from 2 g. of sodium and 90 ml. of ethanol was added 16 g. of **35**. After 10 min., 10 ml. of methyl iodide in 20 ml. of ethanol was added, and the solution was warmed at 60° for 2 hr., concentrated at reduced pressure, and diluted with 50 ml. of water. The product was extracted with ether; the ether was extracted throughly with dilute sodium hydroxide solution, washed, and dried. Distillation furnished 11.8 g. (68%) of **36**, b.p. 112–115° (0.5 mm.), infrared bands at 1710 and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.31; H, 6.94. Found: C, 77.27; H, 7.63.

Reduction of 10.8 g. of **36** with lithium aluminum hydride in the usual manner furnished a mixture of alcohols (no carbonyl band in infrared spectrum) which could be distilled at reduced pressure without dehydration, yielding 7.8 g., b.p. 143–145° (0.3 mm.). A small amount was taken up in acetone and allowed to stand. One of the epimeric alcohols separated and was recrystallized from petroleum ether (b.p. 65–110°), m.p. 135–137°.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.55; H, 8.77.

An attempt to dehydrate the mixture of alcohols by distillation from fused boric anhydride resulted in the formation of an oil which took up less than the calculated amount of bromine and could not be identified as the desired diolefin.

1-Acetyl-1-phenyl-4-tetralone (37).—To the acid chloride from 23 g. of 4,4-diphenyl-5-ketohexanoic acid[33] in 150 ml. of chlorobenzene was added 30 g. of anhydrous aluminum chloride. After the initial reaction had subsided, the mixture was heated on the steam bath for 1 hr., poured over ice–hydrochloric acid, and extracted with ether; the ether was washed free of acid, dried, and evaporated. Distillation of the residue furnished a fraction, b.p. 188–192° (10.5 mm.), 8 g. (33%), which was recrystallized from hexane–benzene, m.p. 99–101°, infrared bands at 1700 and 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.80; H, 6.10. Found: C, 81.53; H, 5.94.

Constituents of *Iva* Species. III. Structure of Microcephalin, A New Sesquiterpene Lactone[1,2]

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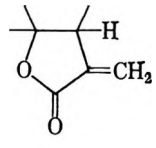
The structure of microcephalin, a sesquiterpene lactone from a variety of *Iva microcephala* Less., has been shown to be **2**.

A systematic search for sesquiterpene lactones in the genus *Iva* has been undertaken to delineate more fully disputed connections between genera related to *Ambrosia* and *Parthenium*[3] and to investigate a possible parallelism between their morphology and chemistry.

In a previous paper[4] we reported the isolation and structure determination of ivalin (**1**) from *Iva microcephala* Less. Collections of this species from the west and north of Tallahassee have given reproducible chemical results,[5] but material collected from the east and southeast frequently furnished little or no ivalin and relatively large amounts of other compounds.[4] The present article deals with the polar substance referred to earlier[4] which has been isolated reproducibly from collections of *Iva microcephala* made in Taylor County, Florida, and which we have named microcephalin. Work is in progress on the less polar constituents.

Microcephalin (**2**), m.p. 206–208°, $[\alpha]^{23}D$ +75°, had the formula $C_{15}H_{22}O_4$. It contained at least one hydroxyl group (infrared band at 3400 cm.$^{-1}$) and one double bond (band at 1660 cm.$^{-1}$) which was conjugated with a γ-lactone function (infrared band at 1760 cm.$^{-1}$) as demonstrated by the ultraviolet absorption at 212 mμ (ϵ 7200). The nature of the double bond was more clearly defined by ozonolysis. This resulted in liberation of formaldehyde and the formation of the enolic α-ketobutyrolactone **3**. Hence microcephalin contains partial structure A.



A

The exocyclic methylene group was saturated by catalytic reduction to dihydromicrocephalin (**4**), infrared bands at 3500 and 1760 cm.$^{-1}$, no ultraviolet absorption, which was oxidized to a dehydroderivative **5**. Since the infrared spectrum of **5** had a new carbonyl frequency at 1720 cm.$^{-1}$ (cyclohexanone), while retaining hydroxyl absorption at 3500 cm.$^{-1}$, the third oxygen atom of microcephalin is part of a secondary hydroxyl, the fourth being presumably incorporated in a tertiary hydroxyl group. A second route to **5** proceeded by way of oxidation of **2** to dehydromicrocephalin (**6**; infrared bands at 3620, 3530, 1765, 1715, and 1665 cm.$^{-1}$) and subsequent catalytic reduction.

Conversion of **5** to the ethylene thioketal was accompanied by dehydration, an observation which lent substance to the suspicion that a tertiary hydroxyl group was present. Desulfurization of the product and simultaneous saturation of the newly formed double bond resulted in formation of tetrahydroalantolactone (**7**) identical in all respects with an authentic sample. This established the carbon skeleton of microcephalin as that of the sesquiterpene lactones previously isolated from *Iva* species.

Since **5** and **6** gave a positive Zimmerman test, the secondary hydroxyl group of microcephalin had to be located in ring A. The tertiary hydroxyl group was attached to C-4 because the n.m.r. spectrum of **5** exhibited *two* methyl singlets at 1.38 and 1.20 and only one methyl doublet at 1.23 p.p.m., but had no low-field proton other than H_8 (triplet of doublets at 4.52 p.p.m.).[6] Now **2**, **3**, **4**, and **5** did not react with periodic acid or lead tetraacetate which limited the locus of the secondary hydroxyl group to C-1 or C-2. The conversion to tetrahydroalantolactone therefore also defines the absolute stereochemistry of microcephalin at C-5, C-7, C-8, and C-10.

Reaction of dihydromicrocephalin (**4**) with methanesulfonyl chloride afforded an unsaturated mesylate (**8**). The presence of an exocyclic methylene group in the latter was demonstrated by the n.m.r. spectrum (two narrowly split signals, J = 1 c.p.s., at 4.71 and 4.58 p.p.m., and only *one* methyl singlet at 0.88 in addition to the methyl doublet at 1.27 and the mesylate singlet at 3.04 p.p.m.) and by ozonolysis to the norketone mesylate **9**. Compound **8** was different from the previously unreported mesylate (**10b**) of dihydroivalin (**10a**), but, since the epimeric C-2 mesylate (β-hydroxyl) was unknown, the latter formulation was not necessarily excluded at this state.

Treatment of **8** with lutidine afforded an unconjugated diene (**11**) which again differed from the conjugated diene **12** (λ_{max} 230 mμ) obtained by similar treatment of **10b**. The n.m.r. spectrum of **11** had certain features of interest, H_1 and H_2 exhibiting the same chemical shift and no spin-coupling to the two protons at H_3 which appeared as a slightly broadened singlet at 3.00 p.p.m. That no rearrangement had occurred during the various elimination reactions was shown by catalytic hydrogenation which transformed **11** and **12** into **7**.

All signs thus pointed to C-1 as the attachment of the secondary hydroxyl group, particularly since the optical rotatory dispersion curve of **5** exhibited the

(1) Previous paper: W. Herz and N. Viswanathan, *J. Org. Chem.*, **28**, 1022 (1964).

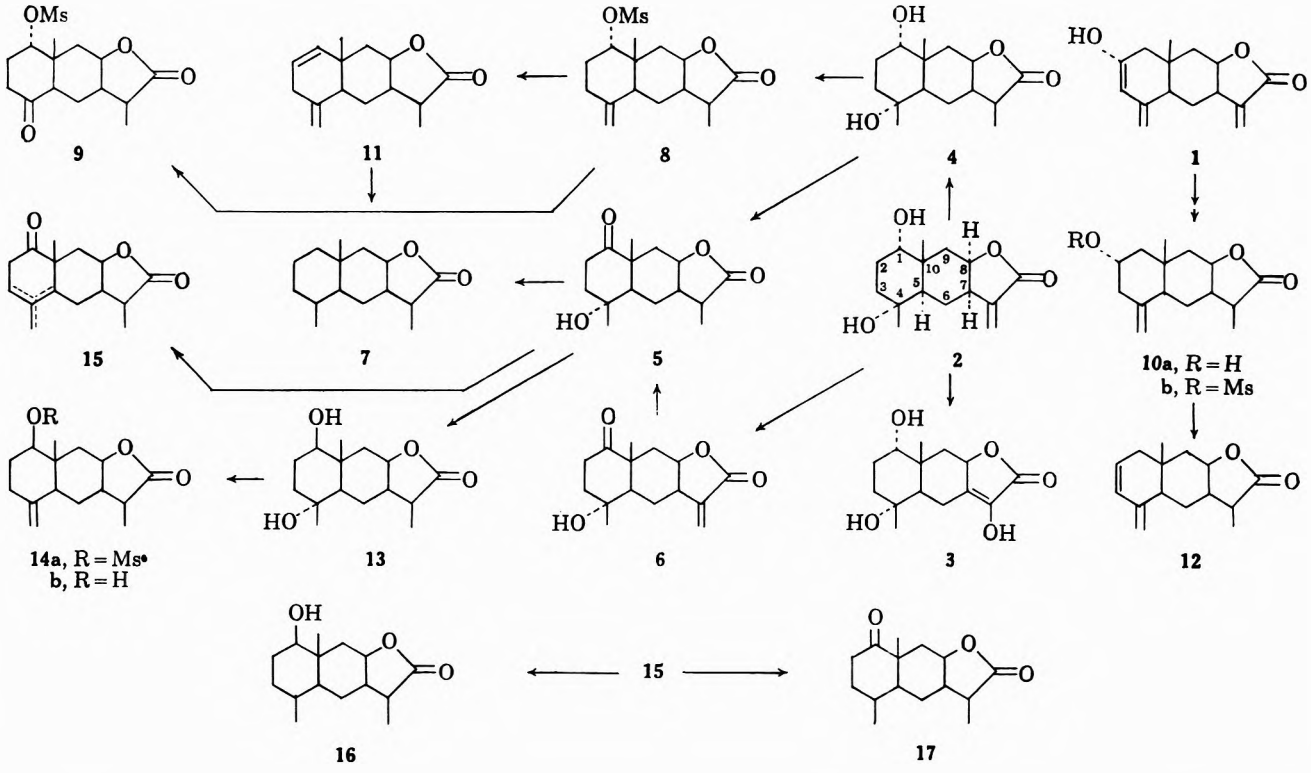
(2) Supported in part by grants from the U. S. Public Health Service (GM-05814) and the National Science Foundation (GP-1962).

(3) For a discussion of the taxonomic problem, see W. Herz and G. Högenauer, *J. Org. Chem.*, **26**, 5011 (1961).

(4) W. Herz and G. Högenauer, *ibid.*, **27**, 905 (1962).

(5) Unpublished work with S. Rajappa and L. R. Tether.

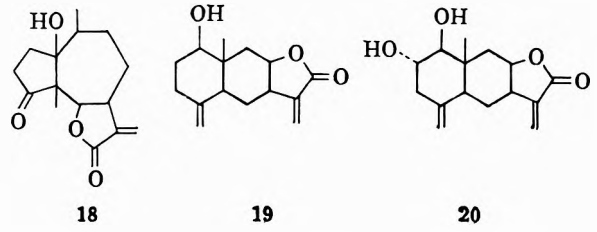
(6) In the n.m.r. spectrum of **6** the methyl doublet is replaced by the two characteristic narrowly split (J = 1 c.p.s.) doublets of the conjugated methylene group at 6.08 and 5.55 p.p.m.



positive Cotton effect of *trans*-9-methyl-1-decalones[7] of appropriate absolute configuration (a = +13). This was confirmed as follows. Sodium borohydride reduction of **5** resulted in the formation of a dihydroxylactone (**13**) epimeric with **4**. Since the newly introduced hydroxyl group is undoubtedly equatorial (rearside attack), it must be axial in **4** and therefore in **2**.[8] Treatment of **13** with methanesulfonylchloride afforded an unsaturated mesylate identical in all respects with the mesylate (**14a**) of dihydroasperilin (**14b**) of established structure and stereochemistry.[1] Dehydration of **5** with formic acid furnished a mixture **15** containing mainly the $\Delta^{4,5}$-isomer which on catalytic hydrogenation (α-attack) led to a mixture of tetrahydroasperilin (**16**) and dehydrotetrahydroasperilin (**17**).

The secondary hydroxyl group of microcephalin is therefore attached to C-1 and, since **8** differs from **14a**, axial and α. The stereochemistry at C-4 (hydroxyl equatorial and α) follows from the direction taken by bimolecular elimination.[9]

An interesting fact emerges from this and previously published[1,3,4,10,11] results. All thoroughly characterized sesquiterpene lactones from *Ambrosia* and *Parthenium* species have been biogenetically "abnormal" pseudoguaianolides[12] such as coronopilin (**18**)[3] and parthenin.[10] On the other hand, all *Iva* species which we have investigated hitherto elaborated only "normally" constituted eudesmanolides such as ivalin (**1**),[4] asperilin (**19**)[1], and ivasperin (**20**),[1] although morphological criteria justifiably place *Iva* closer to *Ambrosia* than *Ambrosia* is to *Parthenium*. Future work may reveal whether this is a generally applicable criterion for differentiating between these genera.



Experimental[15]

Extraction of *Iva microcephala* Less.—*Iva microcephala* was collected in Taylor County, Florida, near State Road 51 in late September, 1961, when in the flowering state. Dried leaves and flowerheads were stripped and extracted in the usual fashion and yielded 420 g. of gum from 9 lb. 12 oz. of leaves and flowerheads. This was dissolved in 800 ml. of chloroform and chromatographed over 5 kg. of alumina (Alcoa F-20). Benzene–chloroform (1:1) eluted most of the less polar substances. The elution was completed by thorough washing with chloroform; the total yield of crude material was 218 g. (thin-layer chromatography showed this to be a mixture). Chloroform–methanol (9:1) eluted microcephalin, the yield of once-recrystallized material was 35 g.

Extraction of leaves and flowerheads collected in the same general vicinity in early October, 1962 and 1963, did not duplicate the yield of nonpolar material from the earlier collection. Thus

(7) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956); C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962).

(8) Although the yield of pure crystalline **13** was less than 50%, thin-layer chromatography of the mother liquors showed the presence of only small amounts of **4**.

(9) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956).

(10) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962).

(11) M. Suchy, V. Herout, and F. Sorm, *Collection Czech. Chem. Commun.*, **28**, 2257 (1963).

(12) We are adopting this term, suggested by Dr. V. Herout, for lactones derived from 1a,4-dimethyl-7-isopropyldecahydroazulenes, a group which also includes tenulin,[13] helenalin,[14] and their congeners.

(13) W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and H. Viswanathan, *J. Am. Chem. Soc.*, **84**, 3857 (1962).

(14) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *ibid.*, **85**, 19 (1963).

(15) Melting points are uncorrected. Analyses were by Dr. F. Pascher, Bonn, Germany. Ultraviolet spectra were determined in 96% ethanol; infrared spectra and rotations were in chloroform unless otherwise specified. N.m.r. spectra were run in deuteriochloroform on a Varian A-60 spectrometer purchased with the aid of a grant from the National Science Foundation. Frequencies are given in parts per million with tetramethylsilane serving as the internal standard. t, d = triplet of doublets.

200 g. of gum, when chromatographed over 1.8 kg. of alumina, furnished only 29 g. of nonpolar substances and 19.6 g. of microcephalin.

Microcephalin (2).—The material eluted with chloroform–methanol was recrystallized from ethyl acetate or acetone, m.p. 206–208°; infrared bands at 3400, 1760, and 1660 cm.$^{-1}$; λ_{max} 212 mμ (ε 7200); $[\alpha]^{23}D$ +75° (c 1.31). It was insoluble in the solvents ordinarily used for n.m.r. spectroscopy.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; O, 24.03. Found: C, 67.36; H, 8.18; O, 24.21.

Acetylation did not furnish crystalline material, but the infrared spectrum (bands at 3500, 1765, 1740, and 1650 cm.$^{-1}$) indicated that the reaction had proceeded with esterification of the secondary hydroxyl group.

Ozonolysis of Microcephalin.—A solution of 1 g. of microcephalin in 100 ml. of methanol was ozonized at −70° in the usual way. Steam distillation of the ozonide into a saturated solution of dimedone, followed by steam distillation of the dimedone solution resulted, on cooling, in the precipitation of only 0.1 g. (9%) of the formaldehyde derivative. The solution containing the decomposed ozonide was evaporated *in vacuo* and the viscous residue was triturated with ethanol, yielding 0.27 g. of crystalline **3** which gave a positive ferric chloride test. Two recrystallizations from ethanol furnished the analytical sample, m.p. 169–170° dec.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51; O, 29.82. Found: C, 62.84; H, 7.80; O, 29.70.

When the ozonolysis was carried out in chloroform solution, the yield of formaldehyde dimedone derivative rose to 46%, but **3** could not be isolated.

Dihydromicrocephalin (4).—A solution of 0.5 g. of microcephalin in 50 ml. of ethanol was hydrogenated at atmospheric pressure with 0.05 g. of 5% palladium–charcoal at 23°; observed hydrogen uptake was 41.8 ml., calculated for one double bond, 45.1 ml. Evaporation of the solution followed by recrystallization from acetone or ethanol–ether furnished 0.28 g. of **7**, m.p. 208–208° (depression on admixture of microcephalin), infrared bands at 3500 and 1700 cm.$^{-1}$, $[\alpha]^{26}D$ +9° (c 3.6, ethanol). In subsequent runs, the yield of recrystallized material averaged 80%.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02; O, 23.96. Found: C, 66.78; H, 8.85; O, 23.96.

Dehydromicrocephalin (6).—A solution of 0.27 g. of 2 in 5 ml. of acetic acid was mixed with 0.13 g. of chromic oxide in 20 ml. of acetic acid and allowed to stand in the refrigerator for 2 hr. Excess oxidizing agent was destroyed by adding a few drops of methanol, the solution was concentrated *in vacuo*, and the residue was extracted with hot benzene several times. The hot benzene extract was centrifuged, and evaporated; the colorless residue was recrystallized from benzene, yielding 0.17 g., m.p. 175-177°; infrared bands at 3620, 3530, 1765, 1715, and 1665 cm.$^{-1}$. The analytical sample was recrystallized from ethyl acetate, n.m.r. signals at 6.08 d and 5.55 d (J = 1 c.p.s., exocyclic methylene), 4.54 t, d (J = 4, 2 c.p.s., H_8), 1.31 and 1.20 p.p.m. (C-4 and C-10 methyls). The substance gave a positive Zimmerman test.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 68.55; H, 7.62; O, 23.91.

Dehydrodihydromicrocephalin (5).—A solution of 1.4 g. of 4 in 30 ml. of acetic acid was allowed to stand in the refrigerator for 24 hr. with 1.00 g. of chromic acid in 80 ml. of acetic acid. The product was worked up as described in the previous paragraph (to remove chromium salts completely, it was necessary to pass the benzene solution through an alumina column), yielding 0.55 g. of 5, m.p. 192–194° (from ethyl acetate); $[\alpha]^{26}D$ +2° (c 7.4, ethanol); infrared bands at 3500, 1770, and 1720 cm.$^{-1}$; n.m.r. signals at 4.52 t, d (J = 4, 2 c.p.s., H_8), 1.38 and 1.20 (C-4 and C-10 methyls), and 1.23 p.p.m. d (J = 7 c.p.s., C-11 methyl); rotatory dispersion curve in dioxane (c 0.85), $[\alpha]_{700}$ 0°, $[\alpha]_{589}$ +11.9°, $[\alpha]_{317}$ +477°, $[\alpha]_{312}$ +473°, $[\alpha]_{308}$ +479°, and $[\alpha]_{272}$° −8°.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; O, 24.03. Found: C, 67.93; H, 8.28; O, 23.83.

This substance was also prepared in 75% yield by catalytic reduction (ethanol, 5% palladium on charcoal) of 6. It gave a positive Zimmermann test but could not be induced to condense with piperonal.

Anhydrodihydromicrocephalin Mesylate (8).—To a chilled solution of 2 g. of 4 in 13 ml. of dry pyridine was added in small portions 9 ml. of methanesulfonyl chloride. The mixture was refrigerated overnight, poured onto crushed ice, and extracted with chloroform, and the chloroform layer was washed, dried, and evaporated. The residue was recrystallized from ethanol, yielding 1.25 g. (51%), m.p. 125–126° dec.; infrared bands at 1760 and 1640 cm.$^{-1}$; $[\alpha]^{20}D$ +59° (c 1.00); n.m.r. signals at 4.71 d and 4.58 d (J = 1 c.p.s., exocyclic methylene), 4.53 c (intensity two protons, H_1 and H_8), 3.04 (three protons, mesylate), 1.27 d (J = 7 c.p.s., C-11 methyl), and 0.88 p.p.m. (C-10 methyl).

Anal. Calcd. for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.36; O, 24.36. Found: C, 58.16; H, 7.32; O, 24.89.

Ozonolysis of 0.5 g. of the mesylate in 50 ml. of chloroform at −70° followed by steam distillation gave 29% of formaldehyde, isolated as the dimedone derivative. The aqueous mother liquor on evaporation furnished a yellow, water-soluble oil which could not be crystallized and gave a positive ferric chloride test. Ozonolysis of 0.2 g. of mesylate in 20 ml. of methanol at −70° for 1 hr., followed by catalytic reduction of the solution with 0.06 mg. of 5% palladium on charcoal at 20 lb./in.^{2}, filtration, evaporation, and chromatography of the residue over alumina (solvent and eluent, chloroform) furnished, after recrystallization from chloroform–petroleum ether (b.p. 35–60°) 0.065 g. of the norketone 9, m.p. 137–139°, infrared bands (KBr) at 1775 and 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{22}O_6S$: C, 54.54; H, 6.71. Found: C, 54.62; H, 7.07.

Bisanhydrodihydromicrocephalin (11).—A mixture of 1 g. of 8 and 50 ml. of 2,6-lutidine was refluxed for 2 days, cooled, diluted with ice, neutralized, and filtered. The precipitate, 0.55 g., was taken up in hot methanol, treated with charcoal, filtered, and cooled. Additional recrystallizations from methanol furnished 0.25 g. of 11, m.p. 162–166°, whose ultraviolet spectrum [λ_{max} 265 mμ (ε 112)] indicated the presence of a small amount of conjugated homoannular diene which could not removed by further recrystallization or chromatography; infrared bands at 1770 and 1650 cm.$^{-1}$; n.m.r. signals at 5.82 s (two protons, H_1 and H_2), 5.22 d and 4.92 d (J = 2 c.p.s., exocyclic methylene), 4.78 c (H_8), 3.0 (slightly broadened singlet, two protons, H_3), 1.32 d (J = 7 c.p.s., C-11 methyl), and 0.91 p.p.m. (C-10 methyl). A mixture melting point with a conjugated diene 12 of m.p. 159–161° from ivalin (*vide infra*) was 158–164°, but the two substances differed in ultraviolet spectrum, infrared spectrum, and gave two distinct spots on thin layer chromatography.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; O, 13.77. Found: C, 77.50; H, 8.66; O, 13.63.

Tetrahydroalantolactone (7). **A.**—A solution of 0.159 g. of 11 in 5 ml. of ethanol was reduced in the presence of platinum oxide until hydrogen absorption ceased. Filtration, evaporation, and recrystallization of the residue from methanol furnished 0.118 mg. of tetrahydroalantolactone, m.p. and m.m.p. (with an authentic sample) 143–144°. The infrared spectra of the two samples were identical.

B.—A mixture of 0.5 g. of dehydrodihydromicrocephalin, 1.5 ml. of ethanedithiol, and 1.5 ml. of boron trifluoride etherate was allowed to stand at room temperature for 4 hr. The usual work-up furnished an oil which could not be induced to crystallize, presumably because it represented a mixture of double bond isomers (treatment of 5 with BF_3 etherate alone resulted in a mixture of dehydration products). The oil was dissolved in 50 ml. of absolute ethanol and refluxed with W-2 Raney nickel for 60 hr. Filtration and evaporation *in vacuo* followed by recrystallization from methanol furnished tetrahydroalantolactone, m.p. 140–142°, m.m.p. (with authentical material) 140–142°. The two samples were undistinguishable by infrared spectroscopy and thin-layer chromatography.

1-Epitetrahydromicrocephalin (13).—A solution of 0.59 g. of dehydrodihydromicrocephalin (5) in 50 ml. of methanol was refluxed with 0.5 g. of sodium borohydride for 3 hr., cooled, acidified with acetic acid, and evaporated *in vacuo*. The residue was extracted with hot ethyl acetate, the extract was evaporated *in vacuo*, and the product was recrystallized from chloroform–ether, yielding 0.253 g. (43%), m.p. 210–212°. The analytical sample had m.p. 214–215°; infrared bands at 3650, 3450, and 1770 cm.$^{-1}$; $[\alpha]^{23}D$ −25° (c 1.00). Thin-layer chromatography of the mother liquors revealed several spots; the intensity ratio of the spots corresponding to 13 and 4 was estimated to be greater than 4:1.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.12; H, 9.02; O, 23.96. Found: C, 67.22; H, 9.10; O, 23.76.

Treatment of 0.131 g. of the above with 1 ml. of methanesulfonyl chloride and 1 ml. of pyridine and work-up in the usual manner resulted in 0.04 g. of a mesylate, m.p. 142–144°, unde-

pressed on admixture of the mesylate (14a) of dihydroasperilin (14b), m.p. 142–144°. Infrared spectra and rotations, $[\alpha]^{23}D$ +41 (*c* 1.00), were identical.

Formic Acid Dehydration of 5.—A mixture of 0.882 g. of 5 and 10 ml. of formic acid was refluxed for 4 hr., concentrated at reduced pressure, diluted with water, and extracted with ether. The ether extract was washed, dried, evaporated, and chromatographed over alumina (Alcoa F-20). The initial fractions were combined and weighed 0.468 g. The infrared spectrum exhibited bands at 1770, 1710, and 1670 cm.$^{-1}$; the n.m.r. spectrum showed that the eluate was a mixture (15) with the $\Delta^{4,5}$-isomer predominating—weak vinyl proton signals at 6.69, 6.55, 5.88, and 5.70 (total intensity one-half proton), 4.5 c (H_8), 1.73 (vinyl methyl singlet, intensity almost three protons), 1.30 (C-10 methyl singlet), and 1.22 d (J = c.p.s., C-11 methyl), with indications of a weak doublet at 1.13 p.p.m. due to the presence of another isomer.

A solution of 0.23 g. of 15 in 6 ml. of acetic acid was hydrogenated with platinum oxide. The oily product was dissolved in benzene and chromatographed over 9 g. of acid-washed alumina. From the benzene eluates was isolated 0.04 g. of somewhat impure dehydrotetrahydroasperilin (17), m.p. and m.m.p. 120–122°, infrared spectra superimposable. From the fractions eluted with chloroform there was isolated 0.015 g. of slightly impure tetrahydroasperilin (16), m.p. and m.m.p. 144–146°, infrared spectra superimposable.

Anhydrodihydroivalin (12).—Reaction of 0.45 g. of dihydroivalin (10a) with methanesulfonyl chloride in the usual manner furnished, after recrystallization from ethanol, 0.5 g. of the mesylate 10b, m.p. 149–150° dec.; infrared bands at 1765 and 1640 cm.$^{-1}$; n.m.r. signals at 5.02 and 4.72 (exocyclic methylene, the second of these was superimposed on the H_2 resonance, complex multiplet centered at 4.72), 4.53 c (H_8), 2.90 (mesyl), 1.06 d (J = 7 c.p.s., C-11 methyl), and 0.735 p.p.m. (C-10 methyl).

Anal. Calcd. for $C_{16}H_{24}O_3S$: C, 58.51; H, 7.36. Found: C, 58.39; H, 7.55.

A solution of 0.8 g. of the mesylate in 50 ml. of lutidine was refluxed for 24 hr., poured onto crushed ice, neutralized with dilute sulfuric acid, and filtered. The solid was taken up in hot ethanol, treated with charcoal, concentrated, and allowed to cool. The colorless needles melted at 159–161° (m.m.p. 158–164° with 11), but the infrared (bands at 1775, 1645, and 1610 cm.$^{-1}$) and ultraviolet spectra [λ_{max} 2300 mμ (ϵ 9850), heteroannular diene] clearly differentiated it from 11. The n.m.r. spectrum could be interpreted most simply on the basis of formula 12, with signals at 6 c (H_2), 5.44 s, and 4.84 s (exocyclic methylene), the latter partially superimposed on a complex signal centered at 4.7 (H_3), 4.45 c (H_4), 1.23 d (J = 7 c.p.s., C-10 methyl), and 0.83 p.p.m. d (J = 2 c.p.s., C-10 methyl).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; O, 13.77. Found: C, 77.50; H, 8.77; O, 14.02.

Catalytic hydrogenation of 12 furnished tetrahydroalantolactone.

Acknowledgment.—We wish to thank the Research Council of Florida State University for a grant-in-aid.

Dithiolium Derivatives. I. 2-Dialkylamino-1,3-dithiolium Perchlorates[1]

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Contribution No. 1201 from the Chemistry Laboratories of Indiana University, Bloomington, Indiana 47405

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A convenient synthesis of some 4-substituted 2-dialkylamino-1,3-dithiolium perchlorates is described which employs mild conditions. A mechanism for the cyclization is proposed, and the structure of the products is discussed with reference to ultraviolet and n.m.r. spectra.

Leaver and Robertson have reported the synthesis of some 1,3-dithiolium salts by the cyclization of phenacyl carbodithioates (I) in ether saturated with hydrogen sulfide and hydrogen chloride.[3,4] We repeated the synthesis of 2,4-diphenyl-1,3-dithiolium chloride (III, R = R′ = Ph), but the yield was considerably less than previously reported. The reaction was found to be accompanied by an interesting color change. Phenacyl dithiobenzoate (I, R = R′ = Ph) was obtained as a brick red solid by the condensation of sodium dithiobenzoate and phenacyl chloride, while the dithiolium chloride product (III, R = R′ = Ph) obtained from it was pale green. A similar and almost instantaneous change was observed when 70% perchloric acid was added to phenacyl dithiobenzoate. The product proved to be 2,4-diphenyl-1,3-dithiolium perchlorate (III, R = R′ = Ph) and was identical with the perchlorate salt obtained *via* the hydrochloride. This mild method of cyclization of β-keto dithio esters into 1,3-dithiolium salts has been fully confirmed by the preparation of the compounds in Table I. The conditions, however, are in marked contrast to those of Leaver, Robertson, and McKinnon,[4] employing boiling mixtures of acetic and perchloric acids with hydrogen sulfide.

Under the latter conditions the reaction was considered to involve an initial conversion of the β-carbonyl group into a thiocarbonyl function either by the action of the hydrogen sulfide directly or by its generation *in situ* by decomposition of the starting material. Because the reaction has been shown to occur in high yields without the use of hydrogen sulfide, it may be regarded as a direct acid-catalyzed cyclization, I → II followed by dehydration to give the pseudoaromatic cation III[5] (see p. 1704).

To extend the yet limited range of known 1,3-dithiolium compounds,[3-9] preparation of 2-dialkylamino derivatives was investigated. Initial experiments to effect the ring closure of β-keto N,N-dialkyldithiocarbamates [I, R = $(CH_3)_2N$ or $(C_2H_5)_2N$] with hydrogen chloride and hydrogen sulfide did not meet with success. The use of 70% perchloric acid, however, readily gave insoluble perchlorate salts irrespective of the nature of the substituent attached to the ketone group.

(1) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. We gratefully acknowledge this support.

(2) American Chemical Society Petroleum Research Fund Postdoctoral Fellow, 1962–1963.

(3) D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc.*, 252 (1960).

(4) D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *J. Chem. Soc.*, 5104 (1962).

(5) E. Klingsberg, *J. Am. Chem. Soc.*, **84**, 3410 (1962). (The term "pseudoaromatic," applied to the 1,3-dithiolium cation, seems well justified because the aromatic conjugation can only exist in the cation molecule, and, even in this state, there is incomplete delocalization of π-electrons.)

(6) W. R. H. Hurtley and S. Smiles, *J. Chem. Soc.*, 1821, 2263 (1926).

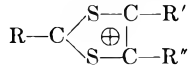
(7) F. Challenger, E. A. Mason, E. C. Holdsworth, and R. Emmott, *Chem. Ind.* (London), 714 (1952); *J. Chem. Soc.*, 292 (1953).

(8) W. Kirmse and L. Horner, *Ann.*, **614**, 4 (1958).

(9) L. Soder and R. Wizinger, *Helv. Chim. Acta*, **42**, 1733, 1779 (1959).

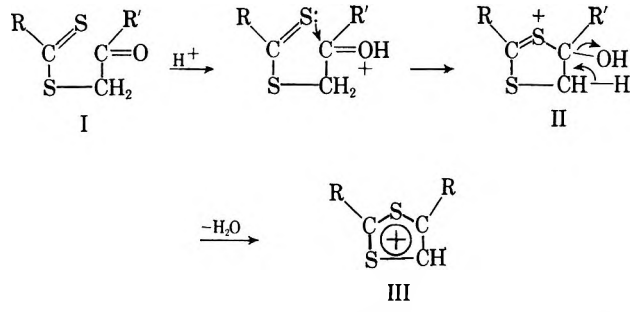
TABLE I

SUBSTITUTED 1,3-DITHIOLIUM PERCHLORATE DERIVATIVES



Compd. no.	R	R′	R″	Recrystn. solvent, ml./g.[a]	Yield, %	M.p., °C.	Formula	Analysis, % Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
1	C_6H_5	C_6H_5	H	220	74	207–209	$C_{15}H_{11}ClO_4S_2$	50.75	3.15	18.05	50.95	3.25	18.1
2	$(CH_3)_2N$	CH_3	H	1[b]	81	104–105[c]	$C_6H_{12}ClNO_5S_2$	25.95	4.35	23.1	25.95	4.4	22.8
				25[d]	52	124[e]	$C_8H_{16}ClNO_5S_2$	31.4	5.25	20.95	31.45	5.45	21.2
3	$(CH_3)_2N$	CH_3	CH_3	1.5[b]	95	112–114[c]	$C_7H_{14}ClNO_5S_2$	28.8	4.85	22.0	28.85	4.7	22.05
4	$(CH_3)_2N$	CH_3	C_2H_5	1[b]	85	87–88[c]	$C_8H_{16}ClNO_5S_2$	31.4	5.3	20.95	31.7	5.5	21.0
5	$(CH_3)_2N$	C_6H_5	H	30	95	178–179	$C_{11}H_{12}ClNO_4S_2$	41.05	3.75	19.95	41.3	3.95	19.9
6	$(C_2H_5)_2N$	C_6H_5	H	110	95	176–178	$C_{13}H_{16}ClNO_4S_2$	44.65	4.6	18.35	44.8	4.75	18.6
7	$(CH_3)_2N$	p-$CH_3C_6H_4$	H	120	86	184–185	$C_{12}H_{14}ClNO_4S_2$	42.9	4.2	19.1	43.15	4.2	19.0
8	$(C_2H_5)_2N$	p-$CH_3C_6H_4$	H	53	88	185–186	$C_{14}H_{18}ClNO_4S_2$	46.2	5.0	17.6	46.4	5.2	17.6
9	$(CH_3)_2N$	p-ClC_6H_4	H	125	77	203–204	$C_{11}H_{11}Cl_2NO_4S_2$	37.1	3.1	18.0	37.3	3.25	18.05
10	$(C_2H_5)_2N$	p-ClC_6H_4	H	10	89	122–123	$C_{13}H_{15}Cl_2NO_4S_2$	40.65	3.95	16.7	40.9	4.05	16.8
11	$(CH_3)_2N$	p-$CH_3OC_6H_4$	H	80	87	165–166	$C_{12}H_{14}ClNO_5S_2$	40.95	4.0	18.25	41.1	4.05	18.5
12	$(C_2H_5)_2N$	p-$CH_3OC_6H_4$	H	4	58	154–155	$C_{14}H_{18}ClNO_5S_2$	44.25	4.8	16.9	44.55	4.8	16.9
13	$(CH_3)_2N$	p-HOC_6H_4	H	150	61	208–209	$C_{11}H_{12}ClNO_5S_2$	39.1	3.6	19.0	39.2	3.65	18.8
14	$(C_2H_5)_2N$	p-HOC_6H_4	H	11	79	148–149	$C_{13}H_{16}ClNO_5S_2$	42.65	4.4	17.55	42.75	4.6	17.6
15	$(CH_3)_2N$	p-$NO_2C_6H_4$	H	480	94	207–208	$C_{11}H_{11}ClN_2O_6S_2$	36.0	3.0	17.5	36.3	3.3	17.55
16	$(C_2H_5)_2N$	p-$NO_2C_6H_4$	H	200	95	193–194	$C_{13}H_{15}ClN_2O_6S_2$	39.55	3.85	16.25	39.9	4.1	16.4

[a] Ml./g. refers to the minimum volume of boiling solvent required to dissolve and recrystallize 1 g. of the compound. Except where otherwise indicated, the solvent was absolute ethanol. [b] 10% perchloric acid. [c] Monohydrate. [d] Ethanol–petroleum ether (b.p. 30–60°) 3:1. [e] Monoethanolate.



I II III

Appropriate N,N-dialkyldithiocarbamoyl esters (Table II) were prepared by the condensation of either sodium N,N-dimethyl- or N,N-diethyldithiocarbamate with the required phenacyl or acetonyl halide. Treatment of these dithiocarbamoyl esters with a minimum (usually one–three parts) of 70% perchloric acid resulted in a considerable heat of reaction, in most cases sufficient to complete solution. The colorless 1,3-dithiolium perchlorates in many instances readily crystallized on cooling; in others, sparing addition of water or ethyl acetate gave the same result. The salts thus obtained were stable enough to be recrystallized from water or ethanol.

The cyclization of β-keto N,N-dialkyldithiocarbamates to give 2-dialkylamino-4-substituted 1,3-dithiolium salts was accompanied by marked changes in spectral features. N,N-dialkyldithiocarbamoyl esters are reported to show two spectral features in the ultraviolet region that have been attributed to transitions to excited states partaking mainly of the character of IV and of V, respectively.[10] An absorption at high wave length (270–280 mμ) has been associated with transition to the immonium state (IV) while a lower wave-length (240–254 mμ) feature is thought to arise from transition to the sulfonium structure (V).[11] Of the N,N-dialkyldithiocarbamates reported in this paper (Table II), those with smaller substituents (compounds 2–6) show both of these absorptions within the ranges indicated. Those dithiocarbamates with *para*-substituted phenyl as a substituent (compounds 7–16) show only one of the spectral features depending on the nature of the *para* substituent. Variations between the dimethylamino and diethylamino series were generally very small, the more basic diethylamino group causing the bathochromic displacement described by Koch.[10]

IV V

In contrast to the open-chain compounds, the ultraviolet spectra of the 1,3-dithiolium derivatives were more complex and subject to variation (Table III). In all aryl derivatives examined, three or four absorptions were found, the longest of these between 315 and 335, and the shortest between 223 and 230 mμ. Those compounds with four spectral features had further bands between 300 and 305 and 235 and 244 mμ. When only three bands were to be found, the third absorption was in the much wider range, 256–292 mμ. *para* substitution of the 4-phenyl group caused an expected bathochromic displacement of the long wave-length feature (315–336 mμ). Those dithiolium salts (2–4) with only alkyl substituents attached to the dithiolium nucleus showed only two peaks at much reduced intensities. However, we believe that these compounds are chemically quite different from those of the aryl series and that future work will show that, in many environments, they are more truly represented as the intermediate 1,3-dithiolan derivatives (II).

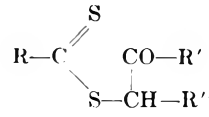
Changes in infrared absorption also reveal the conversion of the open-chain keto dithio esters into 1,3-dithiolium salts upon treatment with 70% perchloric acid. The disappearance of the carbonyl absorption from the region 1656–1689 cm.$^{-1}$ and the appearance of

(10) H. P. Koch, *J. Chem. Soc.*, 401 (1949).

(11) K. C. Kennard and D. M. Burness, *J. Org. Chem.*, **24**, 464 (1959).

TABLE II

β-KETO DITHIO ESTERS

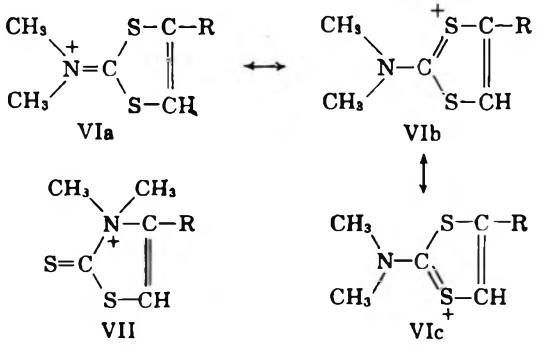


Compd no.	R	R′	R″	Yield,[a] %	M.p., °C.	Formula	Analysis, %—Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S	Ultraviolet spectra,[b] λ_{max}, mμ (log ε)
1	C_6H_5	C_6H_5	H	45	79–80	$C_{18}H_{12}OS_2$	66.15	4.45	23.55	66.05	4.25	23.35	297 (4.22); 243 (4.16)
2	$(CH_3)_2N$	CH_3	H	44	54–55[c]	$C_6H_{11}NOS_2$	40.65	6.25	36.15	40.75	6.15	36.45	275 (4.05); 245 (3.97)
3	$(CH_3)_2N$	CH_3	CH_3	45	33–34	$C_7H_{13}NOS_2$	43.95	6.85	33.5	44.0	6.8	33.3	277 (3.93); 248 (3.90)
4	$(CH_3)_2N$	CH_3	C_2H_5	63	42–43	$C_8H_{15}NOS_2$	46.8	7.35	31.2	47.2	7.5	30.9	276 (4.08); 248 (4.06)
5	$(CH_3)_2N$	C_6H_5	H	95	110–111[d]	$C_{11}H_{13}NOS_2$	55.2	5.45	26.8	55.0	5.6	27.1	275 (4.03); 247 (4.32)
6	$(C_2H_5)_2N$	C_6H_5	H	83	103–104[d]	$C_{13}H_{17}NOS_2$	58.4	6.4	24.0	58.5	6.45	23.95	278 (4.10); 248 (4.36)
7	$(CH_3)_2N$	p-$CH_3C_6H_4$	H	79	113–114	$C_{12}H_{15}NOS_2$	56.9	5.95	25.3	57.0	6.05	25.15	254 (4.03)
8	$(C_2H_5)_2N$	p-$CH_3C_6H_4$	H	63	64–65	$C_{14}H_{19}NOS_2$	59.75	6.8	22.8	59.8	6.8	22.6	255 (4.42)
9	$(CH_3)_2N$	p-ClC_6H_4	H	80	88–89	$C_{11}H_{12}ClNOS_2$	48.25	4.4	23.4	48.1	4.55	23.25	254 (4.42)
10	$(C_2H_5)_2N$	p-ClC_6H_4	H	78	66–67	$C_{13}H_{16}ClNOS_2$	51.7	5.35	21.25	52.1	5.55	20.35	254 (4.40)
11	$(CH_3)_2N$	p-$CH_3OC_6H_4$	H	80	96–97	$C_{12}H_{15}NO_2S_2$	53.5	5.6	23.8	53.7	5.5	23.55	275 (4.41)
12	$(C_2H_5)_2N$	p-$CH_3OC_6H_4$	H	46	48–50	$C_{14}H_{19}NO_2S_2$	56.55	6.45	21.55	56.7	6.25	21.5	276 (4.45)
13	$(CH_3)_2N$	p-HOC_6H_4	H	81	203	$C_{11}H_{13}NO_2S_2$	51.75	5.15	25.1	51.8	5.25	25.15	277 (4.41)
14	$(C_2H_5)_2N$	p-HOC_6H_4	H	75	170–171	$C_{13}H_{17}NO_2S_2$	55.1	6.05	22.65	55.05	6.25	22.55	278 (4.42)
15	$(CH_3)_2N$	p-$NO_2C_6H_4$	H	82	146–148	$C_{11}H_{12}N_2O_3S_2$	46.45	4.25	22.65	46.4	4.5	22.6	267 (4.31)
16	$(C_2H_5)_2N$	p-$NO_2C_6H_4$	H	62	106–107	$C_{13}H_{16}N_2O_3S_2$	50.0	5.15	20.55	50.15	5.4	20.45	267 (4.41)

[a] Yields determined after first recrystallization. [b] Ultraviolet spectra were measured in 95% ethanol using a Cary 14 Model spectrophotometer. [c] J. R. Robinson, D. Craig, and R. B. Fowler [*Can. J. Chem.*, **34**, 1596 (1956)] report m.p. 58°; G. Nachmias [*Ann. chim.* (Paris), **7**, 584 (1952)] report m.p. 76°. [d] S. Yoshida and W. Ishizuka [*J. Pharm. Soc. Japan*, **74**, 331 (1954)] report m.p. 111° for **5** and 102° for **6**.

a very strong and broad band (1050–1110 cm.$^{-1}$) due to the perchlorate anion were spectral changes that were used throughout this work to confirm the nature of the reaction products. Also, the one or two additional bands that appeared at frequencies from 1450–1650 cm.$^{-1}$ could be attributed either to the newly introduced C-4–C-5 double bond or to the stretching vibrations associated with a polar C=N$^+$ bond.[12]

In the cyclization of N,N-dialkyldithiocarbamoyl esters, it is possible for the products to be quaternary N,N-dialkylthiazoline-2-thiones (VII) on the basis that the order of effective electron donor ability in similar cyclizations is usually considered to be N > S > O.[13] Nevertheless, we have assigned the perchlorates the 1,3-dithiolium structure by analogy with the formation of 2,4-diphenyl-1,3-dithiolium perchlorate, since this system would receive greater stabilization from resonance (VIa–c) than the thiazolinium structure (VII), and on the basis of n.m.r. spectral data.



Attempts to resolve the structure of the products by direct chemical means produced no evidence in favor of the thiazolinium structure. No derivative of a thione group present in VII could be prepared, nor were efforts to hydrolyze any such group with mercuric acetate and acetic acid successful. Nuclear magnetic resonance spectra, moreover, indicated that the perchlorates were unlikely to be thiazoline derivatives. When these measurements were made in trifluoroacetic acid, the N,N-dialkyl substituents were found to be nonequivalent; N,N-dimethyl groups were represented by two peaks and N,N-diethyl groups by two triplet and two quartet features.[14] Such a situation is difficult to envisage as arising out of the structure VII where both alkyl groups would be in similar juxtaposition to the positive charge and hence would suffer identical deshielding effects. On the other hand, if the products existed as dithiolium derivatives, then contributions from the resonance form VIa would produce a barrier to rotation about the C–N bond,[15] and the environments of the two N-alkyl groups would be different (*cis* to S–C–R or *cis* to S–C–H). Further evidence is found in the n.m.r. spectrum of compound **3** (Table III). A single peak, representing six protons, is present in the spectrum taken in 70% perchloric acid. This is the expected resonance for two identical ring methyl groups at C-4 and C-5, in VI, but similar methyl groups in VII would not be expected to be identical. On the basis of this and the aforementioned evidence, the perchlorate products described in this paper are considered as 1,3-dithiolium derivatives (VIa–c).

Contributions from the immonium structure (VIa) are also manifested in the chemical shift of the lone dithiolium proton. The spectrum of 2,4-diphenyl-1,3-dithiolium perchlorate (Fig. 1a) showed only the two anticipated features: a complex signal between τ 1.83 and 2.50 and a singlet at 1.25. Integration of the spectrum showed unequivocally that the broad signal

(12) J. Chatt, L. A. Duncanson, and L. M. Venanzi, *Chem. Abstr.*, **51**, 5559d (1957).

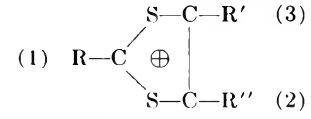
(13) N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Am. Chem. Soc.*, **82**, 4075 (1960).

(14) This was not so when the n.m.r. spectra were measured in deuterated 70% perchloric acid, for then the N,N-dimethyl protons appeared as a single spectral feature integrating for six protons, while the N,N-diethyl protons were found as one triplet pattern (2 × 3 protons) and as one quartet pattern (2 × 2 protons). This may have been the result of poorer resolution in the more viscous solvent, or the existence of the perchlorates more exclusively in the sulfonium states (VIb and c).

(15) J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Company, Inc., New York, N. Y., 1959, Chapter 3.

TABLE III

SPECTRA OF SUBSTITUTED 1,3-DITHIOLIUM PERCHLORATES



Compd. no.	R	R′	R″	Ultraviolet spectra,[a] λ_{max}, mμ (log ε)	Proton magnetic resonance spectra[b] (J) (1)	(2)	(3)
1	C_6H_5	C_6H_5	H	394 (4.18), 310 (3.72)[c] 277 (3.82), 243 (4.17)	1.83–2.50 m[d]	1.25	1.83–2.50 m[d]
2	$(CH_3)_2N$	CH_3	H	303 (3.49), 245 (2.90)[c]	7.00	3.50 q (2)	8.03 d (2)[e]
3	$(CH_3)_2N$	CH_3	CH_3	312 (3.89), 246 (3.50)[c]	7.03	8.20	8.20[e]
4	$(CH_3)_2N$	CH_3	C_2H_5	312 (3.83), 245 (3.03)[c]	7.05	7.80 q (8) 9.32 t	8.20[e]
5	$(CH_3)_2N$	C_6H_5	H	315 (4.08), 300 (4.03),[a,c] 235 (4.15), 225 (4.21)	6.30 6.35	2.63	2.47
6	$(C_2H_5)_2N$	C_6H_5	H	320 (4.06), 300 (3.95), 236 (4.12), 225 (4.18)	6.00 q, 8.42 t (8) 6.05 q, 8.43 t	2.63	2.47
7	$(CH_3)_2N$	p-$CH_3C_6H_4$	H	320 (4.04), 302 (4.03), 242 (4.13), 228 (4.14)	6.32 6.37	2.70	2.53 d, 2.67 d (9) 7.59[e]
8	$(C_2H_5)_2N$	p-$CH_3C_6H_4$	H	325 (4.04), 302 (4.00), 244 (4.12), 228 (4.12)	6.00 q, 8.42 t (8) 6.05 q, 8.43 t	2.70	2.53 d, 2.67 d (9) 7.59[e]
9	$(CH_3)_2N$	p-ClC_6H_4	H	315 (4.15), 305 (4.16), 237 (4.22), 230 (4.23)	6.28 6.33	2.59	2.50
10	$(C_2H_5)_2N$	p-ClC_6H_4	H	320 (4.13), 305 (4.11), 238 (4.21), 230 (4.20)	6.00 q, 8.42 t (7) 6.05 q, 8.43 t	2.62	2.50
11	$(CH_3)_2N$	p-$CH_3OC_6H_4$	H	326 (4.01), 292 (4.12), 256 (4.10)	6.33 6.38	2.75	2.47 d, 2.88 d (9) 6.03[e]
12	$(C_2H_5)_2N$	p-$CH_3OC_6H_4$	H	330 (3.94), 289 (4.05), 260 (4.06)	5.98 q, 8.40 t (7) 6.03 q, 8.42 t	2.69	2.40 d, 2.80 d (9) 5.97[e]
13	$(CH_3)_2N$	p-HOC_6H_4	H	330 (3.96), 292 (4.11), 261 (4.09)	6.35 6.40	2.78	2.55 d, 2.95 d (9)
14	$(C_2H_5)_2N$	p-HOC_6H_4	H	335 (3.96), 288 (4.12), 264 (4.13)	6.05 q, 8.45 t (7) 6.08 q, 8.47 t	2.78	2.55 d, 2.93 d (9)
15	$(CH_3)_2N$	p-$NO_2C_6H_4$	H	323 (4.32), 255 (3.96), 223 (4.32)	6.27 6.32	2.27	1.60 d, 2.11 d (9)
16	$(C_2H_5)_2N$	p-$NO_2C_6H_4$	H	326 (4.33), 256 (3.95), 225 (4.21)	5.95 q, 8.38 t (7) 5.98 q, 8.40 t	2.28	1.60 d, 2.13 d (9)

[a] Measurements were made in 95% ethanol except where otherwise indicated, using the Cary Model 14 recording spectrophotometer. [b] Proton magnetic resonance spectra were examined in trifluoroacetic acid at concentrations between 6 and 8% w./v. at *ca.* 25°. Where compounds were unstable in this solvent, deuterated 70% perchloric acid was used. Spectral measurements were made with a Varian A-60 spectrophotometer operating at 60 Mc./sec. Chemical shifts are recorded on the frequency independent τ-scale relative to an internal tetramethylsilane reference. When 70% perchloric acid was used as the solvent, it was convenient to calculate chemical shifts by using the perchloric acid proton signal (570 cycles downfield from tetramethylsilane) as the internal reference; values recorded, however, are relative to tetramethylsilane. Spin–spin coupling values (J) are in cycles per second measured on the 500-c.p.s. scale. Unless otherwise indicated, values refer to singlet absorptions; for multiple signals the following abbreviations have been used: d = doublet, t = triplet, q = quartet, m = multiplet. [c] Spectra measured in 70% perchloric acid. [d] Approximation; complex multiplet in this range (see Fig. 1a). [e] Absorption due to the *para* substituent.

represented the ten protons of the two aromatic nuclei, and the signal at lower field strength, the lone C-5 proton. Since the resonance of the 2,4-diphenyl derivative is restricted to the equivalent forms of III, τ 1.25 can be taken as the chemical shift to be expected of a proton attached directly to the positively charged dithiolium ring. The dimethylamino protons of 2-dimethylamino-4-phenyl-1,3-dithiolium cation (VI, R = C_6H_5) occurred as two closely spaced peaks at τ 6.35 and 6.30, each integrating for three protons, while the signals arising from the dithiolium and phenyl protons were found at τ 2.63 and 2.47, respectively (Fig. 1b). We suggest that this upfield shift of the dithiolium proton signal is a measure of the increased diamagnetic shielding introduced by the existence of the resonance state VIa in which the positive charge is further removed from the proton in question. The n.m.r. spectra of twelve other dialkylamino derivatives are in accord with this conclusion; in every instance the C-5 proton signals appeared at higher field strength than in the case of the 2,4-diphenyl compound (*cf.* Fig. 1). Variations in the position of the dithiolium and aryl protons within the dialkylamino series appears to be a result of changes in diamagnetic shielding caused by the effect of the *para* aryl substituents.[16] Thus, electron-donating groups were found to increase the shielding in the order OH > OCH_3 > CH_3 > H ≥ Cl (*cf.* Fig. 1c and Table III), while the electron-withdrawing substituent NO_2 reduced the shielding effect (Fig. 1d). It is important to note that variations in the dialkyl proton signals are much less, and we attribute this to their closer proximity to the positive charge (VIa–c) and greater distance from the *para* substituent.

The preparation of 1,3-dithiolium derivatives without stabilizing aryl substituents introduces some interesting chemistry. For example, 2-dimethylamino-4-methyl-1,3-dithiolium perchlorate [III, R = $(CH_3)_2N$; R′ = CH_3] possessed the unusual property that its salts were only characterized as the monohydrate and

(16) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, Chapter 4.

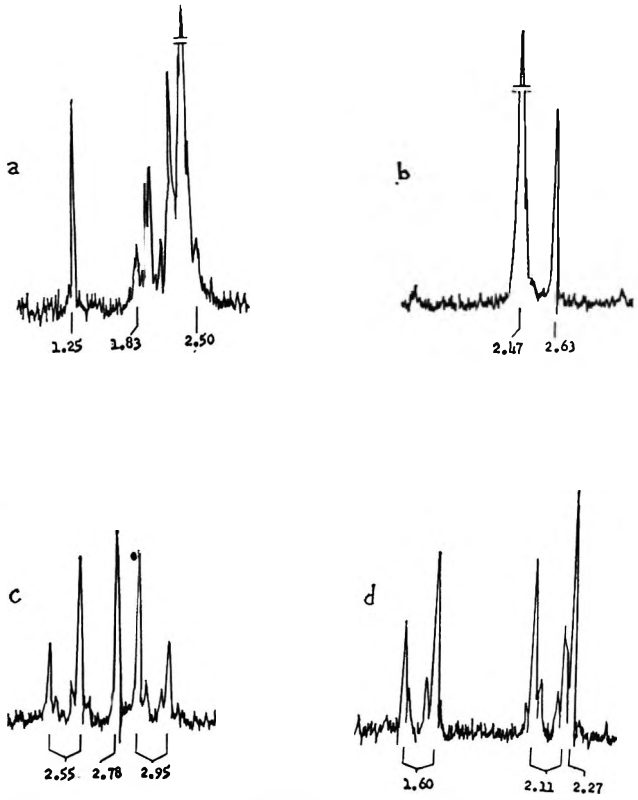
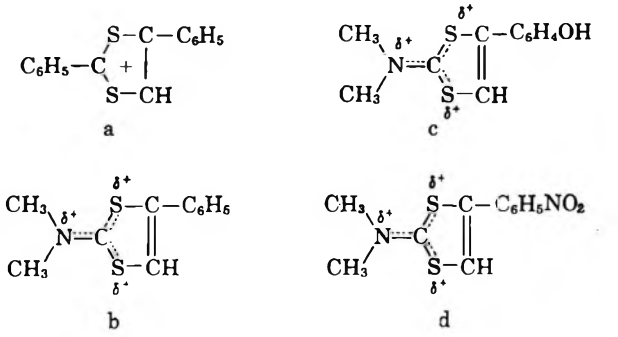


Fig. 1.—N.m.r. spectra showing the signals of the dithiolium and 4-aryl substituent protons measured in trifluoroacetic acid (see a–d below).



as the monoethanolate but could not be obtained free of solvent of crystallization. They were stable in aqueous solution of perchloric acid, but, if their solutions were neutralized to pH 4, ring cleavage occurred to yield the acetonyl N,N-dimethyldithiocarbamate [I, R = $(CH_3)_2N$; R′ = CH_3] from which they had been prepared. Their n.m.r. spectra (Fig. 2a) run in 70% perchloric acid showed the 4-methyl protons as a doublet (τ 8.03) spin coupled (J = 2 c.p.s.) through four bonds to the quartet signal (τ 3.50) from the adjacent C-5 proton. This olefinic-type character of the C-4–C-5 double bond[17] became of greater significance when the spectra of the solvated salts were measured in trifluoroacetic acid (Fig. 2b). Primarily the decoupling of the C-4 methyl and C-5 protons, and the disappearance of the low-field signal suggested that the C-4–C-5 unsaturation no longer existed. In addition, two new coupled signals integrating for two protons appeared at τ 5.76 and 5.93.

(17) Numerous examples showing similar 1,4-coupling of vinyl and allyl hydrogen atoms are given by N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, Varian Associates High Resolution N.M.R. Spectra Catalogue, Varian Associates, Palo Alto, Calif.

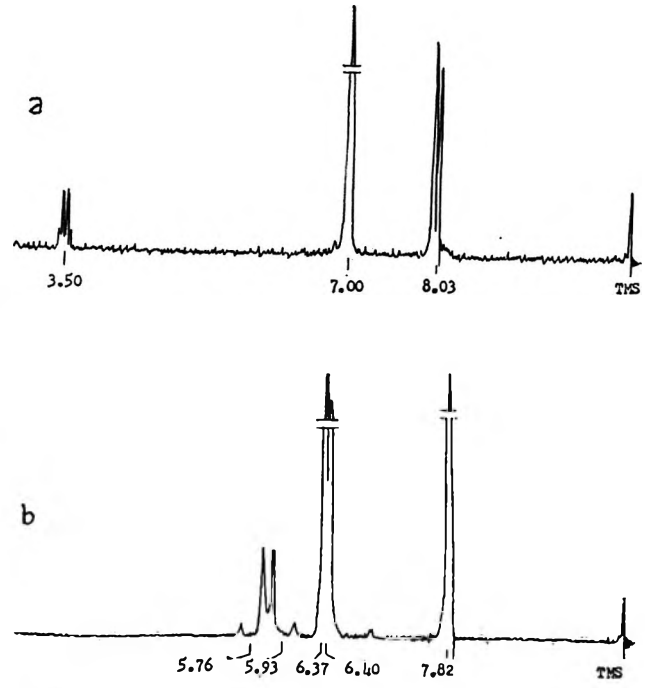
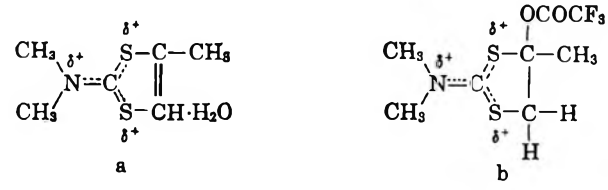


Fig. 2.—N.m.r. spectra of 2-dimethylamino-4-methyl-1,3-dithiolium perchlorate: (a) monohydrate measured in 70% deuterated perchloric acid; (b) in trifluoroacetic acid.



The characteristic shape of these features was typical of nonequivalent methylene protons splitting each other with a coupling constant (J = 13 c.p.s.) very nearly the same magnitude as their separation (17 c.p.s.)[15] This evidence is compatible with a structure in which normal addition of the trifluoroacetic acid solvent to the C-4–C-5 double bond had occurred. 4,5-Dimethyl-2-dimethylamino- and 2-dimethylamino-4-ethyl-5-methyl-1,3-dithiolium perchlorates (Table I and III, compounds **3** and **4**) likewise could only be isolated as monohydrates and showed evidence of trifluoroacetic acid addition to the C-4–C-5 double bond. Attempts to isolate these adducts have so far been unsuccessful.

2-Dimethylamino-4-methyl-1,3-dithiolium perchlorate monohydrate was also observed to undergo a deuterium exchange in the process of recrystallization from 10% perchloric acid in deuterium oxide. The physical properties of the salt did not alter after this exchange, but the n.m.r. spectra no longer showed the C-5 proton signal and the protons of the methyl substituent then appeared as one peak. This exchange probably occurs *via* hydration or hydrolysis of the ring by deuterium oxide, followed by elimination of deuterium hydroxide or recyclization of deuterated I.

In view of these results, the question arises as to whether these salts are really solvated in their solid state or whether in actual fact they are not the 4-hydroxy- and 4-ethoxydithiolan derivatives [II, R = $(CH_3)_2N$] which are postulated as intermediates in the dithiolium synthesis. Unquestionably the n.m.r. spectra of these 4-alkyl derivatives show that

they exist as dithiolium salts in 70% perchloric acid, but it appears that the addition of water, ethanol, or reagents such as trifluoroacetic acid to the C-4–C-5 bond, as well as ring cleavage, may be facile and reversible reactions.

Experimental[18]

Phenacyl Dithiobenzoate.—Dithiobenzoic acid[19] (5.1 g.) in ether (90 ml.) was neutralized by the addition of sodium ethoxide solution (sodium, 0.76 g., to ethanol, 20 ml.). Phenacyl chloride (5.1 g.) in ether (30 ml.) was added dropwise and the mixture refluxed for 30 min. After the precipitated sodium chloride was removed and the solvent was evaporated, the residue was recrystallized from ethanol (ten parts) to give phenacyl dithiobenzoate as a brick red solid (compound 1, Table II).

β-Keto N,N-Dimethyl- and N,N-Diethyldithiocarbamates.—Compounds 2–16, Table II, were prepared by the following general method. The phenacyl or acetonyl halide (0.05 mole) dissolved in a minimum of cold ether (or acetone) was added dropwise to a solution of the sodium N,N-dialkyldithiocarbamate (0.055 mole) in ethanol (20 ml.) under reflux. After 30 min., the solvent was removed *in vacuo*, the oily residue was washed with water until crystallization occurred, and the ester was recrystallized from ethanol.

2,4-Diphenyl-1,3-dithiolium Salts. Chloride.[3,4]—Dry hydrogen chloride and hydrogen sulfide were passed simultaneously into a chilled (0–5°) solution of phenacyl dithiobenzoate (0.68 g.) in ether (50 ml.) for 3 hr. After a further 48 hr. at room temperature, the pale yellow-green **2,4-diphenyl-1,3-dithiolium** chloride (62%), m.p. 134–136°, was collected and recrystallized from 3:1 ethyl acetate–ethanol mixture (56 parts) by the further addition of ethanol (150 parts).

Anal. Calcd. for $C_{15}H_{11}ClS_2$: C, 61.95; H, 3.81; S, 22.05. Found: C, 61.75; H, 4.0; S, 21.9.

Perchlorate. A.—70% Perchloric acid (5 ml.) was added to phenacyl dithiobenzoate (0.5 g.) and the mixture gently was heated on the steam bath until solution had occurred (1 min.). The yellow-green product (74%) obtained on chilling the solution was recrystallized from ethanol (220 parts) and had m.p. 207–209°, lit.[4] m.p. 209–209.5°.

B.—The dithiolium chloride was dissolved in ethanol (ten parts) and treated dropwise with 70% perchloric acid until precipitation of the perchlorate was complete. Recrystallized as in A, the product had m.p. 207–209°, undepressed on admixture with the previous specimen.

2-Dimethylamino- and 2-Diethylamino-1,3-dithiolium Perchlorates.[20]—Compounds in Table I were prepared by the following general method. The β-keto N,N-dialkyldithiocarbamate (0.005 mole, *ca.* 1 g.) was dissolved in the minimum of 70% perchloric acid (usually one–three parts). In many instances, ensuing heat of reaction was sufficient to cause dissolution; at other times the mixture had to be warmed on the steam bath for up to 5 min. to complete the reaction. Dithiolium perchlorate was obtained by chilling and triturating with cold water (three parts) or ethyl acetate. Absolute ethanol was the usual solvent for recrystallization, but the exceptions in Table I should be noted.

Partially Deuterated 70% Perchloric Acid.—Anhydrous perchloric acid[21] (62 g.) was diluted with 99.5% deuterium oxide to 100 ml. The excess heavy water was distilled until the temperature of the distillate reached the boiling point of the 70% azeotrope (203° at 760 mm.). The residual liquid was used, where indicated, as a solvent for n.m.r. measurements and was free of spectral detail until 570 cycles downfield from the tetramethylsilane reference.

Acknowledgment.—It is a pleasure to acknowledge the helpful discussions we have had with our colleague Dr. Walter Meyer concerning the interpretation of the n.m.r. measurements. We are also grateful for some technical assistance given by Talmage Bosin (National Science Foundation Undergraduate Research Participant) during the 1962 summer semester.

(18) All melting points were determined in soft glass capillaries using a Mel-Temp heated-block apparatus and are corrected. Analyses were performed by the Midwest Microlab, Inc., Indianapolis, Ind.

(19) F. Block, *Compt. rend.*, **204**, 1342 (1937).

(20) The inherent danger of an explosion occurring when organic compounds are treated with perchloric acid required the conscientious use of safety screens and face masks. No spontaneous explosions were experienced with the compounds reported in this paper, but, in a related series, two such accidents occurred while using the same experimental procedure. For this reason, all reactions have been limited to relatively small quantities and treated with the utmost care. Attempts were made, as part of a safety program, to induce the 2-dialkylamino-1,3-dithiolium perchlorate derivatives to explode by (a) heating above their melting point, (b) admixing with 70% perchloric acid and heating to dryness, and (c) mechanical grinding with carborundum chips. Only 4-methyl-2-dimethylamino-1,3-dithiolium perchlorate monohydrate (VI, R = CH_3) could be detonated and by b only.

(21) G. F. Smith, *J. Am. Chem. Soc.*, **75**, 184 (1953).

Dithiolium Derivatives. II. Some New 1,3-Dithiolium Perchlorates[1]

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Contribution No. 1202 from the Chemistry Laboratories of Indiana University, Bloomington, Indiana 47405

Received July 8, 1963

The action of 70% perchloric acid on β-keto S-methyltrithiocarbonates and β-keto O-ethyldithiocarbonates is described. Dithiolium derivatives have been obtained from the trithiocarbonate intermediates. The synthesis of some 4-hydroxyl-1,3-dithiolium perchlorates from appropriate carboxymethyl, carbethoxymethyl, and carbamidomethyl esters is also described, and the ultraviolet and nuclear magnetic resonance spectral characteristics of these new compounds are discussed.

The reports[4,5] of unsuccessful attempts to convert β-keto O-ethyldithiocarbonates and β-keto S-methyltrithiocarbonates into 1,3-dithiolium derivatives have prompted us to try the use of 70% perchloric acid to effect this ring closure. These conditions have recently been used with success in the synthesis of 2-dialkylamino-1,3-dithiolium perchlorates.[6] In this manner, phenacyl methyl trithiocarbonate (I, R = CH_3S; R′ = C_6H_5) and *p*-nitrophenacyl methyltrithiocarbonate (I, R = CH_3S; R′ = *p*-$NO_2C_6H_4$) were converted smoothly into 2-methylthio-4-phenyl-1,3-dithiolium perchlorate (IIa, R = CH_3S; R′ = C_6H_5) and 2-methylthio-4-(*p*-nitrophenyl)-1,3-dithiolium perchlorate (IIb, R = CH_3S; R′ = *p*-$NO_2C_6H_4$), respectively, but no product could be isolated after acetonyl methyltrithiocarbonate (I, R = CH_3S; R′ = CH_3) was similarly treated.

(1) This research was supported by a grant from the Petroleum Research Fund, administered by the American Chemical Society. We gratefully acknowledge this support.

(2) A portion of the work described is from the forthcoming Ph.D. thesis of R. D. H.

(3) American Chemical Society Petroleum Research Fund Postdoctoral Fellow, 1962–1963.

(4) D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc.*, 252 (1960).

(5) D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *J. Chem. Soc.*, 5104 (1962).

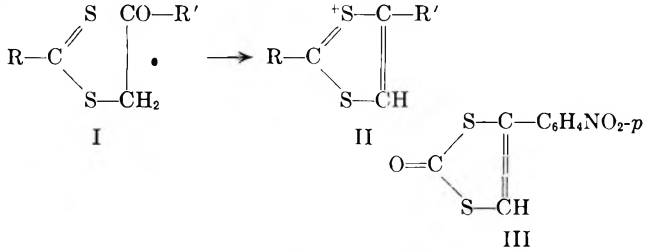
(6) E. Campaigne and N. W. Jacobsen, *J. Org. Chem.*, **29**, 1703 (1964).

TABLE I

ULTRAVIOLET AND N.M.R. DATA

Compound	Ultraviolet,[a] λ_{max} mμ (log ε)	N.m.r.[b] signals of substituents at C-2	C-4	C-5
IIa	373 (4.14), 282 (3.89), 240 (4.27)	6.72	2.27 m	1.47
IIb	368 (4.36), 315 (3.90), 268 (3.98), 232 (4.19)	6.70	1.52 d 2.02 d (9)[d]	1.27
IIc	367 (4.18), 275 (3.47), 244 (3.51)	1.90–2.32 m		2.07
IId	242 (4.19)	6.22		5.08
IIe	305 (4.20), 221 (3.29)	6.60		4.80
III	335 (4.14), 243 (4.03)[c]		1.75 d 2.35 d (9)[d]	2.80

[a] Measurements were made in 70% perchloric acid except where otherwise indicated, using the Cary Model 14 recording spectrophotometer. [b] Proton magnetic resonance spectra were determined in trifluoroacetic acid at concentrations between 6–8% w./v. at about 25°, using a Varian A-60 spectrometer operating at 60 Mc./sec. Chemical shifts are recorded on the frequency independent τ-scale relative to an internal tetramethylsilane reference. Unless otherwise indicated, values refer to singlet absorptions; for multiple signals the following abbreviations have been used: d = doublet, m = multiplet. [c] Spectra were measured in 95% ethanol. [d] Spin–spin coupling values (J) are in parentheses; values are in cycles per second measured on the 500-c.p.s. scale.



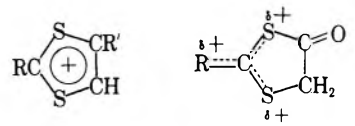
I II III

IIa, R = CH_3S; R′ = C_6H_5
b, R = CH_3S; R′ = p-$NO_2C_6H_4$
c, R = C_6H_5; R′ = OH
d, R = $(CH_3)_2N$; R′ = OH
e, R = CH_3S; R′ = OH

The reaction of a series of β-keto O-ethyldithiocarbonates (I, R = OEt; R′ = p-$NO_2C_6H_4$, p-ClC_6H_4, p-BrC_6H_4, p-$CH_3C_6H_4$, p-HOC_6H_4) with perchloric acid was also investigated but much decomposition occurred and in most cases no product was isolated. S-(p-Nitrophenacyl) O-ethyl dithiocarbonate, however, yielded an insoluble product which was shown to be 2-oxo-4-(p-nitrophenyl)-1,3-dithiole (III) on the basis of analysis and infrared and n.m.r. spectroscopy.

Hitherto, such acid-catalyzed cyclizations of β-keto dithio esters of type I (where R = alkyl, aryl, or dialkylamino and R′ = alkyl or aryl) have been the most convenient method for the synthesis of 1,3-dithiolium salts[4–6] but have restricted substituents in position 4 to alkyl or aryl groups. In an attempt to introduce other groups at this position of the hetero ring, we have investigated the reaction of carboxymethyl (I, R′ = OH), carbethoxymethyl (I, R′ = OEt), and carbamidomethyl (I, R′ = NH_2) dithio esters with perchloric acid. Such esters of N,N-dimethyldithiocarbamic acid all gave 2-dimethylamino-4-hydroxy-1,3-dithiolium perchlorate [IId, R = $(CH_3)_2N$; R′ = OH] in high yield. This hydroxydithiolium perchlorate was found to be stable in the crystalline state and in nonhydroxylic solvents, but in water and ethanol it was converted almost quantitatively back into its carboxymethyl and carbethoxymethyl precursors, respectively. In a similar manner, carboxymethyl dithiobenzoate (I, R = C_6H_5; R′ = OH) gave 4-hydroxy-2-phenyl-1,3-dithiolium perchlorate (IIc, R = C_6H_5; R′ = OH), and carboxymethyl methyl trithiocarbonate (I, R = CH_3S; R′ = OH) gave 4-hydroxy-2-methylthio-1,3-dithiolium perchlorate (IIe, R = CH_3S; R′ = OH). These perchlorates were even less stable than the dialkyl analogs, but their decomposition products are yet unknown.

The ultraviolet spectra of IIa, IIb, and IIc show the long wave-length absorption which has been reported for other alkyl and aryl analogs.[5,6] In contrast, however, IId and IIe are optically transparent in this region and, as well, show less of other spectral features (see Table I). An explanation of this is seen from a comparison of the n.m.r. spectra of these compounds when measured in 70% perchloric acid or in trifluoroacetic acid. Those salts exhibiting the long wave-length ultraviolet absorption (IIa, IIb, and IIc) showed the lone C-5 proton signal at low-field strength (τ 1.47, 1.27, and 2.07, respectively) in the region previously reported for dithiolium hetero ring protons,[6] and so must exist in form IV. The colorless dithiolium salts IId and IIe on the other hand showed no single proton signal in this low-field region, but instead they each gave a signal equivalent to two protons in the methylene region (τ 5.08 and 4.80, respectively). Clearly therefore, in these solvents IId and IIe must exist predominantly in the keto form, V.



IV V

That the C-5 proton signal of IIa occurs at τ 1.47 while the C-5 proton signal of IIb occurs downfield at τ 1.27 is attributed to the decrease in diamagnetic shielding caused by the electron-withdrawing p-nitro substituent. Variation of position of the methyl protons of these derivatives is slight (τ 6.72 and 6.70, respectively), indicating their closer proximity to the positive charge and greater distance from the *para* substituent.

Experimental[7]

2-Methylthio-4-phenyl-1,3-dithiolium Perchlorate (IIa).—Phenacyl methyltrithiocarbonate[5] (1 g.) was reacted with 70% perchloric acid (3 ml.) at 100° for 5 min. The solution was chilled and ethyl acetate (5 ml.) was added to yield IIa (93%). Recrystallized from 70% perchloric acid (three parts) by the addition of ethyl acetate (six parts), it had m.p. 126–127°.

Anal. Calcd. for $C_{10}H_9ClO_4S_3$: C, 36.95; H, 2.8; S, 29.6. Found: C, 37.0; H, 2.95; S, 29.5.

(7) All melting points were determined in soft-glass capillaries using a Mel-Temp heated block apparatus and are corrected. Analyses were performed by the Midwest Microlab, Inc., Indianapolis, Ind.

TABLE II

PREPARATION OF β-KETO O-ETHYLDITHIOCARBONATES (I)

				Analysis, %					
				C		H		S	
R′	% yield	M.p., °C.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
p-BrC_6H_4	85	81–82	$C_{11}H_{11}BrO_2S_2$					20.1	19.9
p-$CH_3C_6H_4$	89	86–87	$C_{12}H_{14}O_2S_2$	56.7	56.7	5.55	5.6	25.2	25.3
p-HOC_6H_4	76	123–124	$C_{11}H_{12}O_3S_2$	51.5	51.6	4.7	4.8	25.0	24.8

2-Methylthio-4-(*p*-nitrophenyl)-1,3-dithiolium Perchlorate (IIb).—*p*-Nitrophenacyl methyltrithiocarbonate (1 g.) and 70% perchloric acid (1.5 ml.) were heated at 100° for 30 min. Addition of ethyl acetate (15 ml.) to the cooled solution gave IIb (75%). After recrystallization from 70% perchloric acid (three parts) by the addition of ethyl acetate (five parts), the heat-sensitive material was dried at room temperature under high vacuum and had m.p. 179–181°.

Anal. Calcd. for $C_{10}H_8ClNO_6S_3$: C, 32.5; H, 2.2; S, 26.0. Found: C, 32.5; H, 2.0; S, 26.0.

S-(*p*-Chlorophenacyl) O-Ethyldithiocarbonate.—A mixture of potassium ethyl xanthate (8 g., 0.05 mole) and *p*-chlorophenacyl chloride (9.5 g., 0.05 mole) in 50% ethanol (150 ml.) was heated on a steam bath until solution was complete (15 min.). The product (87%, m.p. 69–70°) which separated on cooling was recrystallized from *n*-hexane or ethanol.

Anal. Calcd. for $C_{11}H_{11}ClO_2S_2$: C, 48.1; H, 4.0; S, 23.35. Found: C, 48.3; H, 4.2; S, 23.3.

Other analogs prepared by this method are listed in Table II.

2-Oxo-4-(*p*-nitrophenyl)-1,3-dithiole (III).—S-(*p*-Nitrophenacyl) O-ethyldithiocarbonate[8] (2 g.) in 70% perchloric acid (5 ml.) was warmed on a steam bath for 5 min. III crystallized from the hot solution as a yellow solid (73%) and after recrystallization from ethanol (150 parts) had m.p. 205–208°.

Anal. Calcd. for $C_9H_5NO_3S_2$: C, 45.2; H, 2.1; S, 26.8. Found: C, 45.3; H, 2.25; S, 26.6.

4-Hydroxy-2-phenyl-1,3-dithiolium Perchlorate (IIc).—Carboxymethyl dithiobenzoate[9] (1 g.) was heated with 70% perchloric acid (3 ml.) at 100° for 15 min. The solution was chilled and ethyl acetate (3 ml.) was added to induce the product (79%) to crystallize. IIc, an unstable yellow salt, m.p. 129–132° dec., was recrystallized from 70% perchloric acid (two parts) by the addition of ethyl acetate (three parts).

Anal. Calcd. for $C_9H_7ClO_5S_2$: C, 36.65; H, 2.4; S, 21.75. Found: C, 36.65; H, 2.55; S, 21.5.

2-Dimethylamino-4-hydroxy-1,3-dithiolium Perchlorate[10] (IId).

A.—Carboxymethyl N,N-dimethyldithiocarbamate[11,12] (0.5 g.) was warmed with 70% perchloric acid (1 ml.) for 15 min. On cooling, ethyl acetate (3 ml.) was added and the perchlorate (98%) was collected. Recrystallized from 70% perchloric acid (two parts) by the addition of ethyl acetate (20 parts), IId had m.p. 172–173°.

Anal. Calcd. for $C_5H_8ClNO_5S_2$: C, 22.95; H, 3.05; S, 24.5. Found: C, 23.1; H, 3.05; S, 24.2.

B.—Carbamidomethyl N,N-dimethyldithiocarbamate[13] (1 g.) and 70% perchloric acid (2 ml.) were heated at 100° for 1 min. The product (95%) was isolated and recrystallized as above and had m.p. 172° unchanged on admixture with IId (above).

C.—Carboethoxymethyl N,N-dimethyldithiocarbamate[11,13] (1 g.) and 70% perchloric acid (2 ml.) were heated at 100° for 5 min. The product (98%, m.p. 172–173°) was also identical with the perchlorates obtained by methods A and B.

Compound IId was unstable in water and alcohol. Recrystallized from the former (ten parts), a quantitative yield of carboxymethyl N,N-dimethyldithiocarbamate (m.p. 149°[11,12]) was obtained. Refluxed in ethanol and then recrystallized from 50% aqueous ethanol (six parts), IId was converted into carbethoxymethyl N,N-dimethyldithiocarbamate (m.p. 60–62°[11,13]) in high yield.

4-Hydroxy-2-methylthio-1,3-dithiolium Perchlorate[10] (IIe).—Carboxymethyl methyltrithiocarbonate (1 g.) dissolved in 70% perchloric acid (3 ml.) was heated on a steam bath for 3 min. Crystallization of IIe (31%) was induced by chilling in a Dry Ice and alcohol mixture and the addition of ethyl acetate (4 ml.). The unstable product (m.p. 97–98°) was recrystallized from 70% perchloric acid (three parts) by the addition of ethyl acetate (five parts).

Anal. Calcd. for $C_4H_5ClO_5S_3$: C, 18.15; H, 1.9; S, 36.35. Found: C, 18.25; H, 2.1; S, 36.4.

Carboxymethyl Methyltrithiocarbonate.—Chloracetic acid (10.6 g.) in ethanol (100 ml.) was added to a cold (0°) solution of sodium methyltrithiocarbonate[5] (0.115 mole) in ethanol (100 ml.). After 1 hr. at room temperature, the precipitated salt was removed and the solution was evaporated. An extract of the residual oil in ether (100 ml.) was washed with water (10 ml.), dried (magnesium sulfate), and evaporated to yield carboxymethyl methyltrithiocarbonate (24%). Recrystallized from *n*-hexane (200 parts), it had m.p. 75–76°.

Anal. Calcd. for $C_4H_6O_2S_3$: C, 26.35; H, 3.3; S, 52.75. Found: C, 26.5; H, 3.3; S, 53.0.

Acetonyl Methyltrithiocarbonate.—Chloracetone (9.3 ml.) in ethanol (100 ml.) was added to a solution of sodium methyltrithiocarbonate[5] (0.115 mole) in ethanol (100 ml.) at 0°. After stirring for 1 hr. at room temperature, the mixture was poured into water (300 ml.) and the product (53%) was extracted with ether and distilled (b.p. 109–110° at 1.5 mm.).

Anal. Calcd. for $C_5H_8OS_3$: C, 33.3; H, 4.45; S, 53.35. Found: C, 33.35; H, 4.5; S, 53.5.

***p*-Nitrophenacyl Methyltrithiocarbonate.**—*p*-Nitrophenacyl bromide (12.2 g., 0.05 mole) suspended in ethanol (150 ml.) was added with stirring to a solution of sodium methyltrithiocarbonate[5] (0.05 mole) at −40°. The mixture was allowed to warm to room temperature, stirred an additional 2 hr., and then poured into water (1.5 l.). The yellow solid was collected (11.8 g., 85%) and recrystallized twice from alcohol, and melted at 100–102°.

Anal. Calcd. for $C_{10}H_9NO_3S_3$: C, 41.8; H, 3.2; S, 33.5. Found: C, 41.9; H, 3.0; S, 33.5.

(8) W. E. Parham, E. T. Harper, and R. S. Berger, *J. Am. Chem. Soc.*, **82**, 4932 (1960).

(9) A. Kjaer, *Chem. Abstr.*, **45**, 6160 (1951).

(10) Integration of the n.m.r. spectrum revealed that, when dissolved in 70% perchloric acid or trifluoroacetic acid, this compound exists predominantly in the 4-oxo form.

(11) K. Bodendorf, *Chem. Abstr.*, **24**, 3221 (1930).

(12) K. A. Jenson, *J. prakt. Chem.*, **159**, 189 (1941).

(13) G. Nachmias, *Ann. Chem.*, **7**, 584 (1952).

Dithiolium Derivatives. III.[1] Reactions of the 2-Methylthio-4-Substituted 1,3-Dithiolium Cation[2]

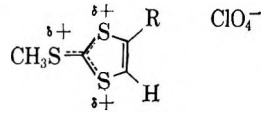
E. CAMPAIGNE AND R. D. HAMILTON[3]

Contribution No. 1203 from the Chemistry Laboratories, Indiana University, Bloomington, Indiana 47405

Received December 2, 1963

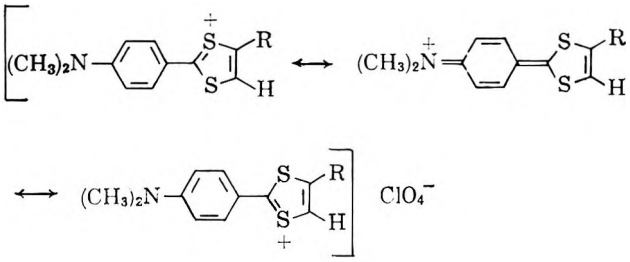
The electrophilic character of the 2-methylthio-4-substituted 1,3-dithiolium cation is demonstrated by condensations with dimethylaniline and with active methylene compounds. Spectral characteristics of the products are discussed. Application of sulfuric acid in the cyclodehydration of β-keto N,N-dialkyl dithiocarbamates, β-keto dithiobenzoates and β-keto methyltrithiocarbonates affords the corresponding 1,3-dithiolium hydrogen sulfates.

The pseudoaromatic 2-methylthio-4-substituted 1,3-dithiolium salts (4-substituted "iso-trithionium salts")[4] have been shown to exist as the charge delocalized species **1** on the basis of n.m.r. and ultraviolet spectral data.[1a] Analogous to these compounds are the 3-



1a, R = *p*-BrC_6H_4
b, R = C_6H_5
c, R = *p*-$NO_2C_6H_4$

methylthio-1,2-dithiolium salts ("trithionium salts"), in which the charge is also distributed between ring and side chain.[5] The electrophilic center of the 1,3-dithiolium cation has been shown experimentally[6,7] and theoretically[8] to be the C-2 carbon atom. In agreement with these results, it has been found that **1** also exhibits electrophilic behavior, attacking dimethylaniline to give the highly colored 2-(*p*-dimethylaminophenyl)-4-substituted 1,3-dithiolium perchlorates (**2**).



2a, R = *p*-BrC_6H_4
b, R = C_6H_5
c, R = *p*-$NO_2C_6H_4$

These products are readily obtained when **1** is warmed with dimethylaniline in glacial acetic acid for 15–30 min. The intense color of these compounds can be attributed to the large charge separation between the dithiolium resonance forms and the quaternary ammonium dithiol resonance form.[9] The ultraviolet spectral data (Table I) are consistent with this postulate; in a weakly acidic medium, acetic acid, a long wave-length feature in the region 538–540 mμ is observed which can be associated with the quaternary ammonium dithiol resonance form. In 70% perchloric acid, however, protonation of the dimethylamino moiety is possible, thus inhibiting the immonium resonance form and rendering the solution yellow. Klingsberg has reported analogous behavior for some dialkyl aminophenyl-1,2-dithiolium dyes.[9] However, this postulate does not clearly account for the fact that **2** shows the long wave-length absorption (535–538 mμ) in trifluoroacetic acid, since n.m.r. studies indicate protonation of the dimethylamino function in this solvent. Unfortunately, the limited solubility of **2** in acetic acid made comparison of extinction coefficients impossible. Evidence that protonation does occur in trifluoroacetic acid comes from comparison of the chemical shifts of the C-5 proton of 2,4-diphenyl-1,3-dithiolium perchlorate and **2b**, which occur at τ 1.25 and 1.00, respectively. One would expect the dialkyl amino moiety of **2b**—being a strong electron-releasing group ($\sigma_{para} = -0.60$[10])—to cause the C-5 proton to be more shielded (thus further upfield relative to the C-5 proton of 2,4-diphenyl-1,3-dithiolium perchlorate in neutral solvents). In trifluoroacetic acid, however, protonation of the dialkyl amino substituent produces the strongly electron-attracting quaternary nitrogen group ($\sigma_{para} \simeq +0.86$[10]) which shifts the position of the C-5 proton downfield as observed.

That the N-methyl protons of **2** occur as a single resonance peak while those of 2-dimethylamino-4-substituted 1,3-dithiolium perchlorates occur as two peaks indicates that in **2** the distant methyl protons are not sufficiently nonequivalent to be resolved under the conditions of measurement although they might be expected to be nonequivalent due to contributions of the immonium form which produces a barrier to rotation about the C–N bond. This point has been discussed[1b] and has been further confirmed by the synthesis of 2-dimethylamino-4,5-diphenyl-1,3-dithiolium perchlorate (**3**), in which both N-methyl groups are in the same electronic environment in the immonium resonance form; as expected, the n.m.r. spectrum in trifluoroacetic acid shows only two resonance peaks, one occurring at τ 2.62 due to the ten equivalent aro-

(1) (a) Paper II: E. Campaigne, R. D. Hamilton, and N. W. Jacobsen, *J. Org. Chem.*, **29**, 1708 (1964); (b) paper I: E. Campaigne and N. W. Jacobsen, *ibid.*, **29**, 1703 (1964).

(2) This research was supported by a grant from the Petroleum Research Fund, administered by the American Chemical Society. We gratefully acknowledge this support.

(3) Abstracted in part from the forthcoming Ph.D. thesis of R. D. H.

(4) A. Lüttringhaus, E. Futterer, and H. Prinzbach, *Tetrahedron Letters*, 1209 (1963).

(5) (a) J. Teste and N. Lozac'h, *Bull. soc. chim. France*, 437 (1955); (b) A. Lüttringhaus and U. Schmidt, *Chem. Ztg.*, **77**, 135 (1953).

(6) E. Klingsberg, *J. Am. Chem. Soc.*, **84**, 3410 (1962).

(7) L. Soder and R. Wizinger, *Helv. Chim. Acta*, **42**, 1779 (1959).

(8) R. Zahradnik and J. Koutecký, *Tetrahedron Letters*, 632 (1961).

(9) E. Klingsberg and A. M. Schreiber, *J. Am. Chem. Soc.*, **84**, 2941 (1962).

(10) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

TABLE I

SPECTRAL DATA OF 2-DIMETHYLAMINOPHENYL-4-SUBSTITUTED 1,3-DITHIOLIUM PERCHLORATES[a]

Compound	Ultraviolet, λ_{max} mμ (log ε) 70% $HClO_4$	CF_3COOH	HOAc	N.m.r., τ-values (J, c.p.s.) $-N(CH_3)_2$	C-5 proton	—Ar
2a		537 (3.91)	538	6.42	1.03	1.65 d (9)
	395 (4.11)	405 (4.06)				1.95 d
		305 (4.15)				
	284 (4.15)	285 (4.22)				2.20 d (9)
	253 (4.24)	262 (4.18)				230 d
2b		535 (3.70)	538	6.38	1.00	1.62 d (9)
	390 (4.08)	398 (4.08)				1.90 d
		300 (4.03)				2.10–2.42 m
	278 (4.01)	275 (4.09)				
	243 (4.19)					
2c		538 (4.44)	540	6.38	0.80	1.60 d (9)
	375 (4.30)	370 (4.21)				1.93 d
	295 (4.13)	283 (4.25)				
	262 (4.04)	265 (4.22)				1.47 d (9)
	225 (4.11)					1.87 d

[a] See ref. 15.

TABLE II

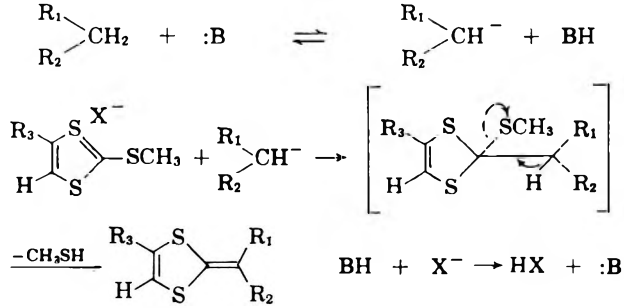
4-SUBSTITUTED 1,3-DITHIOL-2-YLIDENE DERIVATIVES

Compound	Name	% yield	Recrystn. solvent	M.p., °C.	Formula	Analysis, % Calcd. C	H	S	Found C	H	S
4a	4-Phenyl-1,3-dithiol-2-ylidenemalononitrile	67	EtOH–EtOAc	167–168	$C_{12}H_6N_2S_2$	59.48	2.50	26.46	59.29	2.68	26.30
4a	Ethyl 4-phenyl-1,3-dithiol-2-ylidenecyanoacetate	45	Abs. alcohol	131–132	$C_{14}H_{11}NO_2S_2$	58.11	3.83	22.16	58.32	3.85	22.48
4c	3-(4-Phenyl-1,3-dithiol-2-ylidene)pentane-2,4-dione	43	Abs. alcohol	144–146	$C_{14}H_{12}O_2S_2$	60.86	4.35	23.21	60.80	4.32	23.12
4d	Ethyl 4-*p*-bromophenyl-1,3-dithiol-2-ylideneacetoacetate	39	Benzene–cyclohexane	195–197	$C_{15}H_{13}BrO_3S_2$	46.76	3.40	16.64	46.86	3.48	16.79
4e	3-(4-*p*-Bromophenyl-1,3-dithiol-2-ylidene)-pentane-2,4-dione	34	EtOAc	221–223	$C_{14}H_{11}BrO_2S_2$	47.33	3.12	18.05	47.56	3.23	18.20
4f	Ethyl 4-*p*-bromophenyl-1,3-dithiol-2-ylidenecyanoacetate	54	EtOH–EtOAc	229–230	$C_{14}H_{10}BrNO_2S_2$	45.65	2.74	17.41	45.85	2.71	17.83
4g	2-(4-Phenyl-1,3-dithiol-2-ylidene)indane-1,3-dione	77	Benzene–cyclohexane	255–256	$C_{18}H_{10}O_2S_2$	67.05	3.13	19.90	67.03	3.25	19.82

matic protons and one occurring at τ 6.33 due to the six equivalent N-methyl protons.

The aromatic regions of **2a** and **2c** consist of four doublets (A_2B_2); **2b** exhibits two doublets (A_2B_2) and a complex multiplet. In **2b**, the doublets (τ 1.62 and 1.90) are due to the four protons on the 2-*p*-dimethylaminophenyl moiety and the multiplet is due to the 4-phenyl substituent. By analogy, the doublets of **2a** and **2c** (τ 1.65, 1.95 and τ 1.60, 1.93, respectively) can be assigned to the 2-*p*-dimethylaminophenyl substituent, and the other A_2B_2 patterns assigned to the 4-*p*-bromophenyl and 4-*p*-nitrophenyl functions, respectively.

The 2-methylthio-4-substituted 1,3-dithiolium cation was allowed to react with several active methylene compounds in order to demonstrate further its electrophilic properties. The reaction was carried out in boiling glacial acetic acid in the presence of pyridine, and may be considered as a nucleophilic attack of the active methylene carbanion on the electron deficient C-2 site of **1**; subsequent elimination of methyl mercaptan gives the product.

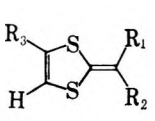


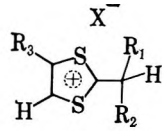
This general reaction has been applied to several substituted 3-methylthio-1,2-dithiolium salts,[11,12] and more recently to a substituted 2-methylthio-1,3-dithiolium salt[4] using much milder conditions than those described here. The products (**4**), 4-substituted 1,3-dithiol-2-ylidene derivatives,[13] are formed in yields of 34–77% (Table II).

(11) U. Schmidt, R. Scheuring, and A. Lüttringhaus, *Ann.*, **630**, 116 (1960).

(12) Y. Mollier and N. Lozac'h, *Bull. soc. chim. France*, 157 (1963).

(13) This class of compounds has been conveniently termed "1,4-dithiafulvenes" by W. Kirmse and L. Horner [*Ann.*, **614**, 4 (1958)].

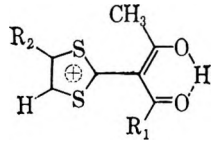




5

4a, $R_1 = R_2 = CN$; $R_3 = C_6H_5$[4]
b, $R_1 = CN$; $R_2 = CO_2Et$; $R_3 = C_6H_5$
c, $R_1 = R_2 = COCH_3$; $R_3 = C_6H_5$
d, $R_1 = COCH_3$; $R_2 = CO_2Et$; $R_3 = p\text{-}BrC_6H_4$
e, $R_1 = R_2 = COCH_3$; $R_3 = p\text{-}BrC_6H_4$
f, $R_1 = CN$; $R_2 = CO_2Et$; $R_3 = p\text{-}BrC_6H_4$
g, R_1 and R_2 = -o-COC_6H_4CO—; $R_3 = C_6H_5$

In a strongly acidic medium it is possible for these compounds to exist in the 1,3-dithiol form (**4**) or in the protonated 1,3-dithiolium form (**5**), depending on their relative basicities. Comparison of the n.m.r. chemical shift data of the C-5 proton of these compounds in trifluoroacetic acid (Table III) suggests that **4c** and **4e** (τ 1.88 and 2.08, respectively) exist as the protonated • charge-delocalized species **6a** and **6b**,



6a, $R_1 = CH_3$; $R_2 = C_6H_5$
b, $R_1 = CH_3$; $R_2 = p\text{-}BrC_6H_4$

respectively, in which additional stabilization can result from hydrogen bonding with the carbonyl function. The derivatives **4a**, **4b**, and **4f**, being less basic, are apparently not protonated and thus exhibit the C-5 proton resonance upfield at τ 2.73, 2.72, and 2.75, respectively, whereas the C-5 proton resonance in **4d** occurs at an intermediate value, τ 2.22. The chemical shift of the C-5 proton of 2-(4-phenyl-1,3-dithiol-2-ylidene)indane-1,3-dione (**4g**) could not be discerned as its position was obscured in the aromatic region (τ 2.28–2.65).

TABLE III

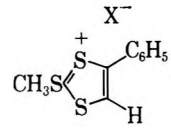
SPECTRAL DATA OF 4-SUBSTITUTED 1,3-DITHIOL-2-YLIDENE DERIVATIVES[a]

Compound	Ultraviolet, λ_{max} mμ (log ε) THF[b]	CF_3COOH	N.m.r. (J, c.p.s.) signals of substituents at C-4	C-5	C-2
4a	380 (4.18)	383 (4.37)	2.50	2.73	
	243 (3.99)				
4b	380 (4.39)	383 (4.44)	2.37	2.72	5.55 q
					8.55 t
4c	390 (4.42)	388 (4.36)	2.30–	1.88	7.20
	243 (4.20)	275 (4.23)	2.47 m		
4d	384 (4.49)	390 (4.31)	2.43 d (9)	2.22	7.18
	245 (4.40)		2.57 d		5.43 q
					8.47 t
4e	389 (4.42)	388 (4.28)	2.40 d (9)	2.08	7.15
	243 (4.32)	280 (4.15)	2.50 d		
4f	382 (4.43)	378 (4.56)	2.42 d (9)	2.75	5.55 q
	247 (4.31)		2.58 d		8.55 t
4g	425 (4.43)	420 (4.60)	2.28– 2.65 m	...	2.28– 2.65 m
		300 (4.21)			
		258 (4.37)			

[a] See ref. 15. [b] THF = tetrahydrofuran.

That **4c** and **4e** are protonated in trifluoroacetic acid is also manifested in the ultraviolet region. In a nonacidic medium such as tetrahydrofuran (THF), all of these compounds (except **4b**) exhibit two absorption peaks, a long wave-length feature occurring at 380–390 mμ and a short wave-length band occurring in the region 243–247 mμ. In trifluoroacetic acid, only the long wave-length absorption (378–390 mμ) can be seen in **4a**, **4b**, **4d**, and **4f**, while **4c** and **4e** show the long wave-length feature and, in addition, exhibit new bands at 275 and 280 mμ, respectively. The appearance of these new bands is probably associated with the 1,3-dithiolium form (**5**) since absorption in this region has previously been observed for some 1,3-dithiolium perchlorates in acid solution.[1a]

During the course of this investigation, it was learned that concentrated sulfuric acid could be used in the conversion of phenacyl methyltrithiocarbonate to 2-methylthio-4-phenyl-1,3-dithiolium hydrogen sulfate (**7**). Although **7** was extremely hygroscopic and could not be isolated in pure form, the impure material was used in some of the condensation reactions. Previous communications from this laboratory described the use of 70% perchloric acid to effect this facile cyclodehydration.[1] Conversion of β-keto N,N-dimethyldithiocarbamates and β-keto dithiobenzoates to 2-dimethylamino- (**8b**) and 2-phenyl- (**9b**) 4-substituted 1,3-dithiolium hydrogen sulfates, respectively, was also achieved using sulfuric acid.



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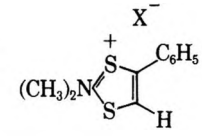
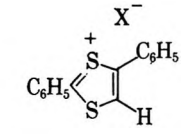


8a, X = ClO_4
b, X = HSO_4
c, X = BF_4
d, X = I
e, X = SCN
f, X = $(NO_2)_3C_6H_2O$



9a, X = ClO_4
b, X = HSO_4
c, X = $(NO_2)_3C_6H_2O$

2-Dimethylamino-4-phenyl-1,3-dithiolium hydrogen sulfate (**8b**) is soluble in water, and addition of another anion (X^-) yields a new water-insoluble 1,3-dithiolium salt in cases where the anion is fluoroborate, iodide, thiocyanate, and picrate. This behavior is analogous to that observed by Klingsberg for the parent 1,3-dithiolium hydrogen sulfate as well as for the 3- and 4-phenyl-1,2-dithiolium hydrogen sulfates.[6,14]

Experimental[15]

2-Dimethylaminophenyl-4-Substituted 1,3-Dithiolium Perchlorates (2a–c).—The general procedure used to prepare these compounds was as follows. To 0.5 g. of **1**[1a] in 20 ml. of glacial acetic acid was added a twofold excess of dimethylaniline, and the mixture was warmed at 100° for 15–30 min. The highly colored solid which separated was collected. **2b** could be re-

(14) E. Klingsberg, *J. Am. Chem. Soc.*, **83**, 2934 (1961).

(15) All melting points were determined in soft-glass capillaries using a Mel-Temp heated block apparatus, and are corrected. Analyses were performed by the Midwest Microlab, Inc., Indianpolis, Ind. All n.m.r. measurements were made in trifluoroacetic acid at concentrations from 6–8% w./v. at about 31°, using a Varian A-60 spectrometer operating at 60 Mc./sec. Chemical shifts are recorded on the frequency independent τ-scale relative to internal tetramethylsilane reference. Spin–spin coupling values (J) are in cycles per second measured on 500-c.p.s. scale. Unless otherwise indicated, values refer to singlet absorptions; for multiple signals the following abbreviations are used: d = doublet, t = triplet, q = quartet, m = multiplet. All ultraviolet measurements were made with the Cary Model 14 recording spectrophotometer in the solvents indicated.

TABLE IV
1,3-DITHIOLIUM SALTS

Compound	% yield	Recrystn. solvent	M.p., °C.	Formula	Analysis, % Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
1a	86	70% $HClO_4$–EtOAc	198–200	$C_{10}H_9BrClO_4S_3$	29.75	2.00	23.83	30.02	2.13	23.84
2a	91	HOAc	240–242	$C_{17}H_{13}BrClNO_4S_2$	42.82	3.18	13.45	42.86	3.26	13.54
2b	86	HOAc	219–220	$C_{17}H_{16}ClNO_4S_2$	51.31	4.05	16.12	51.31	4.41	15.98
2c	84	HOAc	280 dec.	$C_{17}H_{13}ClN_2O_6S_2$	46.10	3.41	14.47	45.95	3.45	14.59
3	91	Abs. alc.	221–222	$C_{17}H_{16}ClNO_4S_2$	51.31	4.05	16.12	51.50	4.06	16.30
8a	87	95% alc.	178–179	[a]						
8b	100	EtOH–EtOAc	232–234	$C_{11}H_{13}NO_4S_3$	41.36	4.10	30.11	41.58	4.24	30.29
8c	82	95% alc.	161–163	$C_{11}H_{12}BF_4NS_2$	42.73	3.91	20.74	43.04	3.99	20.85
8d	74	$CHCl_3$	187–189	$C_{11}H_{12}INS_2$	37.83	3.46	18.36	37.95	3.48	18.27
8e	80	Propanol	163–165	$C_{12}H_{12}N_2S_3$	51.39	4.31	34.30	51.30	4.20	34.51
8f	52	MeOH	178–180	$C_{17}H_{14}N_4O_7S_2$	45.33	3.13	14.24	45.18	3.35	14.18
9b	100	Propanol	173–175	$C_{15}H_{12}O_4S_3$	51.11	3.43	27.29	51.24	3.50	27.22
9c	78	MeOH	197–199	$C_{21}H_{13}N_3O_7S_2$	52.17	2.70	13.26	52.10	2.57	13.18

[a] See ref. 1b.

crystallized from acetic acid. Being more insoluble, **2a** and **2c** were washed twice with boiling acetic acid, dried, and submitted for analysis. See Table IV for experimental details.

4-Substituted 1,3-Dithiol-2-ylidene Derivatives.—Compounds **4a–g** were prepared by the following general method.[12] Two or three grams of one of the 2-methylthio-4-substituted 1,3-dithiolium perchlorates (**4a**, **b**, **d**, **g**) or hydrogen sulfates (**4c**, **e**, **f**) and an equal weight of the active methylene compound were refluxed in 50 ml. of glacial acetic acid containing 1.5 ml. of pyridine for 15–20 hr. The solvent was then removed under reduced pressure, and the residue was extracted twice with 100-ml. portions of hot benzene. The benzene solution was decolorized with Norit and evaporated, affording the adduct, which was recrystallized from the appropriate solvent.

2-Methylthio-4-(*p*-bromophenyl)-1,3-dithiolium Perchlorate (1a).—Three grams of methyl *p*-bromophenacyl trithiocarbonate and 10 ml. of 70% perchloric acid were heated to 100° for 30 min. Addition of 20 ml. of ethyl acetate to the cooled solution gave 3.25 g. (86%) of yellow solid, which was recrystallized from 70% perchloric acid by the addition of ethyl acetate. The ultraviolet spectrum showed $\lambda_{max}^{70\%\ HClO_4}$, mμ (log ε): 375 (4.16); 287 (4.01); 247 (4.29); and 225 (4.11); the n.m.r. spectrum showed τ_{CF_3COOH} 1.53, 2.27 d, 2.43 d (J = 9 c.p.s.), and 6.77.

Methyl *p*-Bromophenacyl Trithiocarbonate.—*p*-Bromophenacyl bromide (13.9 g., 0.05 mole), suspended in 150 ml. of ethanol, was added with stirring to a solution of 0.05 mole of sodium methyl trithiocarbonate[16] at −40°. The mixture was allowed to warm to room temperature, stirred an additional 2 hr., and then poured into 1.5 l. of water. The yellow solid was collected (13.8 g., 87%), and a portion was recrystallized from 95% alcohol. It had m.p. 102–104°.

Anal. Calcd. for $C_{10}H_9BrOS_3$: C, 37.38; H, 2.82; S, 29.94. Found: C, 37.37; H, 2.94; S, 29.85.

α-Phenylphenacyl N,N-Dimethyldithiocarbamate.—α-Chloro-α-phenylacetophenone (4.61 g., 0.02 mole) dissolved in 30 ml. of acetone was added dropwise to a mixture of 3.15 g. (0.022 mole) of sodium N,N-dimethyldithiocarbamate in 35 ml. of refluxing alcohol, and reflux was continued for 30 min. The solvent was evaporated and the oily residue was washed with water several times until crystallization occurred, giving 4 g. (64%) of product. Recrystallization from 95% alcohol gave white needles, m.p. 125–127°; $\lambda_{max}^{95\%\ EtOH}$ 248 mμ (log ε 4.41).

Anal. Calcd. for $C_{17}H_{17}NOS_2$: C, 64.72; H, 5.43; S, 20.33. Found: C, 64.53; H, 5.41; S, 20.28.

2-Dimethylamino-4,5-diphenyl-1,3-dithiolium Perchlorate (3).—One gram of α-phenylphenacyl N,N-dimethyldithiocarbamate and 4 ml. of 70% perchloric acid were warmed together for 5 min. or until complete dissolution occurred. Upon addition of 20 ml. of ethyl acetate to the cooled solution, a white solid separated (1.15 g., 91%). Recrystallization from absolute alcohol afforded white needles, m.p. 221–222°; $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 320 (3.98); 315 (4.00); 230 (4.29); and 210 (4.35); τ_{CF_3COOH} 2.02, 6.33.

2-Methylthio-4-phenyl-1,3-dithiolium Hydrogen Sulfate (7).—Two grams of phenacyl methyltrithiocarbonate[16] and 2 ml. of concentrated sulfuric acid were warmed (50–60°) together for 5 min. Upon cooling and dilution with 20 ml. of ethyl acetate, a yellow solid separated. This material was quite unstable, and could not be isolated in pure form. An n.m.r. spectrum of the material was identical with that of **1b**. If kept dry, **7** could be stored and used for several weeks.

2-Dimethylamino-4-phenyl-1,3-dithiolium Hydrogen Sulfate (8b).—Ten grams of phenacyl N,N-dimethyldithiocarbamate[1b] was warmed with 10 ml. of concentrated sulfuric acid for 5 min. (temperature never exceeding 65°), and then cooled. Ethyl acetate (100 ml.) was added slowly with stirring, and a quantitative yield of white solid which separated was collected, washed with additional ethyl acetate, and dried. Recrystallization of a portion of the material from ethanol, by the addition of ethyl acetate, raised the melting range to 232–234°.

2-Dimethylamino-4-phenyl-1,3-dithiolium Salts.—Compounds **8a** and **8c–f** were prepared by the following general method. One gram of **8b** dissolved in 5 ml. of water was added to a stoichiometric quantity of the anion salt dissolved in 5 ml. of water. An immediate precipitate of the new dithiolium salt occurred. The solid was washed with ethyl acetate, dried, and recrystallized. Warm alcohol (rather than water) was the solvent used for preparation of **8f**. The n.m.r. spectra of **8a–e** in trifluoroacetic acid are identical, and consist of the C-4 phenyl resonance at τ 2.47, the C-5 proton signal at τ 2.63 and the nonequivalent N-methyl protons occurring as two resonance peaks at τ 6.30 and, 6.35. These derivatives are similar in the ultraviolet region, showing four absorption features at 315, 300, 235 and 225 mμ. Differences arise only in the case of the iodide (**8d**), which lacks an absorption feature at 235 mμ, and the picrate (**8f**) which shows no band at 300 mμ. In the infrared region, **8a** shows an intense absorption at 9.0–9.4 μ (ClO_4^-); **8b** shows three intense peaks in the region 8.1–9.5 μ (HSO_4^-); **8c** features a broad peak at 9.0–9.8 μ and a peak at 2.9 μ (BF_4^-); and **8e** is characterized by a strong absorption at 4.9 μ (SCN^-). Additional experimental data are summarized in Table IV.

2,4-Diphenyl-1,3-dithiolium Hydrogen Sulfate (9b).—One gram of phenacyl dithiobenzoate[1b] and 1 ml. of concentrated sulfuric acid were warmed (50–60°) for 5 min. Upon cooling and addition of 20 ml. of ethyl acetate, a yellow solid separated. The solid was collected, washed with ethyl acetate, dried, and recrystallized three times from propanol, and had m.p. 173–175°. The yield was quantitative (Table IV).

2,4-Diphenyl-1,3-dithiolium Picrate (9c).—Five milliliters of alcohol saturated with picric acid was mixed together with a solution of 0.6 g. of **9b** in 5 ml. of warm alcohol. An immediate precipitation occurred. The solid was collected and recrystallized from methanol. The yellow needles melted at 197–199° and weighed 0.8 g. (78%).

(16) D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *J. Chem. Soc.*, 5104 (1962).

Reactions of Ethylenethiourea with α- and β-Halo Acids and Derivatives[1]

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Contribution No. 1200 from the Chemistry Laboratories of Indiana University, Bloomington, Indiana 47405

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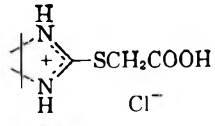
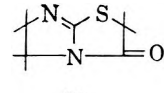
Previous work on the products of the reaction of ethylenethiourea with chloroacetic acid has been confirmed, and the postulated intermediate, 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-one (II), was isolated. Ethylenethiourea was found to react with β-halo propionic acids to produce 3-(β-aminoethyl)-1,3-thiazane-2,4-dione salts (XII) in aqueous solution, but in acetone or ethanol the products were 2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one (XI) salts. XI was obtained in quantitative yield from ethylenethiourea and β-propiolactone in aqueous solution. The probable precursor of XI and XII, 2-(β-carboxyethylmercapto)imidazoline (X), was obtained as its hydrochloride by treatment of ethylenethiourea with acrylic acid in acidic acetone. 2-(β-Cyanoethylmercapto)imidazoline hydrochloride (XVII) was obtained in high yield by the neat reaction of β-chloropropionitrile with ethylenethiourea, but no reaction occurred when the reagents were refluxed in ethanol. The proof of structure and interconversion of X, XI, and XII are described.

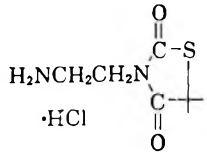
Johnson and Edens[3] refluxed ethylenethiourea with 2 equiv. of chloroacetic acid in water for 3 hr. and isolated a crystalline salt melting at 223°, to which they assigned the structure 2-carboxymethylmercaptoimidazoline hydrochloride (I). Later VanAllan[4] re-



I

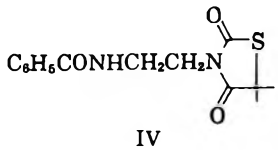


II

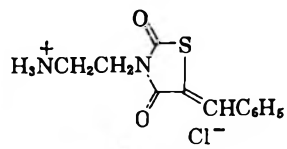


III

investigated this synthesis and showed that the compound was actually the hydrochloride of 3-β-aminoethylthiazolidinedione (III), formed by ring closure of I to the postulated bicyclic intermediate, 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-one (II), followed by acid hydrolysis of the dihydroimidazo ring at position 7–7a to yield III. Evidence for structure III included formation of a monobenzoyl derivative (IV), trimethylammonium salt on exhaustive methylation, a benzal derivative (V), and similarity of the ultraviolet and infrared spectra of 2,4-thiazolidinedione.



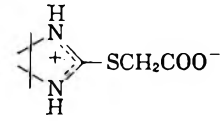
IV



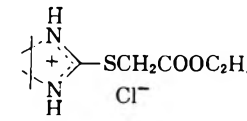
V

We have confirmed the work of VanAllan, by converting the zwitterion VI into I (m.p. 129–130°) by treatment with hydrochloric acid. Our inability to convert the chloroacetic acid–ethylenethiourea adduct into the zwitterion VI by neutralization with sodium acetate or on a basic ion-exchange column is also evidence against structure I for this adduct, especially in view of the fact that II hydrochloride could be hydrolyzed to VI in the presence of aqueous sodium acetate.

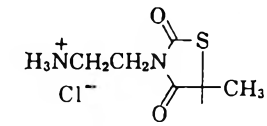
Stephen and Wilson[5] claimed to have prepared II, melting at 159°, by refluxing ethylenethiourea with ethyl chloroacetate in pyridine. We were unable to repeat this preparation, but have obtained an authentic sample of VanAllan's postulated intermediate, II, melting at 94°, by treating an ethanolic solution of 2-(carbethoxymethylmercapto)imidazoline hydrochloride (VII) with ammonia. II forms a picrate and a hydrochloride and also was converted to the same benzylidene



VI



VII



VIII

derivative prepared by VanAllan[4] from VI. II hydrochloride also was obtained from VI by heating with concentrated acid. VII was obtained by refluxing ethylenethiourea and ethyl chloroacetate in ethanol, or by stirring these reactants in pyridine at room temperature. Crystallization of hydrochloride VII from pyridine indicates that S-carbethoxymethylethyleneisothiourea is a stronger base than pyridine, even though ethylenethiourea itself does not form a hydrochloride.[6]

Reaction of ethylenethiourea with chloroacetyl chloride in benzene or cold ether did not yield isolable products, but, from refluxing acetone, the hydrochloride III was obtained on crystallization. Treatment of III with ammonia forms among other things a white amorphous polymeric substance insoluble in water or common organic solvents.

As further confirmation of the structure assignments of the compounds obtained from ethylenethiourea and

(1) This work was supported by Contract No. DA-49-193-MD-2096 with the office of the Surgeon General, U. S. Army Medical Research and Development Command. Presented in part before the Medicinal Division at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

(2) This work is taken from a thesis submitted by M. C. W. to Indiana University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, October, 1961.

(3) T. B. Johnson and C. D. Edens, *J. Am. Chem. Soc.*, **64**, 2708 (1942).

(4) J. A. VanAllan, *J. Org. Chem.*, **21**, 24, 193 (1956).

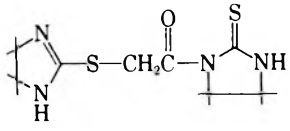
(5) H. W. Stephen and F. J. Wilson, *J. Chem. Soc.*, 2531 (1926).

(6) P. C. Guha and D. N. Dutta, [*J. Indian Chem. Soc.*, **6**, 65 (1929)] in connection with the reactions of ethylenediamine and diethylxanthic formic ester (sic) report the isolation of ethylenethiourea hydrochloride, m.p. 304–305°. These authors do not report any elemental analysis. However, according to A. W. Hofman [*Ber.*, **5**, 240 (1872)] ethylenethiourea crystallizes unchanged from acids. We have confirmed Hofman's observation. It is probable that Guha and Dutta mistook ethylenediamine dihydrochloride (m.p. 345° dec.) for ethylenethiourea hydrochloride.

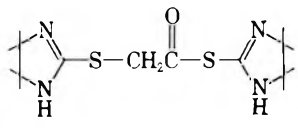
chloroacetic acid, VanAllan's benzoyl derivative (IV) was prepared unequivocally by the condensation of the potassium salt of 2,4-thiazolidinedione[7] with β-benzamidoethyl bromide.[8] The melting points, mixture melting point, and infrared spectra of these two benzoyl derivatives obtained by the two different routes were identical.

Reaction of ethylenethiourea and α-chloropropionic acid in water led to the formation of a high-melting salt, assigned the structure of 3-β-aminoethyl-5-methyl-2,4-thiazolidinedione hydrochloride (VIII), on the basis of the infrared spectrum, which was very similar to that of III.

Several rather interesting related reactions have been observed. Passing an aqueous solution of III over an ion-exchange column containing the hydroxide form of Dowex^{R} 1-X8, in an effort to convert it to the zwitterion VI, led instead to the formation of ethyleneurea. This suggests that under basic conditions, III may again be converted to II, which may then be further hydrolyzed. The reaction of ethylenethiourea and ethyl chloroacetate in ethanol in the presence of sodium acetate was carried out in the hope of isolating the free base of VII. Instead, a compound having two moieties of ethylenethiourea was isolated, which must have structure IXa or b. Such a compound can only arise by reaction of



IXa



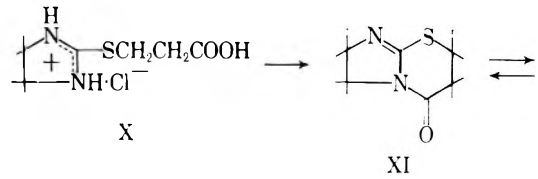
IXb

ethylenethiourea with the free base of VII, or with the reactive bicyclic compound II. The latter is more likely, since esters are not known to react with ethylenethiourea. It was not possible to distinguish between IXa and IXb by infrared analysis, since amide and thiol ester carbonyl absorption bands overlapped. Treatment with hydrochloric acid converted IX to II hydrochloride, which suggests that the more readily hydrolyzable IXb is the more likely structure.

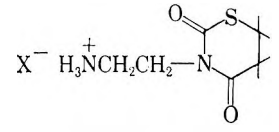
Although Baer and Lockwood[9] reported that ethylenethiourea did not react with β-halo propionic acids or derivatives in refluxing ethanol, we have found that reaction does occur between these reagents under a variety of experimental conditions to give three types of products, represented by X, XI, and XII. This represents a series of related compounds similar to I, II, and III, in that XI may be formed by cyclization of X, and XII by ring opening of XI.

Refluxing β-halo propionic acids with ethylenethiourea in either water or alcohol led to 3-(β-aminoethyl)-1,3-thiazane-2,4-dione salts (XIIa or b) in low yield. XIIa was subjected to benzoylation under aqueous conditions and a dibenzoyl derivative (XIII) was obtained. Formation of a dibenzoyl derivative indicates the compound cannot have structure X, which could only form a monobenzoyl derivative. Assignment of XII as the structure of this product is further supported by the fact that benzoylation in pyridine gave a monobenzoyl derivative (XIV), whose infrared spectrum showed a strong –NH band at 3430 cm.$^{-1}$, and

(7) C. Lo and E. Y. Shropshire, *J. Org. Chem.*, **22**, 999 (1957).
(8) S. Gabriel, *Ber.*, **22**, 2222 (1899).
(9) J. E. Baer and R. G. Lockwood, *J. Am. Chem. Soc.*, **76**, 1162 (1954).



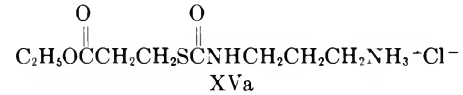
X XI



XIIa, X = Cl
b, X = Br

by the synthesis of 3-(β-benzamidoethyl)-1,3-thiazane-2,4-dione (XIV) from a salt of 1,3-thiazane-2,4-dione and β-benzamidoethyl bromide.

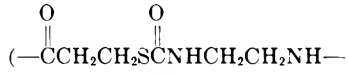
Salts of XII were easily cleaved at the imide linkage in weakly acid or basic solution. For example, heating XIIa in a large volume of alcohol, and allowing it to stand overnight, converted it to an open-chain ester salt, whose analysis and infrared spectrum were consistent with either XVa or b. Warming XV in 1 *N* hydrochloric acid reconverted it to XIIa, a reaction



XVa

XVb

which can be considered as evidence favoring structure XVa for the structure of this product. The alternate, XVb, would be expected to cleave at the thio ester linkage under these conditions. Treatment of XIIb with aqueous base converted it to a white amorphous insoluble high-melting solid, which may be a polymer of structure XVI. XVI could be formed by intermolec-



XVI

ular aminolysis of the thiazanedione ring by the free base XII.

Thiourea hydrochloride reacts with α,β-unsaturated acids to produce addition products.[10a] Although ethylenethiourea does not form a hydrochloride salt, we have now found that treatment of an acetone solution of ethylenethiourea and acrylic acid with dry hydrogen chloride at room temperature causes the formation of 2-carboxyethylmercaptoimidazoline hydrochloride (X). This compound is distinctly different from its isomer, XIIa, and can be cyclized to the bicyclic XI hydrochloride[10b] by refluxing in ethanol, but not in refluxing acetone. Although VI was quite easily isolated,[4] attempts to convert the hydrochloride X to the homologous zwitterion were unsuccessful. Instead, XI was apparently formed and further hydrolyzed during these experiments.

2,3,6,7-Tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one (XI) and its salts are formed readily. Refluxing

(10) (a) H. Behringer and P. Zillikens, *Ann.*, **574**, 140 (1951); (b) C. G. Overberger and H. A. Friedman [*J. Org. Chem.*, **29**, 1720 (1964)] report the isolation of XI by the reaction of ethylenethiourea and acrylyl chloride in acetone. We wish to thank Dr. Overberger for the opportunity to examine his manuscript before publication.

ethylenethiourea with β-chloropropionic acid in ethanol or acetone gave only traces of XI hydrochloride, but β-bromopropionic acid in these solvents or in water gave moderate yields of XI hydrobromide. However, when ethylenethiourea was heated with an equimolar amount of the appropriate β-halo acid or ester in an open flask without solvent, it was converted in good yield to a salt of XI. The free base of XI was obtained in nearly quantitative yield from ethylenethiourea and β-propiolactone in aqueous solution, but in acidic ethanol this reaction was unsuccessful.

It was possible to obtain XI from XII in low yield by careful neutralization of salts of XII and immediate extraction into chloroform. Apparently the extraction technique produces the free base of XII in high dilution, so that cyclization occurs, rather than the intermolecular reaction to form XVI. X was also converted to XI under similar conditions, as shown by extraction of a small amount of XI by chloroform, or isolation of the picrate of XI if the reaction were carried out in ethanol.

Since XI salts can be converted into XII salts by refluxing in aqueous acid, we have now isolated and characterized the three new compounds, X, XI, and XII, and have shown that X can be converted to XI and XII, XI can be converted to XII, and XII back to XI, but we have been unable to convert either XII or XI back to X. On the basis of these experiments, and the earlier work of VanAllan,[4] it seems reasonable to presume that XII salts are formed from ethylenethiourea and β-halo propionic acids in aqueous solution by initial alkylation of sulfur to form X salts, followed by cyclization to XI and hydrolysis to XII. In contrast to the sequence I → II → III, in which II is obtained only with difficulty, XI, which contains the 5,6-fused ring system, is much more stable and easily isolated.

The analog of X, 2-(β-cyanoethylmercapto)imidazoline hydrochloride (XVII) was obtained in excellent yield by the neat reaction of ethylenethiourea and β-chloropropionitrile. However, when these reagents were refluxed in ethanol for 16 hr., ethylenethiourea was recovered unchanged. Since boiling XVII in water led to the formation of some XI hydrochloride, it is probable that initial hydrolysis of the cyano group leads to cyclization in this case.

A homolog of XI, 7-methyl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one hydrochloride (XVIII) was obtained in good yield from the reaction of ethylenethiourea with either 3-chlorobutyric acid neat, or by the acid-catalyzed addition to crotonic acid in ethanol. Apparently the methyl group enhances the ring closure in this case, since the open-chain system X was obtained with acrylic acid under these conditions. Refluxing ethylenethiourea and 3-chlorobutyric acid in aqueous solution produced the thiazanedione XIX in satisfactory yield.

Experimental[11]

Preparation of the Zwitterion 2-Carboxymethylmercaptoimidazoline (VI).—This compound, originally prepared by Rylander,[12] has since been described by VanAllan.[4] A mixture of 20 g. (0.21 mole) of chloroacetic acid, 21.6 g. (0.21 mole) of ethylenethiourea, and 10 g. (0.21 mole) of sodium acetate in 150 ml. of ethanol was refluxed for 30 min. The alcohol was evaporated under reduced pressure, dilute sodium bicarbonate was added, and 23 g. (67%) of a precipitate, which after two recrystallizations from dilute ethanol melted at 182–183° dec., was obtained; ν_{max}^{KBr} (cm.$^{-1}$): 3448 (NH), 2857 (CH), 3135 and 2632 (NH^+), 1538 (C=NH^+), 1600, 1364 (COO^-).

Anal. Calcd. for $C_5H_8N_2O_2S$: C, 37.46; H, 4.96; N, 17.48; S, 19.97. Found: C, 37.72; H, 4.92; N, 17.41; S, 20.18.

2-Carboxymethylmercaptoimidazoline Hydrochloride (I).—One gram of finely powdered VI was suspended in 25 ml. of ether and treated with a few drops of concentrated hydrochloric acid. When ethanol was added dropwise with constant stirring to the oily mass, the hydrochloride melting at 128–129°, as reported by VanAllan,[4] crystallized in almost quantitative yield (1.1 g.).

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazol-3-one Hydrochloride (II·HCl). A. **From VI.**—A solution of 1 g. of VI in 2.5 ml. of concentrated hydrochloric acid was heated on a steam bath for 5 min., according to the direction of VanAllan[4] for preparing I. However, on evaporation of the solution under reduced pressure, and recrystallizing the residue from isopropyl alcohol, 0.5 g. of II·HCl, melting at 205–206° dec., was obtained.

B. **From IX.**—A suspension of 0.2 g. of IX in 25 ml. of ether was treated with a few drops of concentrated hydrochloric acid. Ether was decanted from the oily mass which separated, and it was triturated with ethanol to produce 0.1 g. (69%) of white crystals of II hydrochloride.

C. **From II.**—A benzene solution of II (see below) was treated with a few drops of concentrated hydrochloric acid, and the sticky oily mass which separated was washed with ethanol, giving a pure white product which melted to a red oil at 205–206°; ν_{max}^{KBr} (cm.$^{-1}$): 3509, 2469 (NH^+), 2941 (CH), 1751 (CO), 1610 (C=N).

Anal. Calcd. for $C_5H_7ClN_2OS$: N, 15.69; S, 18.02. Found: N, 15.59; S, 18.28.

Hydrolysis of II Hydrochloride to Form VI.—An aqueous solution (5 ml.) of 0.177 g. (1.0 mmole) of II·HCl and 0.136 g. (1.0 mmole) of sodium acetate was refluxed for 0.5 hr., evaporated, and the residue was treated with 2 ml. of ice-cold water. The compound insoluble in cold water melted at 182–183° (0.060 g., 37%) and was identified as VI by comparison of infrared spectra.

2-Carbethoxymethylmercaptoimidazoline Hydrochloride (VII). A. **From Ethanol.**—A solution of 20.4 g. (0.2 mole) of ethylenethiourea and 24.5 g. (20.1 ml., 0.2 mole) of ethyl chloroacetate in 150 ml. of absolute ethanol was refluxed for 2 hr. Excess solvent was removed under reduced pressure, and the crude product (35 g., 80%) crystallized from ethanol as needles melting at 143–144°.

B. **From Pyridine.**—A pyridine solution (50 ml.) of 10 g. (0.1 mole) of ethylenethiourea and 12.2 g. (10 ml., 0.1 mole) of ethyl chloroacetate was stirred at room temperature for 7 hr. On scratching the sides of the reaction flask, 8 g. (35%) of VII separated, m.p. 143–144°, identical with the above; ν_{max}^{KBr} (cm.$^{-1}$): 3096, 2273 (NH^+), 2941 (CH), 1721 (CO), 1563 (C=NH^+).

Anal. Calcd. for $C_7H_{13}ClN_2O_2S$: Cl, 15.78; N, 12.47; S, 14.27. Found: Cl, 15.90; N, 12.88; S, 13.98.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazol-3-one (II).—Three grams of VII in 50 ml. of absolute ethanol was treated with ammonia gas for a few minutes. The precipitated ammonium chloride was filtered and removal of ethanol under reduced pressure at room temperature gave 1.15 g. (60%) of II, which after crystallization from ethyl acetate melted at 94–95°; ν_{max}^{KBr} (cm.$^{-1}$): 3003 (CH), 1712 (CO), 1629 (C=N).

Anal. Calcd. for $C_5H_6N_2OS$: N, 19.7; S, 22.55. Found: N, 19.44; S, 22.44.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazol-3-one Picrate.—Finely ground II was stirred into a saturated ethanolic solution of picric acid, and a precipitate formed immediately. It recrystallized from absolute ethanol as golden yellow needles melting at 184–185° dec. The same picrate was also obtained in small amounts from the concentrated mother liquors from the preparation of VI and VII.

Anal. Calcd. for $C_{11}H_9N_5O_8S$: N, 18.86; S, 8.62. Found: N, 18.97; S, 8.76.

2-Benzylidene-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-one.—A solution of 0.426 g. (3.0 mmoles) of II, 0.318 g. (3.0 mmoles) of benzaldehyde, and 0.358 g. (3.0 mmoles) of piperidine in 10 ml. of ethanol was refluxed for 8 hr. The excess solvent was removed under reduced pressure, and the crystalline pale yellow residue (0.120 g., 17%) was washed several times with ether and melted at 179–180° as reported by VanAllan.[4]

(11) All melting points are corrected. Analyses were by Midwest Microlab, Inc., Indianapolis, Ind.

(12) P. N. Rylander, Ph.D. thesis, Indiana University, 1948.

3-(β-Aminoethyl)-2,4-thiazolidinedione Hydrochloride (III).—A solution of 5.1 g. (0.05 mole) of ethylenethiourea and 9.4 g. (0.1 mole) of chloroacetic acid in 50 ml. of water was refluxed for 3 hr., and then concentrated to a sirup. On pouring the cooled concentrate into 50 ml. of cold methanol, 8 g. (81%) of needles separated, which melted at 225–227°.[3,4]

A similar reaction in 95% ethanol gave a 51% yield of III, and refluxing ethylenethiourea with chloroacetyl chloride in acetone also produced III, in 23% yield. Saturating a solution of 1.61 g. of VI in 50 ml. of 95% ethanol with dry hydrogen chloride produced needles of pure III in 25% yield after 3 days. Concentration of the mother liquor in this case led to intractable oils; ν_{max}^{KBr} (cm.$^{-1}$): 3448, 2519 (NH^+), 2941, 2841, 2762 (CH), 1701, 1629 (CO), 1587 (NH_3^+).

Anal. Calcd. for $C_5H_9ClN_2O_2S$: C, 30.53; H, 4.58; N, 18.05. Found: C, 30.59; H, 4.54; N, 18.00.

3-(β-Benzamidoethyl)-2,4-thiazolidenedione (IV). A. Benzoylation of III.—To a stirred solution of 5 g. of III and 6 g. of sodium acetate in 25 ml. of water was added slowly and with stirring 4 g. of benzoyl chloride at 15–20°. After 2 hr., 4 g. of sodium bicarbonate was added and stirring was continued for 0.5 hr. more. The white solid which had separated was removed by filtration, resuspended in a dilute aqueous solution of sodium bicarbonate and again filtered. Two crystallizations from ethanol yielded 6 g. (80%) of white crystals, m.p. 135–136°.[4]

B. From 2,4-Thiazolidinedione.—Five grams of 2,4-thiazolidinedione was dissolved in 20 ml. of hot ethanol containing 2.62 g. of potassium hydroxide, stirred for 2 hr., and then cooled in an ice bath. The crystalline potassium salt (6 g.) was collected, washed with ethanol, and air-dried. A mixture of 1.55 g. of this salt[7] (0.01 mole) in 25 ml. of dimethylformamide and 2.28 g. (0.01 mole) of β-benzamidoethyl bromide,[8] was heated on a steam bath for 4 hr., excess solvent was removed under reduced pressure, and the residue was treated with 20 ml. of ice-cold water and 2 ml. of concentrated hydrochloric acid. The product (0.87 g., 33%) melting at 135–136° after two crystallizations from ethanol was identical with the one prepared by method A, by mixture melting points and infrared spectra.

3-β-Aminoethyl-5-methyl-2,4-thiazolidinedione Hydrochloride (VIII).—When 9.4 g. (0.09 mole) of α-chloropropionic acid was treated with ethylenethiourea in water as described for III, 85% of crude white solid separated, which melted at 249–251° after recrystallization from ethanol in plates; ν_{max}^{KBr} (cm.$^{-1}$): 3425, 3125, 2551 (NH^+), 2933, 2841, 2762 (CH), 1718, 1653 (CO), 1582 (C=N).

Anal. Calcd. for $C_7H_{11}ClN_2O_2S$: Cl, 16.8; N, 13.3. Found: Cl, 16.6; N, 13.7.

Preparation of IX.—A solution of 10.2 g. (0.1 mole) of ethylenethiourea, 10 ml. (0.1 mole) of ethyl chloroacetate, and 8.2 g. (0.1 mole) of fused sodium acetate in 225 ml. of anhydrous ethanol was refluxed for 45 min. On cooling, undissolved sodium acetate and sodium chloride were removed by filtration, and the solution was concentrated under reduced pressure. The residue was crystallized three times from ethyl acetate to give 2.5 g. (21%) of crystals melting at 129–130°; ν_{max}^{KBr} (cm.$^{-1}$): 3500 (NH), 2941 (CH), 1701 (CO), 1580 (C=N).

Anal. Calcd. for $C_9H_{12}N_4OS_2$: C, 39.3; H, 4.95; N, 22.93; S, 26.25. Found: C, 39.43; H, 5.05; N, 22.93; S, 26.16.

3-(β-Aminoethyl)-1,3-thiazane-2,4-dione (XII) Hydrohalides. A. Hydrochloride (XIIa).—An aqueous solution (100 ml.) of 10.2 g. (0.1 mole) of ethylenethiourea and 10.84 g. (0.1 mole) of β-chloropropionic acid was refluxed for 3 hr. Excess solvent was removed under reduced pressure, the oily residue was dissolved in ethanol, and ether was added. The white solid (6.6 g., 31%) that separated was recrystallized from ethanol containing 1 drop of concentrated hydrochloric acid and melted at 157–159°. No other identifiable product could be obtained from the ethanolic mother liquor. Refluxing these reagents in ethanol for 40 hr. (at the end of 20-hr. reflux period unchanged ethylenethiourea could still be isolated) gave only 5% of XIIa after recrystallization; ν_{max}^{KBr} (cm.$^{-1}$): 2941 (CH), 2755, 2370 (NH_2^+), 1701, 1629 (CO).

Anal. Calcd. for $C_6H_{11}ClN_2O_2S$: N, 13.30; S, 15.22. Found: N, 13.51; S, 15.31.

B. Hydrobromide (XIIb).—An aqueous solution (50 ml.) of 5.1 g. (0.05 mole) of ethylenethiourea and 7.5 g. (0.05 mole) of β-bromopropionic acid, refluxed for 3 hr., gave 5.2 g. (40%) of XIIb melting at 185–186° after crystallizing from isopropyl alcohol. The infrared spectrum was identical with that of XIIa, above. An aqueous solution (15 ml.) of 2.37 g. (0.01 mole) of XI hydrobromide and 1 ml. of 48% hydrobromic acid, refluxed for 24 hr., concentrated, and recrystallized from isopropyl alcohol, gave 1.25 g. (50%) of crystals identical in melting point and infrared spectrum with XIIb.

Anal. Calcd. for $C_6H_{11}BrN_2O_2S$: N, 10.98; S, 12.54. Found: N, 10.89; S, 12.66.

3-(β-Dibenzoylaminoethyl)-1,3-thiazane-2,4-dione (XIII).—To a stirred solution of 5.25 g. (0.025 mole) of XIIa and 6.8 g. (0.05 mole) of sodium acetate in 25 ml. of water was added slowly with stirring 4 g. of benzoyl chloride at 15–20°. After 2 hr., 4 g. of sodium bicarbonate was added and stirring was continued for 3 hr. more. The yellow sticky solid which had separated was removed by filtration, resuspended in a dilute aqueous solution of sodium bicarbonate and again filtered and washed with water. Three recrystallizations from methanol yielded 1.5 g. (15%) of XIII melting at 172–173°. The infrared spectrum of this compound is characterized by the absence of NH stretch in the 3400-cm.$^{-1}$ region; ν_{max}^{KBr} (cm.$^{-1}$): 2940 (CH), 1701, 1629 (broad, CO).

Anal. Calcd. for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.71; N, 7.33; S, 8.37. Found: C, 62.38; H, 4.82; N, 7.45; S, 8.40.

3-(β-Benzamidoethyl)-1,3-thiazane-2,4-dione (XIV).—To a solution of 0.525 g. (0.0025 mole) of XIIa in 5 ml. of dry pyridine and 10 ml. of dry benzene was added, dropwise, 0.5 ml. of benzoyl chloride. The resulting mixture was heated on a steam bath at 60–70° for 0.5 hr. and then was poured into 100 ml. of cold water. The benzene layer was separated and the aqueous solution was washed once with 10 ml. of benzene. The combined benzene solutions were washed with 5% sodium carbonate solution and with water and dried with anhydrous magnesium sulfate. The oily residue left after benzene was removed under reduced pressure was treated with 2 ml. of ethanol and 25 ml. of petroleum ether (b.p. 30–60°). The white product (0.200 g., 28%) melted at 160° after recrystallization from dilute ethanol; ν_{max}^{Kbr} (cm.$^{-1}$): 3436 (NH), 3155, 3012 (CH), 1704, 1629 (CO).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: N, 10.08; S, 11.51. Found: N, 10.32; S, 11.62.

To a solution of 3.93 g. (0.03 mole) of 1,3-thiazane-2,4-dione, prepared by the method of Hendry[13] in 83% yield, in 20 ml. of dimethylformamide was added slowly and under constant stirring over a period of 1 hr. 1.6 g. (slight excess) of 52.7% sodium hydride in mineral oil.[14] The resulting suspension of sodium salt was treated with 6.8 g. of β-benzamidoethyl bromide[8] in 10 ml. of dimethylformamide, and the reaction mixture was heated on a steam bath under constant stirring for 4 hr. Excess solvent was removed under reduced pressure, 200 ml. of cold water was added, the aqueous suspension was extracted with 25 ml. of ether, and the residue (0.520 g., 6%) insoluble in water and ether crystallized from dilute ethanol. It melted at 159–160°, and the infrared spectrum of this compound is identical with that of XIV, above.

Ethanolysis of XIIa.—A white pasty mass of crude XIIa, obtained from 1.0 mole of each of the reagents in a liter of water (see above) and melting at 152–154° after drying *in vacuo*, was dissolved in 750 ml. of 95% ethanol and, on cooling overnight, 90 g. (34%) of a colorless crystalline solid XV melting at 109–110° was obtained; ν_{max}^{KBr} (cm.$^{-1}$): 3280 (NH), 2965 (CH), 2750, 2375 (NH_3^+), 1725, 1635 (CO), 1504 (C=N).

Anal. Calcd. for $C_8H_{17}ClN_2O_3S$: C, 37.65; H, 6.82; Cl, 13.84; S, 12.55. Found: C, 37.68; H, 7.19; Cl, 14.12; S, 12.57.

When 90 g. of XV was dissolved in 1 l. of 1 *N* hydrochloric acid, heated on a steam bath for 3 hr., and concentrated to one-third volume, the white solid which crystallized melted at 157–159° dec. and weighed 44 g. (60%). The infrared spectrum of this compound was identical with that of pure XIIa.

Hydrolysis of XIIb.—A concentrated aqueous solution of XIIb was treated with concentrated ammonium hydroxide. The white amorphous powder that separated was washed with water, ethanol, acetone, and ether. No suitable solvent to recrystallize the product could be found. It melted from 216–219°; ν_{max}^{KBr} (cm.$^{-1}$): 3365 (NH), 2976 (CH), 1645 (CO).

Anal. Calcd. for $C_6H_{10}N_2O_2S$: N, 16.09; S, 18.42. Found: N, 15.94; S, 18.36.

2-β-Carboxyethylmercapto-2-imidazoline Hydrochloride (X).[15]—Hydrogen chloride gas was passed through a solution of 5.1 g.

(13) C. M. Hendry, *J. Am. Chem. Soc.*, **80**, 973 (1958).

(14) G. deStevens, A. Halamondaris, and L. Dorfman, *ibid.*, **30**, 5198 (1958).

(15) L. Fedor, Ph.D. thesis, Indiana University, 1963.

(0.05 mole) of ethylenethiourea and 3.6 g. (0.05 mole) of acrylic acid in 500 ml. of acetone at 28° for 0.5 hr., at the end of which a white solid had precipitated. The compound was washed with acetone and a total of 7.9 g. (91%) of solid was obtained, m.p. 133–135°; ν_{max}^{KBr} (cm.$^{-1}$): 2941 (CH), 2900, 2760 (w, NH$^+$), 1710 (CO), 1538 (C=N).

Anal. Calcd. for $C_6H_{11}ClN_2O_2S$: N, 13.30; S, 15.22. Found: N, 13.51; S, 15.60.

2,3,6,7-Tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one (XI) Hydrohalides. A. Hydrochloride.—A mixture of 10.1 g. (0.1 mole) of ethylenethiourea and 10.84 g. (0.1 mole) of β-chloropropionic acid was heated slowly to 115° in an open flask containing a thermometer. Ethylenethiourea went into solution completely accompanied by a rise in temperature to 160°. The reaction flask was cooled to 135° and maintained at this temperature for an additional 10 min. The cooled reaction mixture solidified and yielded 12 g. (63%) of XI hydrochloride, melting at 276–278° after recrystallizing from methanol; ν_{max}^{KBr} (cm.$^{-1}$): 2933 (CH), 2703, 2326 (NH$^+$), 1721 (CO), 1587 (C=N).

Anal. Calcd. for $C_6H_9ClN_2OS$: N, 14.55; S, 16.62. Found: N, 14.81; S, 16.69.

When 1 g. (4.7 mmoles) of X was refluxed in ethanol for 4 hr., 0.65 g. (72%) of XI hydrochloride crystallized on cooling, as shown by mixture melting point (277–278°) and identity of infrared spectra. Similar treatment in refluxing acetone for 2 hr. gave only starting product. The neat reaction of ethylenethiourea and ethyl β-chloropropionate, heated to 150° for 15 min., gave only 36% of XI hydrochloride.

Attempted Reaction of Ethylenethiourea with β-Propiolactone.—A solution of 10.1 g. (0.1 mole) of ethylenethiourea in 50 ml. of ethanol previously saturated with hydrogen chloride was mixed with 7.2 g. (0.1 mole) of β-propiolactone and the reaction mixture was stirred at room temperature for 30 hr. From the oily mass left behind after the removal of 6.7 g. (67%) of ethylenethiourea, 0.20 g. (3%) of XI hydrochloride was isolated.

B. XI Hydrobromide.—When 5.1 g. (0.05 mole) of ethylenethiourea and 7.65 g. (0.05 mole) of β-bromopropionic acid was heated for 5 min. at 105° in an open flask with vigorous stirring, the reaction mixture solidified. The temperature of the mixture was raised slowly to 120° and stirring continued for an additional 10 min. It then was cooled to room temperature and stirred with 50 ml. of ethanol. The white crystals (8 g., 76%) melted at 285–286° after recrystallization from methanol and had an infrared spectrum identical with that of XI hydrochloride (above).

Anal. Calcd. for $C_6H_9BrN_2OS$: Br, 33.74; N, 11.84; S, 13.50. Found: Br, 33.91; N, 12.09; S, 13.84.

The preparation of this hydrobromide by refluxing the reagents in a solvent, such as water, ethanol, or acetone, was much less satisfactory.

2,3,6,7-Tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one (XI).—A mixture of 10 g. (0.1 mole) of ethylenethiourea and 7.2 g. (0.1 mole) of β-propiolactone in 50 ml. of water was stirred continuously for 45 min. Excess solvent was removed at reduced pressure, and the crude product (15 g., 96%) melted at 144–145° after two crystallizations from methanol; ν_{max}^{KBr} (cm.$^{-1}$): 2941 (CH), 1664 (CO), 1587 (C=N).

Anal. Calcd. for $C_6H_8N_2OS$: N, 17.95; S, 20.51. Found: N, 17.99; S, 20.67.

When a cold solution of 2.62 g. (12.5 mmoles) of XIIa in 25 ml. of water was mixed with 5 ml. of water containing 1.7 g. (12.5 mmoles) of sodium acetate and the mixture was extracted immediately with 25 ml. of cold chloroform, 0.326 g. (16.7%) of XI was obtained on evaporation of the dried chloroform under reduced pressure. Similar treatment of XI hydrobromide produced XI in 30% yield, and by this means X was converted to XI in 5% yield.

Picrate.—A solution of XI in absolute ethanol was treated with an equal amount of a saturated ethanolic solution of picric acid, and a yellow picrate melting at 183–184° dec. crystallized on cooling. This same product was obtained in 16% yield when a solution of 1 g. of X (5 mmoles) in 20 ml. of absolute ethanol was stirred with 0.41 g. (5 mmoles) of sodium acetate, sodium chloride was filtered, the solvent was removed, and the resulting oil was redissolved in ethanol and treated with picric acid.[15]

Anal. Calcd. for $C_{12}H_{11}N_5O_8S$: N, 18.18; S, 8.31. Found: N, 18.43; S, 8.43.

2-(β-Cyanoethylmercapto)-2-imidazoline Hydrochloride (XVII).—The product of the neat reaction of 7 g. (0.07 mole) of ethylenethiourea in an excess (15 ml.) of β-chloropropionitrile was triturated with 25 ml. of ether. The white solid (13 g., 97%) melted at 134–135° after recrystallization from isopropyl alcohol; ν_{max}^{KBr} (cm.$^{-1}$): 2941 (CH), 2632 (NH$^+$), 2273 (C≡N), 1550 (C=N).

Anal. Calcd. for $C_6H_{10}ClN_3S$: N, 21.94; S, 16.71. Found: N, 21.82; S, 16.60.

A solution of 3.6 g. (0.02 mole) of XVII was boiled in 10 ml. of water for 5 min. Removal of the water at reduced pressure and recrystallization of the residue from absolute ethanol gave 0.3 g. (7%) of XI hydrochloride, melting at 277–278°.

Picrate.—An alcoholic solution of XVII was mixed with a saturated solution of picric acid in ethanol, and golden yellow needles of XVII picrate, melting at 164–165° after recrystallization from ethanol, were collected.

Anal. Calcd. for $C_{12}H_{12}N_6O_7S$: N, 21.87; S, 8.33. Found: N, 22.29; S, 8.40.

7-Methyl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one Hydrochloride (XVIII). A. From 3-Chlorobutyric Acid.—A mixture of 10 g. (0.1 mole) of ethylenethiourea and 12.25 g. (0.1 mole) of 3-chlorobutyric acid was heated slowly to 155° in a round-bottom flask. After 0.5 hr. the mixture was cooled and stirred with 50 ml. of absolute ethanol, giving a white solid (12 g., 58%) which melted at 262–264° after crystallization from methanol. No other product could be obtained from the ethanolic filtrate. The infrared spectrum was very similar to that of XI hydrochloride; ν_{max}^{KBr} (cm.$^{-1}$): 2976 (CH), 3261, 2247 (NH$^+$), 1715 (CO), 1587 (C=N).

Anal. Calcd. for $C_7H_{11}ClN_2OS$: N, 13.56; S, 15.50. Found: N, 13.28; S, 15.63.

B. From Crotonic Acid.[16]—In a 100-ml. flask equipped with a condenser and gas inlet tube was placed 2.15 g. (0.025 mole) of crotonic acid, 2.55 g. (0.025 mole) of ethylenethiourea, and 50 ml. absolute ethanol. Hydrogen chloride gas was bubbled through the refluxing ethanolic solution for 2 hr. On cooling, the solution yielded 2.1 g. (40%) of white crystals, which on recrystallization from methanol melted at 262–263° and showed no depression of melting point when mixed with XVIII above. The infrared spectra of the two products were identical.

3-(β-Aminoethyl)-6-methyl-1,3-thiazane-2,4-dione Hydrochloride (XIX).—A solution of 5.1 g. (0.05 mole) of ethylenethiourea and 8.6 g. (0.05 mole) of 3-chlorobutyric acid in 50 ml. of water was refluxed for 4 hr. Work-up in the usual way and recrystallization from acetone gave 5.8 g. (43%) of XIX, melting at 161–163°; ν_{max}^{KBr} (cm.$^{-1}$): 3077 (NH$^+$), 3005 (CH), 1709, 1642 (CO).

Anal. Calcd. for $C_7H_{13}ClN_2O_2S$: N, 10.41; S, 11.91. Found: N, 10.47; S, 11.97.

The Reaction of Unsaturated Acid Chlorides with Substituted Thioureas

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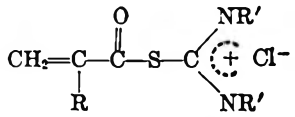
Acrylyl and methacrylyl chloride have been found to react with ethylenethiourea to yield 2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazin-5-one hydrochloride and its 6-methyl analog, respectively. Similarly, *sym*-diphenylthiourea yields the thiazine derivative, 2,3,5,6-tetrahydro-2-phenylimino-3-phenyl-4H-1,3-thiazin-4-one hydrochloride, and its 5-methyl analog. The free bases of the above compounds were also characterized. The reaction of acrylyl chloride with *sym*-diphenylthiourea, in the presence of triethylamine, yields a low molecular weight polymer with a degree of polymerization (DP) of 6–7.

The reaction of thioureas with acyl chlorides to yield N-acylthioureas has been reported[2-4]; the initial product, an S-acylisothiuronium chloride, undergoes rearrangement to the N-substituted compound upon heating, with the evolution of hydrogen chloride.

In addition to reactions with alkylating or acylating agents, thiourea has also been shown to be capable of addition to an activated double bond, in the presence of an acid. Thus, addition has been effected to α,β-unsaturated acids to give S-(β-carboxyalkyl)isothiuronium chloride,[5] to acrylonitrile and acrylamides to yield S-(β-cyanoethyl)- and S-(β-carboxamidoethyl)-isothiuronium salts,[6] and to 2- and 4-vinylpyridines to yield S-[2-(2- and 4-pyridinium)ethyl]isothiuronium salts.[7] Reaction of α,β-unsaturated diacid diesters with thiourea in the presence of hydrogen chloride or bromide yielded 2-imino-4-oxo-3,5-H-1,3-thiazin-6-carbonic acid ester[8] *via* ring closure.

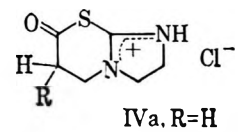
In an attempt to prepare the unsaturated isothiuronium salts Ia–d, as potential antiradiation drugs, acrylyl and methacrylyl chloride reacted with N,N′-ethylene- and N,N′-diphenylthiourea. The product isolated in all instances was not the S- or N-acylthiourea, but rather a heterocyclic compound derived from a ring-closure reaction.



I

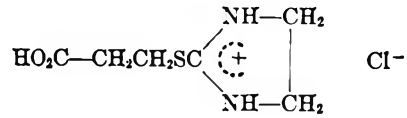
a, R = H; R′ = CH_2
b, R = CH_3; R′ = CH_2
c, R = H; R′ = C_6H_5
d, R = CH_3; R′ = C_6H_5

Elemental analysis for the product of the reaction of acrylyl chloride with N,N′-ethylenethiourea, for example, was in close agreement with three possible structures, II, IIIa, and IVa. Structure II was ruled out on the basis of infrared and ultraviolet spectra (by comparison with S-benzyl-N,N′-ethyleneisothiuronium chloride) and nuclear magnetic resonance spectra (which indicated the lack of vinyl protons and the presence of more than one type of methylene proton). Structure IVa was eliminated by the unequivocal synthesis of 2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-



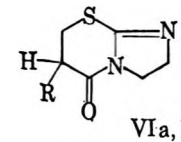
IVa, R=H
b, R=CH_3

thiazin-5-one hydrochloride (IIIa) from β-carboxyethyl-N,N′-ethyleneisothiuronium chloride (V).[9] The



compound thus prepared proved identical with that obtained by reaction of acrylyl chloride and N,N′-ethylenethiourea. In a similar fashion, 6-methyl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazin-5-one hydrochloride (IIIb) was synthesized by using methacrylyl chloride.

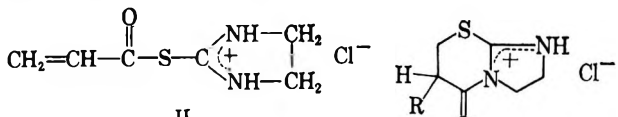
The bases VIa and b were prepared from the salts by reaction with diethylamine. Attempts to prepare these compounds directly by conducting the reaction



VIa, R=H
b, R=CH_3

in the presence of triethylamine resulted in polymer formation. These polymers could not be characterized.

Reaction of acrylyl or methacrylyl chloride with *sym*-diphenylthiourea gave the thiazine derivatives, 2,3,5,6-tetrahydro-2-phenylimino-3-phenyl-4H-1,3-thiazin-4-one hydrochloride (VIIa) and its 5-methyl analog, VIIb, respectively. These salts are unstable to heat and readily decompose affording their conjugate bases, VIIIa and b, with the evolution of hydrogen chloride. The structure of VIIIa was proved by an un-



II

IIIa, R=H
b, R=CH_3

(1) Taken from a portion of the dissertation submitted to the faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, 1964.

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(3) M. L. Moore and F. S. Crossley, *J. Am. Chem. Soc.*, **62**, 3273 (1940).

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(8) R. Zimmerman, *Angew. Chem.*, **74**, 906 (1962).

(9) M. C. Wani, Ph.D. thesis, Indiana University, 1962, p. 92. Information also kindly furnished by Professor E. Campaigne in report to Office of Surgeon General.

TABLE I

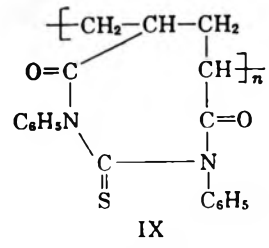
N.M.R. SPECTRA

Compound	Solvent	Proton	Chemical shift, τ	J, c.p.s.
VIa[a]	D_2O[b]	$=N-CH_2-CH_2-N=$	6.04[c]	
		$-CH_2-S-$	6.73	*ca.* 4.9[d]
		$-CH_2-C=O$	7.02	*ca.* 4.9[d]
VIb	D_2O[b]	$=N-CH_2-CH_2-N=$	6.08[c]	
		$-CH_3$	8.52[e]	6.4
		$-S-CH_2-CH-C=O$	6.78[f]	
IIIa	D_2O[b]	$=N-CH_2-CH_2-N=$	5.72, 5.55	*ca.* 3.7[d]
		$-CH_2-C=O$	6.69	*ca.* 5.5[d]
		$-CH_2-S-$	6.24	*ca.* 5.5[d]
IIIb	D_2O[b]	$=N-CH_2-CH_2-N=$	5.78, 5.16	*ca.* 2.1[d]
		$-CH_3$	8.44[e]	6.5
		$-S-CH_2-CH-C=O$	6.86–6.24, 6.41[g]	
VIIIa	$CDCl_3$[h]	$-CH_2-CH_2-$	7.18[c]	
		o-H's of C_6H_5	3.55–3.18[f]	
		m- and *p*- H's of C_6H_5	3.18–2.50[f]	
VIIIb	$CDCl_3$[h]	$-CH_2-CH-$	7.07[f]	
		$-CH_3$	8.65[e]	4.9
		o-H's of C_6H_5	3.38–3.05[f]	
		m- and *p*-H's of C_6H_5	3.05–2.50[f]	

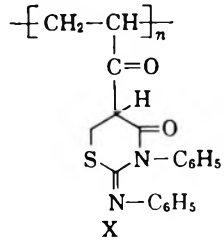
[a] Taken at 66°. [b] CH_3CN, calibrated against tetramethylsilane in D_2O, used as internal standard. [c] Singlet. [d] Symmetrical A_2B_2 system, $J_{AB} = J_{AB'}$. [e] Doublet. [f] Complex multiplet. [g] Main peak. [h] Tetramethylsilane used as internal standard.

equivocal synthesis from β-iodopropionic acid and *sym*-diphenylthiourea.[10]

When acrylyl chloride reacted with *sym*-diphenylthiourea in the presence of triethylamine a low molecular weight polymer was obtained. Elemental analysis and a molecular weight determination of the compound indicated a repeating unit composed of two acrylyl groups and one *sym*-diphenylthiourea moiety with a DP of 6–7. Structure[11,12] IX or X is suggested for the repeating unit on the basis of spectral evidence.



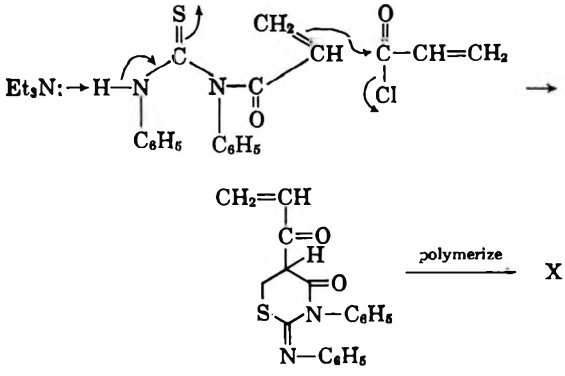
IX



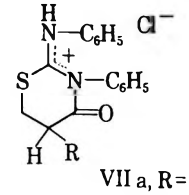
X

(10) Langlet, *Ofversigt K. Vetensk.-Akad. Forhandligar*, 41 (1895); Beilstein's Handbuch Der Organischen Chemie, **27**, 248 (1919).

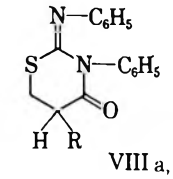
(11) Similarities in the infrared spectrum of the polymer with both *sym*-diphenylthiourea and VIIIa do not permit a definite assignment of structure. The formation of IX could be accomplished by a cyclopolymerization of N,N'-diphenyl-N,N'-diacrylylthiourea, whereas X could be formed by reaction of N,N'-diphenyl-N-acrylylthiourea with triethylamine and acrylyl chloride in the following way.



(12) A ferric chloride test was carried out, in chloroform, in an attempt to distinguish between structures IX and X. However, anomalous results were obtained. The procedure followed was that to be found in N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd Ed., Interscience Publishers, New York, N. Y., 1957, p. 228, section B.



VII a, R = H
b, R = CH_3



VIII a, R = H
b, R = CH_3

A similar reaction with methacrylyl chloride did not lead to polymer formation.

Alkaline hydrolysis of compounds VIIIa and b, as well as the polymer, led to formation of *sym*-diphenylthiourea. The polymer yielded, in addition, a polymeric acid. It is interesting that no *sym*-diphenylurea could be isolated. Bhargava and Ram[13] reported that alkaline hydrolysis of the five-membered analog of VIIIa, 3-phenyl-2-phenylimino-4-ketotetrahydrothiazole, gives *sym*-diphenylurea. The hydrolysis of compound VIIIa (as well as VIIIb and the polymer) could take place *via* a hydrolytic route.

The infrared, ultraviolet, and nuclear magnetic resonance spectra of these compounds were reasonably definitive. The key peaks in the infrared appear to depend upon the structure of the heterocycle involved. These are to be found in the Experimental section.

It may be noted that the substitution of a phenyl group for an alkyl group on the lactam nitrogen, such as in VIIIa and b resulted in a shift of the carbonyl stretching frequency of the lactams by 25–30 cm.$^{-1}$. The shift in the same frequency of these compounds upon protonation may be attributed to a delocalization of the electron density over a three-atom system which includes both nitrogen atoms. This inductive effect would be similar to that experienced by the carbonyl group of an ester.

The ultraviolet spectra of the compounds are to be found in the Experimental section. Note that the spectra of the bases and of the polymer are similar for the most part. The protonated derivatives exhibited a bathochromic shift of wave length.

(13) P. M. Bhargava and P. Ram, *J. Indian Chem. Soc.*, **38**, 127 (1961).

The nuclear magnetic resonance spectra of the salts are more complex than that of their corresponding free bases. These differences are summarized in Table I. The n.m.r. spectrum of the polymer did not yield useful information, other than to indicate the lack of vinyl protons. The bands are too broad to be of diagnostic value in assigning a definite structure to the compound.

Experimental[14,15]

Reaction of Unsaturated Acid Chlorides with Ethylenethiourea. A. 2,3,6,7-Tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazin-5-one Hydrochloride (IIIa) and Its Free Base, VIa.—Ethylenethiourea (5.1 g., 0.05 mole) was added to 50 ml. of anhydrous acetone (dried over molecular sieves). A solution of acrylyl chloride (4.5 g., 0.05 mole) in 25 ml. of anhydrous acetone was added slowly to the reaction flask. The slurry was magnetically stirred for 3 hr. while in an ice bath. A drying tube protected the mixture from moisture. The yield of crude product was quantitative. A 3-g. sample yielded 2 g. (66.7%), m.p. >250° dec., upon one recrystallization from 95% ethanol. Four recrystallizations from the solvent gave analytically pure sample, m.p. >250° dec. (m.p. 277–278°, prepared by the reaction of ethylenethiourea and acrylic acid in the presence of hydrogen chloride followed by refluxing the product in ethanol[9]).

The infrared absorption spectrum of the salt showed absorption at 1730, 1715 (shoulder, s, C=O), 1600 (s, C=N), and 2650–3200 cm.$^{-1}$ (m, NH^+). The ultraviolet absorption spectrum showed $\lambda_{max}^{H_2O}$ 238 mμ (ε 13,180).

Anal. Calcd. for $C_6H_9ClN_2OS$: C, 37.41; H, 4.71; N, 14.54; S, 16.65. Found: C, 37.45; H, 4.81; N, 14.34; S, 16.62.

Recrystallization of the purified salt from absolute ethanol containing sufficient diethylamine to neutralize the acid gave its free base in a yield of 46.5%, m.p. 138–141°. Recrystallization of this base from absolute ethanol yielded colorless crystals, m.p. 142–144.5° (m.p. 144°, prepared by reaction of the hydrobromide of VIa with ammonium hydroxide[9]).

The infrared absorption spectrum of the base showed absorption at 1670, 1660 (shoulder, s, C=O), and 1600 cm.$^{-1}$ (s, C=N). The ultraviolet absorption spectrum showed $\lambda_{max}^{CH_3OH}$ 229 mμ (ε 11,600).[16]

Anal. Calcd. for $C_6H_8N_2OS$: C, 46.13; H, 5.16; N, 17.93; S, 20.53. Found: C, 46.25; H, 5.38; N, 17.65; S, 20.24.

B. 6-Methyl-2,3,6,7-tetrahydro-5H-imidazo-[2,1-*b*]-1,3-thiazin-5-one Hydrochloride (IIIb) and Its Free Base, VIb.—Compound IIIb was prepared by using a procedure similar to the above. Methacrylyl chloride replaced the acrylyl chloride used. The crude product was isolated in a yield of 95%. One recrystallization of a 6-g. sample from 95% ethanol yielded 3 g. (50%) of the compound, m.p. 260–280°. Recrystallization of the compound from the solvent to constant melting point gave a colorless solid, m.p. 275–280° dec.

The infrared absorption spectrum of the salt showed absorption at 1710 (s, C=O), 1600 (s, C=N), and 2630–3100 cm.$^{-1}$ (m, NH^+). The ultraviolet absorption spectrum showed $\lambda_{max}^{H_2O}$ 238 mμ (ε 13,020).

Anal. Calcd. for $C_7H_{11}N_2ClOS$: C, 40.68; H, 5.36; N, 13.55; S, 15.51. Found: C, 40.87; H, 5.32; N, 13.05; S, 15.75.

The free base of the above salt was prepared by stirring a slurry of 5 g. of the purified salt in 25 ml. of acetone containing a slight excess of diethylamine, for about 5 min. The solid remaining, diethylamine hydrochloride, was filtered. Evaporation of the supernatant liquid yielded a crude sample of the base. The compound was dissolved in hot benzene and filtered. Evaporation of the benzene followed by extraction of cyclohexane gave 2.5 g. (60.7% based on moles of salt used), m.p. 76–79°. Recrystallization of the base to constant melting point from cyclohexane yielded an analytical sample, m.p. 77–79.5°.

The infrared absorption spectrum of the base showed absorption at 1670 (s, C=O), and 1600 cm.$^{-1}$ (s, C=N). The ultraviolet absorption spectrum showed $\lambda_{max}^{CH_3OH}$ 231 mμ (ε 10,930).

Anal. Calcd. for $C_7H_{10}N_2OS$: C, 49.39; H, 5.92; N, 16.46; S, 18.84. Found: C, 49.64; H, 5.93; N, 16.15; S, 18.66.

All of the above compounds were found to be soluble in water and ethanol. Compound IIIa, upon being placed in refluxing toluene for 17 hr., did not lose hydrogen chloride and was recovered unchanged.

Reaction of Unsaturated Acid Chlorides with *sym*-Diphenylthiourea. A. 2,3,5,6-Tetrahydro-2-phenylimino-3-phenyl-4H-1,3-thiazin-4-one Hydrochloride (VIIa) and Its Conjugate Base, VIIIa.—Acrylyl chloride (9.0 g., 0.1 mole), dissolved in 50 ml. of chloroform, was slowly added to a solution of *sym*-diphenylthiourea (22.8 g., 0.1 mole) in 50 ml. of chloroform. The mixture was magnetically stirred for 3 hr. and was cooled in an ice bath. A drying tube protected the reaction mixture from moisture. Evaporation of the chloroform yielded a yellow semisolid.

The reaction was worked up in two ways. To obtain the salt VIIa, the mixture was extracted with benzene. A white powder (26.5 g., 83.3% yield) was obtained which was insoluble in the benzene. Upon standing, the powder became lumpy and somewhat difficult to handle. Attempted purification of the salt from a variety of solvents led to evolution of hydrogen chloride with the formation of the base, VIIa. Refluxing solvents led to the complete transformation of the salt to the base. To obtain the base, the salt could either be decomposed in isopropyl alcohol or the original semisolid isolated could be crystallized from the solvent. In the latter case, the combined fractions yielded 21.1 g. (75% yield) of product. Recrystallization of a 3.5-g. sample from isopropyl alcohol yielded 3.0 g. (85.6%) of the compound, m.p. 167–170°. Several recrystallizations from the solvent yielded an analytical sample, m.p. 168.5–170.5°.

The infrared absorption spectrum of the salt showed absorption at 1740 (s, C=O), 1538 (s, C=N), and 2600–3050 cm.$^{-1}$ (m, NH^+). The base showed its abosrption at 1695 (s, C=O) and 1590 cm.$^{-1}$ (s, C=N). The ultraviolet absorption spectrum of the base showed $\lambda_{max}^{CH_3OH}$ 227 mμ (ε 22,300), and 268–281 (4000).[17]

Anal. Calcd. for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; S, 11.36. Found: C, 68.34; H, 5.16; N, 9.40; S, 11.24.

The compound was unequivocally synthesized from β-iodopropionic acid and *sym*-diphenylthiourea in acetic anhydride using the method of Langlet,[10] m.p. 168.5–170.5°, lit. m.p. 106°. This compound was identified as the same compound as VIIIa by melting point, mixture melting point, and an infrared spectral comparison.

B. 5-Methyl-2,3,5,6-tetrahydro-2-phenylimino-3-phenyl-4H-1,3-thiazin-4-one Hydrochloride (VIIb) and Its Free Base, VIIIb.—A procedure similar to the above was followed in preparation of compounds VIIb and VIIIb. Methacrylyl chloride (10.4 g., 0.1 mole) was used in place of acrylyl chloride. The yield of the crude salt VIIb obtained by the above procedure was 20 g. (60.1% yield based on the salt). The properties of this compound were the same as that of VIIa. The base VIIIb may be obtained by decomposing the salt by crystallization from isopropyl alcohol. This afforded 14 g. of the free base, m.p. 128–131°. Several recrystallizations from the solvent yielded an analytical sample, m.p. 131–133°.

The infrared absorption spectrum of the salt showed absorption at 1740 (s, C=O), 1538 (s, C=N), and 2600–3050 cm.$^{-1}$ (s, NH^+). The base showed its absorption at 1700 (s, C=O and 1590 cm.$^{-1}$ (s, C=N). The ultraviolet absorption spectrum of the base showed $\lambda_{max}^{CH_3OH}$ 227.5 mμ (ε 23,000), 268–281 (4150).[17]

Anal. Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.78; H, 5.65; N, 9.66; S, 10.54.

The ability to isolate the salts in the above two procedures is dependent upon the degree of decomposition that takes place during the course of the reaction.

The yield of the free bases depends upon the amount of impurities present in the solutions before their respective work-up.

Reaction of Unsaturated Acid Chlorides with *sym*-Diphenylthiourea in the Presence of Triethylamine.—Triethylamine (15.2 g., 0.15 mole) was added to a solution of *sym*-diphenylthiourea (11.4 g., 0.05 mole) in 50 ml. of chloroform. Acrylyl chloride (9.1 g., 0.1 mole), dissolved in 25 ml. of chloroform, was added dropwise to the solution. The mixture was magnetically stirred for 8 hr. and was cooled in an ice bath during the period of addition of the acid chloride. A drying tube was used to protect the reaction from moisture. Evaporation of the solvent left an orange semisolid from which triethylamine hydrochloride was separated upon the addition of acetone. Concentration of the acetone solution and dropwise addition to ten times its volume of isopropyl alcohol yielded 10.5 g. (78.9% yield) of a cream-colored

(14) All melting points are uncorrected.

(15) Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, 77, N. Y.

(16) The λ_{max} for these compounds did not change when the solvent was changed to water.

(17) Plateau.

polymer. The polymer was purified by dissolution in methanol and reprecipitation from isopropyl alcohol. Repetition of this procedure yielded an analytical sample. The compound was soluble in acetone, chloroform, and acetonitrile.

The infrared absorption spectrum of the polymer showed absorption at 1695, 1718 (shoulder, s), and 1595 cm.$^{-1}$ (s, C=N). The ultraviolet absorption spectrum showed $\lambda_{max}^{CH_3CN}$ 230 mμ (ϵ 18,130) and 277 (5130).

Anal. Calcd. for $(C_{19}H_{16}N_2O_2S)_n$: C, 67.83; H, 4.79; N, 8.33; S, 9.53. Found: C, 67.63; H, 4.85; N, 8.49; S, 9.45; mol. wt. (T.E.M.), 2300. This corresponds to an average value of n as 6.8.

The above reaction was also carried out using methacrylyl chloride in place of acrylyl chloride. However, no characterizable product was obtained.

The infrared spectra of all the compounds were taken in potassium bromide on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer and the nuclear magnetic resonance spectra were determined on a Varian instrument operating at 60 Mc.

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cis Addition of Performic Acid to Indene and Nuclear Magnetic Resonance Spectra of 1,2-Disubstituted Indanes

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The addition of performic acid to indene has been shown to give *cis*-2-formyloxy-1-hydroxyindane (IV). The unexpected location of the formate group at C-2 was proved by chemical and n.m.r. evidence. The conversions of IV, its *trans* isomer (VI), and both *cis*- (I) and *trans*-1,2-dihydroxyindane (III) to 2-indanone by treatment with aqueous acid are discussed and a mechanism is proposed which differs from the mechanism previously proposed. The n.m.r. spectra of fifteen indane compounds are listed, and the data are interpreted in terms of nonplanar five-membered rings.

The addition of performic acid to indene in an aqueous formic acid medium has been found to give two major products, *cis*-1,2-dihydroxyindane (I) and *cis*-2-formyloxy-1-hydroxyindane (IV). Our study of the products from performic acid oxidation of indene stemmed from our interest in the synthesis of 2-indanone oxime and its subsequent reduction[2a] to 2-aminoindane hydrochloride, a potent nonnarcotic analgesic.[2b] Horan and Schiessler[3] recently described the preparation of 2-indanone in high yield by performic acid oxidation followed by dilute sulfuric acid treatment of the intermediate (incorrectly assumed to be 1-formyloxy-2-hydroxyindane). Thin-layer chromatographic examination of samples of the performic acid oxidation reaction showed that indene reacted rapidly with the performic acid to give approximately equal amounts of I and IV, only traces (less than a total of 3–5%) of the corresponding *trans* isomers III and VI, and a small amount of a less polar material (possibly 1,2-diformyloxyindane).[4] Under the reaction conditions, *cis* and *trans* isomers were not equilibrated, so the *cis* products clearly resulted from a *cis* addition rather than from a secondary equilibration. It is not possible to say whether I or IV is the primary product, or whether both products form simultaneously, because equilibration of I and IV occurs fairly rapidly in the reaction mixture.

The addition of deuterium bromide to indene was recently shown by Dewar and Fahey[5] to give 80% *cis*- and only 15–20% *trans*-1-bromo-2-deuterioindane. The proposed mechanism involved formation of an ion pair, consisting of a benzyl-type carbonium ion and a solvated bromide ion, which either collapsed directly to the *cis* adduct or isomerized and then collapsed to the *trans* adduct. The Dewar and Fahey mechanism[5] would predict the unknown *cis*-1-formyloxy-2-hydroxyindane as the primary product of performic acid addition to indene; this predicted product would have to undergo rapid acyl migration to give the isolated ester product (IV). The observed products I and IV cannot be explained by formation of an epoxide and its acid-catalyzed opening to a benzyl-type carbonium ion (or alternatively, attack of OH^+ to give this carbonium ion directly), followed by *cis* attachment of formate ion and subsequent acyl migration, because treatment of 1,2-epoxyindane[6,7] under the conditions of the performic acid oxidation gave a complex mixture of *cis*- and *trans*-disubstituted derivatives. One possible mechanism for the formation of IV is *cis* addition of performic acid to indene, either as a four-centered or as a

(1) To whom inquiries should be directed at Cambridge Research, Inc., Roselle, N. J. 07203.

(2) (a) W. E. Rosen and M. J. Green, *J. Org. Chem.*, **28**, 2797 (1963); (b) L. B. Witkin, C. F. Huebner, F. Galdi, E. O'Keefe, P. Spitaletta, and A. J. Plummer *J. Pharmacol. Exptl. Therap.*, **133**, 400 (1961).

(3) J. E. Horan and R. W. Schiessler, *Org. Syn.*, **41**, 53 (1961).

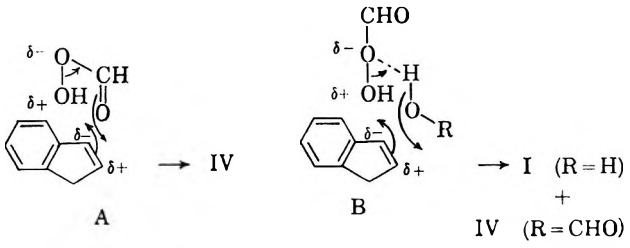
(4) (a) W. Nagata and T. Terasawa [*Chem. Pharm. Bull* (Tokyo), **9**, 745 (1961)] reported the formation of some *cis*-2-benzoyloxy-1-hydroxy product from perbenzoic acid oxidation of 6-methoxy-3,4-dihydronaphthalene. The only *trans* isomer isolated was the *trans*-1-benzoyloxy-2-hydroxy product, presumably resulting from displacement of the intermediate epoxide with benzoate anion at C-1. The authors suggested that the *cis*-2-benzoyloxy-1-hydroxy product resulted from acyl migration of an initially formed *cis*-1-benzoyloxy-2-hydroxy isomer (*not* isolated). (b) After this paper had been submitted for publication, the authors became aware of the report by E. Vogel, W. Frass, and J. Wolpers [*Angew. Chem.*, **75**, 979 (1963)] on the *cis* hydroxylation of dibenzocyclooctatriene with performic acid.

(5) M. J. S. Dewar and F. C. Fahey, *J. Am. Chem. Soc.*, **85**, 2248 (1963).

(6) Originally, there was was some doubt as to whether peracid addition to indene preceded epoxide formation or whether epoxide formation preceded disubstitution [see, for example, J. Böeseken and G. Elsen, *Rec. trav. chim.* **48**, 363 (1929); J. Böeseken and G. C. C. C. Schneider, *J. prakt. Chem.*, **131**, 285 (1931)]. Recent workers have concluded that the epoxide is the initial product [*e.g.*, B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955)] and that disubstituted products result from opening of the epoxide ring [*cf.* R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959)]. Although exceptions to the normal *trans* opening of the epoxide ring have been observed [*e.g.*, C. C. Tung and A. J. Speziale, *J. Org. Chem.*, **28**, 2009 (1963)], such a *cis* opening of 1,2-epoxyindane would be expected to lead to *cis*-1-formyloxy-2-hydroxyindane.

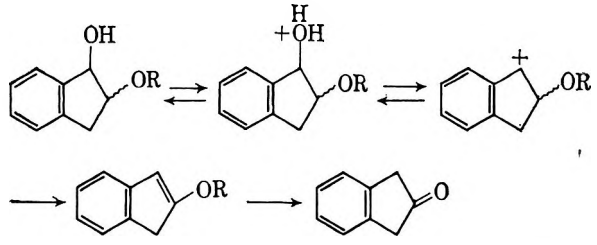
(7) (a) The opening of 1,2-epoxyindane with aqueous acid to give mixtures of *cis*- and *trans*-1,2-dihydroxyindane was reported by Böeseken (ref. 22); (b) H. Bodot, J. Jullien, and E. Leblanc [*Bull. soc. chim. France*, 41 (1962)] described the treatment of 1,2-epoxyindane with hydrogen chloride in dioxane to give 9% 2-indanone, 21% *trans*-1-chloro-2-hydroxyindane, and 64% *cis*-1-chloro-2-hydroxyindane. They attributed the lack of specificity to an intermediate benzyl-type carbonium ion.

six-centered reaction (see structure A). A possible explanation for a simultaneous formation of I and IV is a trimolecular reaction of indene, performic acid, and either water or formic acid (see structure B).



When the performic acid oxidation mixture was held at −15°, a 35% yield of *cis*-2-formyloxy-1-hydroxyindane (IV) was isolated. When heat (steam bath, 1 hr.) was applied, some of the *trans* isomers (VI and III) were generated. Interestingly, the crude reaction mixture, which included *trans* isomers, gave the same yield of 2-indanone on treatment with aqueous sulfuric acid as did pure *cis*-2-formyloxy-1-hydroxyindane (IV). In fact, examination of pure *cis* and *trans* glycols and their corresponding 2-formates (see Table III) showed that each of these components of the crude reaction mixture was converted by aqueous sulfuric acid to 2-indanone at approximately the same rate and in about the same yield.

The mechanism proposed previously[8] for conversion of *trans* glycol (III) to 2-indanone involved prior isomerization to the *cis* glycol (I). This proposal was based in part on the known interconversion of *cis* glycol (I) and *trans* glcyol (III) in aqueous acid,[9] and in part on a consideration of the rates of formation of 2-indanone from I and III. From the similarity in the rates of conversion of the four compounds, I, III, IV, and VI, in strong aqueous acid (see Table III) and from the dependence of the rate of 2-indanone formation on acid concentration (see Fig. 1), we suggest instead that all four compounds are converted to 2-indanone by protonation of the 1-hydroxyl group and elimination of water followed by elimination of a proton and ketonization of the resulting enol or enol ester. The attack of water on the benzyl carbonium ion intermediate, generating either starting material or its 1-epimer, would account for the interconversion of the glycols.



The monoformate product (IV), from performic acid oxidation of indene was shown to be *cis* by saponification to the known *cis*-1,2-dihydroxyindane (I)[9,10] and by formylation of I back to IV. A similar interconversion was carried out between *trans*-2-formyloxy-1-hydroxyindane (VI) and *trans*-1,2-dihydroxyindane (III). As described previously,[9,10] the *cis* glycol (I) but not the *trans* glycol (III) formed an acetonide derivative (II) after short treatment with acetone in the presence of acid catalyst. From the methods of preparation of the compounds (*e.g.*, I from potassium permanganate oxidation of indene[11] and III from aqueous alkaline treatment of 1,2-epoxyindane[10b]) and from their chemical reactions (*e.g.*, I but not III forms an acetonide derivative under mild conditions[10b] and also increases the conductivity of a boric acid solution[10b]), the stereochemical descriptions of both glycols I and III may be considered unambiguous. The position of attachment of the formyl group in compounds IV and VI has been shown by chemical conversions and by interpretations of nuclear magnetic resonance spectra.

Chromic anhydride–pyridine oxidation of IV and of VI gave 2-formyloxy-1-indanone (V) in high (90–100%) yield.[12] The ultraviolet absorption spectrum of V (λ_{max} 248 mμ, ε 13,350) was consistent with those of known 2-substituted 1-indanones. In contrast to the moderate instability of 2-acetoxy-1-indanone,[13] V was quite stable on prolonged standing at room temperature. The 2,4-dinitrophenylhydrazone derivative of V formed readily, and its ultraviolet absorption spectrum (λ_{max} 384 mμ, ε 32,000) confirmed[14] the 2-substituted 1-indanone structure. Short warming of V in aqueous ethanol with semicarbazide hydrochloride and sodium acetate, however, caused hydrolysis of the formate grouping, and gave 2-hydroxy-1-indanone semicarbazone.

An attempt was made to convert IV and VI to 1-methoxy-2-indanone (VIII), in order to provide chemical proof of the C-2 location of the formate groups of IV and VI. The hydroxyl groups at C-1 were etherified with diazomethane in methylene chloride, using fluoboric acid catalyst, giving *cis*-2-formyloxy-1-methoxyindane (VII) from IV and *trans*-2-formyloxy-1-methoxyindane (IX) from VI. Saponification of either VII or IX to the corresponding 2-hydroxy-1-methoxyindane, followed by sodium dichromate oxidation, was expected to give pure VIII. In fact, both VII and IX gave mixtures of products in which VIII was presumably only one component. Attempts to isolate pure VIII by vapor phase chromatography were unsuccessful. The ultraviolet and infrared absorption spectra of the two product mixtures were the same, and ultraviolet absorption intensity measurements suggested that less than 25% of a 1-keto product was present (possibly as a 1,2-diketone[13]). When either product mixture was treated with 2,4-dinitrophenylhydrazine under mild conditions, only the osazone X was isolated. Osazone formation must have resulted either from reaction of indane-1,2-dione in the product mixture, or from oxidation of VIII by 2,4-dinitrophenylhydrazine.[14,15] The isomer of VIII, 2-methoxy-1-indanone, was reported to form its 2,4-dinitrophenylhydrazone derivative without difficulty.[14,16]

(8) C. M. Suter and H. B. Milne, *J. Am. Chem. Soc.*, **62**, 3473 (1940).

(9) P. H. Hermans, *Ber.*, **57**, 824 (1924).

(10) (a) C. van Loon, dissertation; Delft, 1919; (b) C. van Loon, *Koninkl. Akad. Wetenschap. Amsterdam*, **28**, 213 (1919); *Chem. Zentr.*, I, 331 (1920); (c) P. E. Verkade, J. Coops, Jr., C. J. Maan, and A. Verkade-Sandbergen, *Ann.*, **467**, 217 (1928); (d) S. Winstein and R. M. Roberts, *J. Am. Chem. Soc.*, **75**, 2297 (1953).

(11) F. Heusler and H. Schieffer, *Ber.*, **32**, 28 (1899).

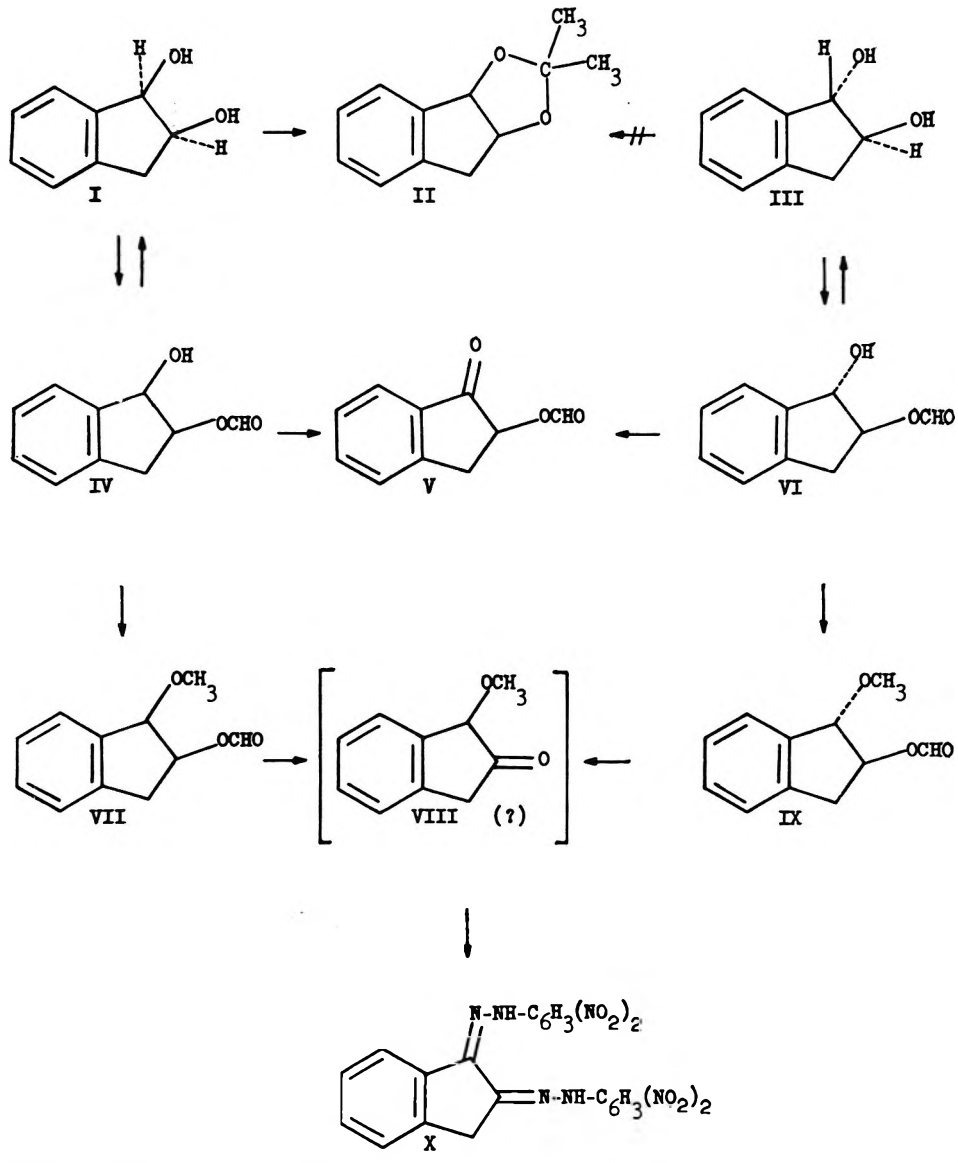
(12) With the *cis* monoformate, this evidence by itself is inconclusive in establishing the location of the formyloxy group, because formyl migration from the C-1 oxygen to the C-2 oxygen followed by oxidative attack on the active benzyl hydrogen would also result in formation of V. Such migration of the formyl group with the *trans* monoformate, however, is less likely.

(13) F. Ishiwara, *J. prakt. Chem.*, **108**, 194 (1924).

(14) F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, **75**, 6026 (1953).

(15) The oxidizing capacity of 2,4-dinitrophenylhydrazine has been discussed by E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 1762 (1951).

(16) W. Treibs and W. Schroth, *Ann.*, **639**, 204 (1961).



The chemical evidence from oxidation reactions (to V and VIII), therefore, suggested that the formyloxy group was at C-2. Unambiguous proof of this assignment, however, was obtained only by study of the n.m.r. spectra.

Nuclear Magnetic Resonance Spectra.[17]—In both *cis*- and *trans*-1,2-dihydroxyindanes, the hydrogen at C-1 appeared at the lowest field, followed in turn at higher fields by the hydrogen at C-2 and the two hydrogens at C-3, as expected. The assignments of the formate groups of compounds IV and VI to the C-2 positions were confirmed by the paramagnetic shifts of 64 and 54 c.p.s., respectively, for the C-2 proton signals of the *cis* and *trans* compounds. These values are in agreement with those observed for acylation of secondary alcohols.[18]

The *cis* and *trans* derivatives differed significantly in their spin–spin coupling patterns for the hydrogens at C-3 (see Table I). In the *trans* compounds, these hydrogens were split into an octet (AB of an ABXY type, in which Y has only a minimal influence on AB). In the *cis* compounds, these hydrogens were split into a doublet or into two nearly superimposable doublets between which there was no observable coupling of the AB (C-3) hydrogens. In both *cis* and *trans* derivatives, the C-2 hydrogen signal, although undoubtedly complex, appeared as a quartet having a 1:3:3:1 intensity ratio. This quartet implies that the three hydrogens adjacent to the C-2 hydrogen act as almost equivalent neighbors, all having coupling constants of approximately 5 c.p.s. In both *cis* and *trans* derivatives, the C-1 hydrogen signal appeared as a doublet, having a coupling constant with the C-2 hydrogen of *ca.* 5 c.p.s.

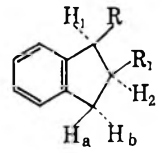
In Table I, the larger coupling constant has been assigned to the C-3 hydrogen (H_b) which is *cis* to the C-2 hydrogen (H_2). This assignment is consistent with the expected difference in dihedral angles between *cis*- and *trans*-related hydrogens (see discussion below). Since the stereochemical structures of the *cis* and *trans* glycols and their derivatives have been proved chemically, the relationship of the hydrogen at C-1 (H_1) to the hydrogen at C-2 (H_2) is known. In a given *cis* compound, the coupling constant between H_1 and H_2 was

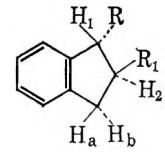
(17) The spectra were obtained with a Varian A-60 spectrometer at 60 Mc./sec. using deuteriochloroform (or pyridine as indicated). All data are reported in cycles per second (c.p.s.) from tetramethylsilane as internal standard. Since the differences in the chemical shifts of the individual protons were large compared with their coupling constants, a first-order treatment (ABX and ABXY) was given to the spectra. The coupling constants for H_1 *cis* and *trans* to H_2, therefore, may be in error by a small amount (*ca.* 1 c.p.s.), but this small error would not affect the conclusions reached.

(18) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Ltd., London, 1959, p. 55.

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR *cis*- AND *trans*-1,2-DISUBSTITUTED INDANE DERIVATIVES



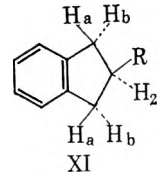


R	R_1		H_a[a]	H_b[a]	H_2[a]	H_1[a]	Other hydrogens[a]
OH	OH	*cis*	175 d (4.4)	177 d (5.2)	259 m	291 d (5.3)	OH 205
		cis[b]	189 d (4.2)	191 d (5.1)	282 m	316 d (5.4)	
		trans[b]	206 q (7.0, 15.7)	183 q (8.2, 15.7)	296 m	333 d (5.6)	
OH	OCHO	*cis*	190 d (3.9)	189 d (5.6)	335 m	314 q (4.9, 7.5)[c]	OH[c] 142 d (7.5), CHO 488
		cis[b]	185 d (4.2)	190 d (6.0)	346 m	330 d (5.1)	
		trans[b]	172 q (5.6, 16.1)	213 q (6.7, 16.1)	350 m	338 d (6.0)	
OCH_3	OCHO	*cis*	188 d (5.6)		335 m	284 d (5.0)	OCH_3 206, CHO 486
		trans	167 q (4.3, 15.9)	211 q (6.9, 15.9)	329 m	286 d (3.3)	OCH_3 208, CHO 480
$OCOCH_3$	OCHO	*cis*	192 d (5.6)	193 d (6.0)	340 m	376 d (5.5)	CH_3CO 124, CHO 485
OH	Br	*trans*[f]	216 q (6.8, 16.2)	190 q (7.6, 16.2)	255 m	318 d (5.5)	OH 156
Br	Br	*trans*[g]	192 q (1.8, 17.7)	228 q (5.0, 17.7)	292[d]	338 d (*ca.* 1)[c]	
OH	NH_2	*trans*[h]	159 q (5.2, 15.9)	185 q (6.2, 15.9)	215 m	285 d (5.4)	OH, NH_2, 153

[a] d = doublet, q = quartet, m = multiplet, ( ) = coupling constant in c.p.s. [b] The solvent was pyridine instead of deuteriochloroform. [c] On addition of D_2O, the hydroxyl doublet was reduced to a singlet and the H_1 quartet became a doublet. [d] The H_2 signal was a doublet and each peak of the doublet was split into a triplet, J = *ca.* 1 c.p.s. [e] The C-3 hydrogens appeared to be long range coupled with the C-1 hydrogen, J = *ca.* 1.5 c.p.s. [f] For preparation, see W. J. Pope and J. Read, *J. Chem. Soc.*, **99**, 2071 (1911); **101**, 758 (1912); and ref. 8. For stereochemistry, see ref. 23. [g] For preparation, see ref. 10d. [h] For preparation, see ref. 1.

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR 2-MONOSUBSTITUTED INDANE DERIVATIVES AND FOR 2-FORMYLOXY-1-INDANONE (V)



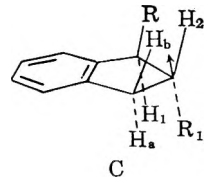
XI

	H_a[a]	H_b[a]	H_2[a]	Other hydrogens
XI, R = NH_2[b]	157 q (5.2, 15.4)	191 q (6.6, 15.4)	228[c]	NH_2 78
XI, R = NH_2[b,d]	158 q (5.8, 15.6)	187 q (6.7, 15.6)	227[c]	NH_2 99
XI, R = $NHCOCH_3$[b]	165 q (5.2, 16.0)	197 q (6.9, 16.0)	280[c]	NH 390
XI, R = $NHOH \cdot H_2O$[b]	167 q (4.8, 16.2)	188 q (5.8, 16.2)	233[c]	
V	187 q (5.3, 17.6)	227 q (7.8, 17.6)	340 dd[e]	CHO 507

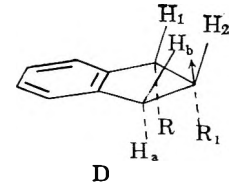
[a] d = doublet, q = quartet, ( ) = coupling constant in c.p.s. [b] See ref. 4. [c] Two overlapping triplets. [d] The solvent was pyridine instead of deuteriochloroform. [e] dd = double doublet.

closer in value to that of H_2 and H_b whereas, in a given *trans* compound, the coupling constant between H_1 and H_2 was closer to that of H_2 and H_a. However, without an unambiguous replacement of one of the C-3 hydrogens by deuterium, these assignments cannot be considered rigorous.

The data can be interpreted in terms of a nonplanar five-membered ring.[19] In the *trans* compounds, a planar ring would give dihedral angles of 120° between H_2 and H_a and of 0° between H_2 and H_b. On the basis of Karplus' values,[20] a difference of *ca.* 4 c.p.s. in spin–spin coupling constants would be expected between such pairs of vicinal hydrogens, the *cis*-related hydrogens having the higher coupling constant. In fact, the difference between these coupling constants is only *ca.* 1–3 c.p.s. Distortion of C-2 from the plane of the five-membered ring, resulting in dihedral angle increases of both the *cis*-related and *trans*-related hydrogens (see structure C), would account for the observed coupling constants. Such increases in dihedral angles would result in a slightly lower coupling constant than expected for the *cis*-related hydrogens and a much higher coupling constant for the *trans*-related hydrogens. The multiplicity of the signals from the C-3 hydrogens in the *trans* compounds and their difference in chemical shift (23–44 c.p.s.) is expected since these hydrogens lie in quite different environments. The striking feature of *cis* compounds is the equivalence or near equivalence in chemical shift of the two C-3 hydrogens. This similarity in chemical shift may be a result of distortion of



C



D

(19) Cyclopentene compounds (including compounds I and III) have been studied experimentally and theoretically by F. V. Brutcher, Jr., and E. L. James [*Dissertation Abstr.*, **24**, 1398 (1963)], who found that puckering of the ring corresponded to a minimum energy conformation.

(20) (a) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963); (b) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959). (c) The compounds discussed here are far from ideal. In addition to the strain of the five-membered ring, factors such as altered carbon–carbon bond lengths and the presence of electronegative substituents are hard to evaluate. Hydrogen bonding effects almost certainly influence the structures of hydroxyl-containing compounds. Nevertheless, a neglect of these factors and consideration only of dihedral angles seems to give a simple qualitative interpretation of the data.

C-2 from the plane such that the C-2 substituent exerts nearly identical magnetic anisotropy on both C-3 hydrogens (see structure D). Such a distortion would relieve the steric hindrance of eclipsed functional groups in the *cis* compounds

The n.m.r. spectra described in Table II may also be interpreted in terms of a nonplanar five-membered ring. With the 2-monosubstituted indane compounds, the small difference in coupling constants (1–2 c.p.s.) between *cis*-related and *trans*-related hydrogen pairs was similar to the difference observed in the *trans*-1,2-disubstituted indane compounds. These 2-monosubstituted compounds show octets which differ from those of the C-3 hydrogens in the *trans*-1,2-disubstituted compounds only in that they represent four hydrogens instead of two. The two quartets representing the two H_a hydrogens (*trans* related to H_2) are superimposed, as are also the two quartets representing the two H_b hydrogens. Support for the equivalence of both H_a–H_2 couplings and of both H_b–H_2 couplings was provided by the two nearly superimposable triplets representing the C-2 hydrogen (H_2). The n.m.r. spectrum of 2-formyloxy-1-indanone was also similar to that of the *trans*-1,2-disubstituted indane compounds, having an octet for the C-3 hydrogens and a small difference in the coupling constants between H_2–H_a and H_2–H_b.

Experimental[21]

Preparation of *cis*-2-Formyloxy-1-hydroxyindane (IV) from Indene.[3]—A mixture of 350 ml. of 90% formic acid, 18 ml. of distilled water, and 60 ml. of 35% hydrogen peroxide, added to a 1-l. flask in that order, was stirred and warmed to 35° over 15 min. A total of 58.1 g. (0.50 mole) of indene was added over 2 hr., the reaction temperature being maintained at 35–40° by gentle water cooling. The reaction mixture was stirred at 35° for 1 hr. and then at room temperature overnight. Chilling at −15° for 3 days deposited white needles which were collected and washed with cold ethyl acetate, giving 31.1 g. (35.0%) of *cis*-2-formyloxy-1-hydroxyindane (IV), m.p. 127–130°. One crystallization from ethyl acetate gave 24.0 g. of white needles of IV, m.p. 132–134°; ν_{max} 3235, 3130, 1709, 1190 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{10}O_3$ (178.19): C, 67.41; H, 5.66; Found: C, 67.54; H, 5.65

A solution of 5.00 g. of *cis*-2-formyloxy-1-hydroxyindane (IV) in 35 ml. of pyridine was cooled to 0–5° and 4.00 ml. (4.42 g., 100% excess) of acetyl chloride was added dropwise over 15 min. with stirring and cooling. After 1 hr. at 0–5°, the suspension was warmed to room temperature for 1 hr., diluted with 300 ml. of benzene, and washed with water, 1.2 *N* hydrochloric acid, water, 5% aqueous sodium bicarbonate, and water. The solution was dried over anhydrous sodium sulfate, filtered, and stripped to dryness at reduced pressure, leaving 7.80 g. of tacky red solid. Crystallization from isopropyl alcohol (decolorizing with activated charcoal) gave 4.09 g. (69.5%) of orange crystals, m.p. 72–76°. Two additional crystallizations from isopropyl alcohol gave white prisms of 1-acetoxy-2-formyloxyindane, m.p. 74–77°; ν_{max} 1745 (broad), 1238, 1180 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{12}O_4$ (220.23): C, 65.45; H, 5.49. Found: C, 65.57; H, 5.47.

(21) Melting points were determined in an electrically heated aluminum block using open capillaries, and are uncorrected. Ultraviolet absorption spectra were determined in ethanol and infrared absorption spectra were determined as Nujol mulls, unless otherwise specified. Analytical samples were routinely dried *in vacuo* at 75° for 3–5 hr. Thin-layer chromatograms were carried out on silica gel G (E. Merck A. G., Darmstadt) using chloroform–ethyl acetate (1:1) as developing solvent. The plates were of standard thickness (250 μ) and were developed three times (dried between runs), the solvent mixture traveling 15 cm. each time. The *R* (cm.) values (distance traveled in centimeters after the three developments) were: I, 6.0; II, 13.5; III, 5.0; IV, 11.0; V, 12.5; and VI, 12.0. Nonpolar compounds such as indene, indene oxide, *trans*-2-bromo-1-hydroxyindane, 1-indanone, 2-indanone, and the acetyl derivatives of IV and VI all had values of 13.5–14.0.

Preparation of 2-Indanone from Indene.[3]—The reaction mixture described above in the preparation of *cis*-2-formyloxy-1-hydroxyindane (IV), after standing at room temperature overnight, had a total active oxygen content (hydrogen peroxide plus performic acid plus diformyl peroxide) of 0.10%. Addition of a freshly prepared solution of 10.6 g. of ferrous sulfate heptahydrate in 53 ml. of distilled water reduced the concentration of active oxygen to less than 2 p.p.m.

The dark amber solution was concentrated to 170 ml. (one-third volume) at reduced pressure, diluted with a warm mixture of 140 ml. of concentrated sulfuric acid in 860 ml. of water, and steam distilled. Two liters of steam distillate was extracted with three 100-ml. portions of methylene chloride, and the combined extract was washed once with water and dried over anhydrous sodium sulfate. After filtration, the solution was evaporated at reduced pressure to a light yellow oil which solidified to an off-white crystalline cake of 2-indanone weighing 59.4 g. (90% yield from indene). The 2-indanone may be purified by another

TABLE III

PREPARATION OF 2-INDANONE OXIME FROM 1,2-DISUBSTITUTED INDANES

Starting material	% sulfuric acid (medium[a])	Reflux time (min.)	Yield of oxime (%)[c]
I	25 (A)	30	73.4
	25 (A)	60	75.1
	20 (A)	30	73.9
	20 (A)	60	75.8
	20 (A)	*b*	79.0
III	25 (A)	30	75.3
	25 (A)	60	77.5
	20 (A)	30	73.6
	20 (A)	60	76.5
	20 (A)	*b*	68.9
VI	20 (A)	60	75.8
	20 (A)	*b*	81.1
IV	30 (A)	15	74.8
	30 (A)	30	73.6
	30 (A)	60	70.5
	25 (A)	15	74.8
	25 (A)	30	76.3
	25 (A)	60	75.3
	20 (A)	15	66.4
	20 (A)	30	74.6
	20 (A)	60	77.0
	20 (A)	*b*	78.0
	20 (B)	60	72.7
	20 (B)	*b*	81.9
	15 (A)	15	43.8
	15 (A)	30	60.8
	15 (A)	60	73.1
Crude I and IV	25 (A)	30	66.7
	25 (A)	60	66.0
	25 (B)	30	64.6
	25 (B)	60	59.2
	20 (A)	30	66.7
	20 (A)	60	68.1
	20 (A)	*b*	79.6
	20 (B)	30	66.7
	20 (B)	60	66.0
	20 (B)	*b*	77.0

[a] A = water medium, B = water–formic acid (6:1) medium. [b] Direct steam distillation over 1 hr. [c] Oxime was obtained as follows: 50 ml. of a preheated aqueous acid solution was added to 28.1 mmoles of starting material (*e.g.*, 4.21 g. of I or 5.00 g. of IV), and the mixture was refluxed for the specified time. After the mixture was rapidly cooled in an ice bath, it was extracted with four 20-ml. portions of methylene chloride. The combined extract was washed with water, dried, and concentrated at reduced pressure; the 2-indanone was removed by steam distillation. The work-up of the steam distillate by extraction, and the conversion of the extracted 2-indanone to oxime, is described in detail elsewhere in the Experimental section.

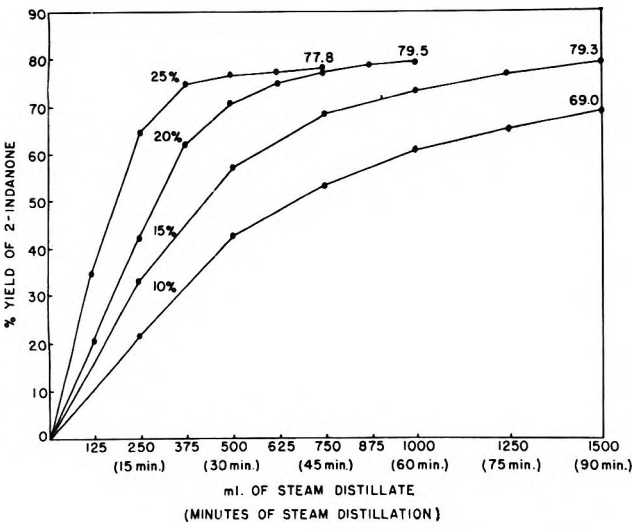


Fig. 1.—Rates of formation of 2-indanone by steam distillation from crude I and IV using different concentrations of sulfuric acid (in water–formic acid, 6:1); yields of 2-indanone are based on starting indene.

steam distillation (allowing pure 2-indanone to crystallize from the distillate) or it may be used directly for preparation of derivatives. Purified 2-indanone had m.p. 57–59°, lit.[3] m.p. 57–58°; ν_{max} 1740 cm.$^{-1}$; λ_{max} 261 mμ (ε 735), 268 (1050), 275 (1100), 296 (sh, 58).

The preparation of 2-indanone oxime from crude 2-indanone, by the method described previously,[1] gave an 85% yield of oxime, m.p. 154–155°. The yellow-orange 2-indanone 2,4-dinitrophenylhydrazone had m.p. 198–198.5°; $\lambda_{max}^{diglyme}$ 250–261 mμ (plateau, ε 12,120), 267 (12,060), 275 (sh, 10,430), 362 (23,390).

Anal. Calcd. for $C_{15}H_{12}N_4O_4$ (312.29): C, 57.69; H, 3.87; N, 17.94. Found: C, 57.80; H, 3.96; N, 17.63.

For comparison purposes, a sample of 1-indanone [m.p. 42–45°; $\nu_{max}^{CHCl_3}$ 1708, 1620 cm.$^{-1}$; λ_{max} 242–243 mμ (ε 12,890), 286–289 (2700), 291–292 (2720)] was converted to its orange-red 2,4-dinitrophenylhydrazone derivative, m.p. 257–258°; $\lambda_{max}^{diglyme}$ 298 mμ (sh, ε 8630), 312 (6820), 387 (31,310); lit.[14] $\lambda_{max}^{CHCl_3}$ 386 mμ (ε 30,200).

Anal. Calcd. for $C_{15}H_{12}N_4O_4$ (312.29): C, 57.69; H, 3.87; N, 17.94. Found: C, 57.76; H, 4.12; N, 17.90.

Preparation of *cis*-1,2-Dihydroxyindane (I) from *cis*-2-Formyloxy-1-hydroxyindane (IV).—A solution of 5.00 g. of *cis*-2-formyloxy-1-hydroxyindane (IV) in 17 ml. of ethanol and 17 ml. of 6 *N* aqueous sodium hydroxide was refluxed for 2.5 hr. The yellow solution was extracted with five 40-ml. portions of ether, and the combined extract was dried over anhydrous potassium carbonate. The filtered solution was stripped to dryness, leaving 4.14 g. (98.3%) of *cis*-1,2-dihydroxyindane, m.p. 94–97°. One crystallization from ethyl acetate raised the melting point to 99–101°, whereas one crystallization from toluene raised the melting point to 107–110° (two crystalline forms, m.p. 101° and m.p. 108°, have been reported[10c,22]), ν_{max} 3240–3340 cm.$^{-1}$.

A 1.00-g. sample of I in 20 ml. of acetone containing 0.5% sulfuric acid was heated on the steam bath for 5 min., cooled to room temperature, diluted with 100 ml. of benzene, and washed well with water, aqueous sodium bicarbonate, and water. The dried benzene solution was stripped to dryness at reduced pressure, leaving 1.22 g. (96%) of *cis*-1,2-dihydroxyindane acetonide (II), m.p. 69–72°. One crystallization from methanol–water gave white crystals, m.p. 70–71°, whose infrared spectrum showed no hydroxyl bands; ν_{max} 1260, 1210, 1052 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42. Found: C, 75.31; H, 7.27.

A stirred solution of 1.00 g. of *cis*-1,2-dihydroxyindane (I) in 30 ml. of pyridine was cooled to 5° and treated dropwise over 1 hr. at 5–10° with a previously prepared and cooled mixture of 20 ml. of formic acid (98–100%) and 8 ml. of acetic anhydride. After 30 more min. at 5–10°, the reaction mixture was allowed to stand overnight at room temperature, cooled, and diluted with 20 ml. of water. After 4 hr., the clear solution was further diluted with 150 ml. of water and was extracted with four 25-ml. portions of methylene chloride. The combined extract was washed free of pyridine with dilute hydrochloric acid washes, and the sodium sulfate dried solution was stripped to dryness at reduced pressure, leaving 1.29 g. of a white solid residue, m.p. 65–108°. Crystallization from ethyl acetate gave a first crop of 0.11 g. (9.3%) of white crystalline *cis*-2-formyloxy-1-hydroxyindane, m.p. 128–128.5°, no depression of melting point when mixed with authentic IV; the infrared spectrum was identical with that of authentic IV.

Anal. Found: C, 67.39; H, 5.78.

Preparation of *trans*-1,2-Dihydroxyindane (III) from *trans*-2-Bromo-1-hydroxyindane.[23]—A suspension of 41.2 g. of *trans*-2-bromo-1-hydroxyindane[8] in a solution of 48.4 g. of sodium carbonate in 725 ml. of water was stirred and refluxed for 3 hr., with a stream of nitrogen bubbling through the suspension. The hot reaction mixture was filtered, and the yellow filtrate was allowed to stand at room temperature overnight. The light brown solid was collected and dried *in vacuo* at 60°, and the 11.3 g. of crude material was thoroughly stirred with toluene, giving 9.2 g. (31.8%) of *trans*-1,2-dihydroxyindane (III), m.p. 157–159°. Crystallization from ethyl acetate gave 8.0 g. (27.7%) of white solid III, m.p. 160–163°, ν_{max} 3130–3210 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{10}O_2$ (150.18): C, 71.98; H, 6.71. Found: C, 71.68; H, 6.83.

Treatment of the acid-sensitive *trans*-1,2-dihydroxyindane (III) with 0.5% sulfuric acid in acetone (the same conditions under which the *cis* isomer I gave a 96% yield of acetonide, heat for 5 min.) resulted in the recovery of 61% crude III.

Preparation of *trans*-2-Formyloxy-1-hydroxyindane (VI) from *trans*-1,2-Dihydroxyindane (III).—A fine powder of 50.0 g. of *trans*-1,2-dihydroxyindane (III) in 750 ml. of 85% formic acid was stirred at 0–5° for 1 hr. and then stored at −20°. The monoformate VI deposited steadily, affording 15.6 g. (26%) of white solid, m.p. 139–140°, after 24 hr., and a total of 37.5 g. (63.2%) of white solid, m.p. 138–139°, after 4 months. A crystallization from ethyl acetate, followed by a crystallization from methanol–isopropyl alcohol, raised the melting point to 141–143°; ν_{max} 3270, 3170, 1731, 1239 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{10}O_3$ (178.19): C, 67.41; H, 5.66. Found: C, 67.40; H, 5.79.

Saponification of *trans*-2-formyloxy-1-hydroxyindane (VI) under the conditions described for converting IV to I (except that the *trans* glycol was extracted from the aqueous solution by ether continuously in a liquid–liquid extractor over 2 days) gave 87.0% *trans*-1,2-dihydroxyindane, m.p. 159–161°. One crystallization gave pure III, which had a melting point and mixture melting point with authentic III of 160–163°, and whose infrared spectrum was identical with that of authentic material.

Preparation of 2-Formyloxy-1-indanone (V) from *cis*-2-Formyloxy-1-hydroxyindane (IV).—To a thick yellow suspension of 4.00 g. of chromic anhydride in 40 ml. of dry pyridine was added 4.00 g. of *cis*-2-formyloxy-1-hydroxyindane (IV) at room temperature with stirring. The brown suspension was stirred overnight at room temperature, filtered (insolubles washed well with pyridine), diluted with 200 ml. of benzene, and washed free of pyridine with cold 6 *N* hydrochloric acid. The benzene solution was further washed with water and aqueous sodium bicarbonate, and dried over anhydrous sodium sulfate. The filtered solution was stripped to dryness at reduced pressure, leaving 3.55 g. (89.9%) of a pale green oil which crystallized on standing at 5°, m.p. 62–66°. Recrystallization from isopropyl alcohol followed by recrystallization from methanol–water gave 2.42 g. of colorless long needles of 2-formyloxy-1-indanone (V), m.p. 65–68°; λ_{max} 248 mμ (ε 13,350), 292 (2600); ν_{max} 1736, 1715, 1160 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_8O_3$ (176.17): C, 68.18; H, 4.58. Found: C, 68.30; H, 4.75.

The 2,4-dinitrophenylhydrazone derivative had m.p. 232–234° dec.; $\lambda_{max}^{diglyme}$ 267 mμ (sh, ε 11,460), 302 (sh, 4930), 316 (4510), 385 (29,460).

Anal. Calcd. for $C_{16}H_{12}N_4O_6$ (356.30): C, 53.94; H, 3.39; N, 15.73. Found: C, 54.25; H, 3.59; N, 15.99.

Preparation of 2-Hydroxy-1-indanone Semicarbazone from 2-Formyloxy-1-indanone (V).—To a warm solution of 0.25 g. of 2-formyloxy-1-indanone in 0.5 ml. of 95% ethanol and 0.5 ml. of water was added 0.20 g. of semicarbazide hydrochloride and 0.30 g. of sodium acetate. The mixture was warmed in boiling water for 1 min. and then cooled in an ice bath, to give 0.13 g. (39%) of a white solid, m.p. 175–178°. One crystallization from ethanol–water gave the semicarbazone, m.p. 183–185°; λ_{max}

(22) J. Böeseken, *Rec. trav. chim.*, **47**, 683 (1928).

224 mμ (ε 12,760), 231 (sh, 9150), 273 (16,220), 282 (17,470), 299 (17,330), 311 (16,080).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$ (205.22): C, 58.53; H, 5.40; N, 20.48. Found: C, 58.37; H, 5.46; N, 20.50.

Preparation of 2-Formyloxy-1-indanone (V) from *trans*-2-Formyloxy-1-indanone (IV).—Oxidation of *trans*-2-formyloxy-1-hydroxyindane (VI) with chromic anhydride in pyridine under the same conditions as that described above for the *cis* isomer (IV) gave a 98.4% yield of crude V, m.p. 61–64°. One crystallization from isopropyl alcohol gave a 76.6% yield of V, identical with that prepared from the *cis* isomer, m.p. 63–67°; λ_{max} 248 mμ (ε 12,900), 293 (2450); same infrared spectrum as V from IV. The 2,4-dinitrophenylhydrazone derivative had m.p. 239–240°; $\lambda_{max}^{diglyme}$ 266 mμ (sh, ε 12,500), 302 (sh, 5490), 317 (4980), 384 (32,000); same infrared spectrum as the derivative prepared using V from IV.

Anal. Found: C, 54.22; H, 3.41; N, 15.86.

Preparation of *cis*-2-Formyloxy-1-methoxyindane (VII) from *cis*-2-Formyloxy-1-hydroxyindane (IV).—A solution of 5.00 g. of *cis*-2-formyloxy-1-hydroxyindane (IV) in 400 ml. of methylene chloride was cooled to 0–5°, and 0.40 ml. of fluoroboric acid (purchased from the General Chemical Division of Allied Chemical Corp.; material nominally 48–50% was concentrated at reduced pressure to 62–64%, calculated by weight loss) was added. A cold solution of diazomethane was prepared by adding 17.0 g. of N-nitroso-N-methylurea over 45 min. to a stirred mixture of 32.0 g. of 50% potassium hydroxide solution and 200 ml. of methylene chloride at 0 to −10°, diluting with 100 ml. of ice-cold water, and drying the methylene chloride layer over potassium hydroxide pellets for 30 min. The cold diazomethane solution was added over 45 min. to the stirred solution of IV at 0–5°, and the solution was maintained at 0–5° for an additional 1.5 hr. The reaction mixture was washed with water, aqueous sodium bicarbonate, and water, dried over anhydrous sodium sulfate, filtered, and stripped to dryness. The 5.78 g. of yellow oil, which solidified when stored at −15°, was dissolved in 15 ml. of isopropyl alcohol at room temperature and the solution was treated with decolorizing charcoal, filtered, and chilled at −15° to give 1.63 g. (30.5%) of VII, m.p. 62–64°. One recrystallization from methanol–isopropyl alcohol gave fine white needles, m.p. 62–64°, which showed no hydroxyl absorption in the infrared, ν_{max} 1710 and 1190 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{12}O_3$ (192.22): C, 68.74; H, 6.29. Found: C, 68.54; H, 6.32.

Preparation of *trans*-2-Formyloxy-1-methoxyindane (IX) from *trans*-2-Formyloxy-1-hydroxyindane (VI).—Methylation of 10.0 g. of VI was carried out with diazomethane in cold methylene chloride using fluoroboric acid catalyst, as described above for methylation of the *cis* isomer (IV). The crude reaction mixture, after washing, drying, and evaporating to dryness, gave 12.41 g. of yellow oily residue which was crystallized from petroleum naphtha (b.p. 60–90°) to give 9.16 g. (84.8%) of off-white platelets of IX, m.p. 51–52.5°. The analytical sample was prepared by one additional crystallization from petroleum naphtha, and had m.p. 52–54°, no hydroxyl band in the infrared, ν_{max} 1704 and 1192 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{12}O_3$ (192.22): C, 68.74; H, 6.29. Found: C, 68.99; H, 6.26.

Preparation of 1-Methoxy-2-indanone (VIII) from *cis*-2-Formyloxy-1-methoxyindane (VII).—A solution of 1.00 g. of *cis*-2-formyloxy-1-methoxyindane (VII) in 4.0 ml. of anhydrous ethanol and 3.2 ml. of 6 *N* aqueous sodium hydroxide was refluxed for 1 hr. The cooled solution was extracted with three 25-ml. portions of ether, and the combined ether extract was washed with water, dried over anhydrous sodium sulfate, filtered, and stripped to dryness, to give 0.84 g. (99%) of a pale yellow-green oil, whose infrared spectrum (liquid) showed a strong broad hydroxyl band (*ca.* 3440 cm.$^{-1}$) but no carbonyl band. The intermediate *cis*-2-hydroxy-1-methoxyindane was dissolved in 1.3 ml. of benzene, cooled to 0–5°, and treated with a cold solution of 0.84 g. of sodium dichromate dihydrate in 2 ml. of glacial acetic acid. The brown reaction mixture was allowed to stand at 0–5° for 2 days, diluted with 25 ml. of water, and extracted with three 25-ml. portions of benzene. The combined benzene extract was washed three times with water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness at reduced pressure, leaving 0.63 g. (75%) of crude 1-methoxy-2-indanone (VIII) as a pale yellow-green oil; λ_{max} 238 mμ (ε 3100), 271 (1480) 290 (sh, 540). The infrared spectrum (liquid) showed strong carbonyl absorption at 1723 cm.$^{-1}$ (plus a shoulder at 1700 cm.$^{-1}$) and only weak absorption in the 3400-cm.$^{-1}$ region.

A solution of 0.55 g. of 2,4-dinitrophenylhydrazine in 1.2 ml. of concentrated sulfuric acid, 2.8 ml. of water, and 8.2 ml. of methanol was added to a solution of 0.40 g. of crude 1-methoxy-2-indanone (VIII) in 2 ml. of methanol at room temperature. A yellow-orange solid formed immediately, and, after 15 min. of stirring and 5 min. of cooling, the solid was collected, washed first with cold methanol and then with cold water, and dried *in vacuo* at 60°, giving 0.31 g. of material, m.p. 106–108.5°. Crystallization from ethyl acetate afforded 0.08 g. (6%) of orange crystals, m.p. 203–204° dec.; $\lambda_{max}^{diglyme}$ 257 mμ (sh, ε 16,150), 375 (48,100).

Anal. Calcd. for $C_{21}H_{14}N_4O_8$ (506.39): C, 49.80; H, 2.79; N, 22.13. Found: C, 49.35; H, 3.19; N, 21.71.

Preparation of 1-Methoxy-2-indanone (VIII) from *trans*-2-Formyloxy-1-methoxyindane (IX).—A solution of *trans*-2-formyloxy-1-methoxyindane (IX) in aqueous ethanolic sodium hydroxide was treated as described above for saponification of the *cis*-2-formyloxy isomer (VII) to the *cis*-2-hydroxy isomer. Evaporation of the ether extracts left a quantitative yield of *trans*-2-hydroxy-1-methoxyindane (broad strong hydroxyl absorption in the infrared at 3340–3400 cm.$^{-1}$, but no carbonyl absorption) as a pale green oil. Oxidation of the oily intermediate with sodium dichromate dihydrate, as described above for the *cis* isomer, gave a 74% yield of crude 1-methoxy-2-indanone (VIII) as a pale green oil; λ_{max} 237 mμ (ε 2840), 271 (1370). The oil had an infrared spectrum (liquid) which was the same as that of the oil formed from the *cis* isomer VII, and like the oil from the *cis* isomer it gave with 2,4-dinitrophenylhydrazine a small amount of orange solid, m.p. 199–200°; $\lambda_{max}^{diglyme}$ 257 mμ (sh, ε 23,200) and 374 (45,700), same infrared spectrum.

Anal. Found: C, 49.80; H, 3.49.

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Nuclear Magnetic Resonance Studies of Some Condensation Products of 2,4-Pentanedione with Formalin and Acetaldehyde

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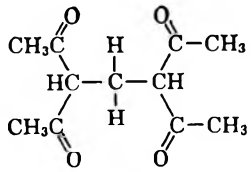
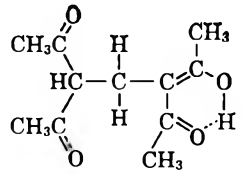
High-resolution proton magnetic resonance (n.m.r.) spectra have been obtained and interpreted for two tautomers of 3,5-diacetyl-2,6-heptanedione, 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone, and 3-acetyl-3-penten-2-one. The tautomeric forms of the two diacetylheptanediones have been established. Long-range spin–spin coupling through four σ-bonds was observed for the hydroxyl group of 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone. Two different carbonyl absorptions in the infrared spectrum and two different acetyl absorptions in the n.m.r. spectrum were found for 3-acetyl-3-penten-2-one. Changes in the hydroxyl and acetyl resonance positions with solvent and on dilution were studied for various alcohols and ketones.

In an investigation of the reaction between formalin and 2,4-pentanedione, Wilson[1] obtained four crystalline products melting at 41.5–42.5°, 55–56°, 89–90°, and 176–177°.

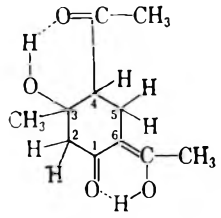
The analyses fit the formula $C_{11}H_{16}O_4$ for the first three products and $C_{17}H_{24}O_6$ for the last. On the basis of the n.m.r. spectra the structures proposed for the first three are, respectively, I, II, and III following. No structure is proposed for the fourth.



I, m.p. 41.5–42.5°



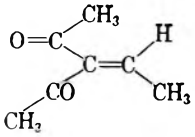
II, m.p. 55–56°



III, m.p. 89–90°

The first two products were obtained in the absence of any catalyst. The third and fourth were isolated when the condensation was catalyzed by different basic materials. Because of their high stability, these tautomers can be isolated as pure individuals and their n.m.r. spectra can be determined with little, if any, interconversion.

A fifth compound, b.p. 44–45° (0.04 mm.), was obtained in a reaction between 2,4-pentanedione and acetaldehyde. The structure deduced from its n.m.r. spectrum is shown.



Experimental

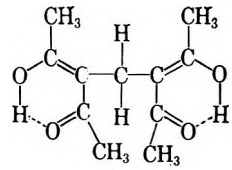
All spectra were obtained at 60 Mc./sec. with a Varian dual purpose V-4302 n.m.r. spectrometer. The spectra of 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone, as well as those of the ketones and alcohols used as model compounds to determine the hydroxyl resonance positions, were obtained with the spectrometer equipped with a field homogeneity control unit.

Calibration of spectra was done by the side-band modulation technique,[2] with 3% by volume of tetramethylsilane (TMS) as an internal reference in all samples. The Hewlett-Packard wide range oscillator, Model 200 CD, was checked at all times against a Hewlett-Packard electronic counter, Model 521C. The average (within replicate) standard deviation of our measurements, based on three solutions of the substituted methylcyclohexanone, is 0.4 c.p.s. at 60 Mc. (0.0067 p.p.m.). Spectra were run at 22°.

Materials.—In addition to the compounds mentioned previously, 3-methyl-2,4-pentanedione and 1-methylcyclohexanol were prepared in these laboratories by B. D. Wilson and S. W. Cowan, respectively. 2-Pentanol was obtained from Columbia Organic Chemicals and 4-hydroxy-2-pentanone from K. and K. Laboratories. The other compounds used were Eastman Grade chemicals, except for carbon tetrachloride, methylene chloride, and acetonitrile, which were Spectro Grade, and 2-pentanone, which was Eastman practical grade. They were used without further purification.

Discussion

Spectra of the Heptanediones.—The two compounds obtained without a basic catalyst might be two of the three following tautomers: I, a tetraketo; II, a monoenol H-bonded internally; or IV, a dienol H-bonded internally.



IV

A. Compound Melting at 55–56° (II).—Data from the n.m.r. spectrum of this compound in 30% solution in methylene chloride are given in Table I. The data in Table II show that the resonance position for an enolic hydroxyl of a β-diketone occurs at approximately −15 to −17 p.p.m. relative to TMS. Therefore, the peak at −17 p.p.m. indicates strongly that the compound melting at 55–56° exists as an enolized β-diketone in methylene chloride solution.[3]

The following observations show that this compound is the monoenol II rather than the dienol IV: (1) the presence of two singlets of about equal intensity at

(1) B. D. Wilson, *J. Org. Chem.*, **28**, 314 (1963).

(2) J. T. Arnold and M. G. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).

(3) (a) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain *J. Am. Chem. Soc.*, **71**, 1068 (1949); (b) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 142.

TABLE I

CHEMICAL SHIFTS[a] OF TWO TAUTOMERS OF 3,5-DIACETYL-2,6-HEPTANEDIONE[b]

P.p.m.	Band contour	Assignment
	Compound II, m.p. 55–56°	
−2.155	Singlet	Enol CH_3^-
−2.193	Singlet	Keto CH_3^-
−2.747	Doublet	$-CH_2-$
−2.867		
−3.818	Triplet	$-CH<$
−3.925		
−4.052		
−16.908	Singlet	Chelated OH
	Compound I, m.p. 41.5–42.5°	
−2.188	Singlet	Keto CH_3^-
(−2.13)[c]	Triplet	$-CH_2-$
(−2.23)[c]		
−2.348		
−3.565	Triplet	$-CH<$
−3.660		
−3.768		

[a] Relative to TMS as internal standard. [b] 30% in CH_2Cl_2, 3% TMS. [c] Hypothesized.

nonchelated carbonyls do not participate in the equilibrium.

For the spectra of this compound and the following one, integrated intensities were not available. However, judged from peak heights, the intensities are in good agreement with both assignments.

B. Compound Melting at 41.5–42.5° (I).—The n.m.r. data for this compound, together with assignments for the resonances observed, are also given in Table I. There is no line in the region −15 to −17 p.p.m., corresponding to an enolic hydroxyl; nor is there any singlet near −3.0 p.p.m., which could be assigned to a $-CH_2-$ attached to two doubly bonded carbon atoms.

The strong singlet at −2.188 p.p.m. agrees well in position with the lines found for the keto methyl groups in acetylacetone, 3-methyl-2,4-pentanedione, and the other 3,5-diacetyl-2,6-heptanedione which melts at 55–56°. These facts indicate this is the tetraketo form.

The triplet at −3.660 p.p.m., which is about 0.265 p.p.m. higher than the corresponding triplet in the monoenol form, is assigned to $HC<$. The corresponding resonance in the enol form is at lower field because of the carbon–carbon double bond present in the enolic hydroxyl.

TABLE II

HYDROXYL RESONANCE POSITIONS[a] IN ALCOHOLS AND KETONES

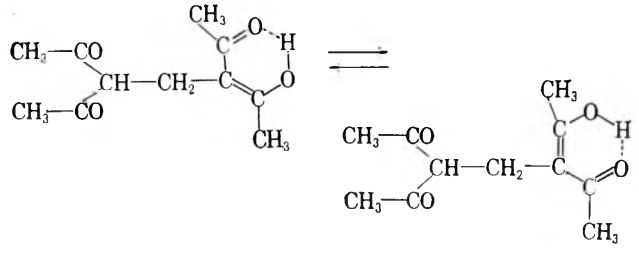
	Solvent			
		CCl_4, mole %		CH_2Cl_2, mole %	
	Neat	12.5	2.5	8.5	1.7
Acetylacetone	−15.463				
3,5-Diacetyl-2,6-heptanedione (m.p. 55–56°)				−16.908	
3-Methyl-2,4-pentanedione	−16.505			−15.217	−15.220
2-Acetylcyclohexanone			−15.683	−15.902	−15.922
o-Hydroxyacetophenone	−12.170		−12.067	−12.220	−12.232
4-Hydroxy-4-methyl-2-pentanone	−4.145	−3.550	−3.233	−3.683	−3.618
2-Methyl-2-pentanol	−4.262	−2.942	−1.447	−1.810	~−1.38
4-Hydroxy-2-pentanone	−4.317	−3.668	−3.013		
2-Pentanol	−5.155	−3.775	−1.933		
	−5.085				
sec-Butyl alcohol	−5.063	−3.525	−1.755		
	−5.003				
Cyclohexanol	−5.12[b]	−3.928	−2.228	−2.470	
1-Methylcyclohexanol	−4.197	−2.790		−1.743	−1.317

[a] Chemical shifts in p.p.m. relative to TMS as internal standard. [b] Calculated from Humble Oil Company Catalog of NMR Spectra, No. 162.

−2.155 and −2.193 p.p.m., arising from the enol and keto methyls, respectively; (2) the triplet centered at −3.925 p.p.m., arising from $HC<$; (3) the doublet due to methylene, centered at −2.867 p.p.m.

The peak at −2.155 p.p.m. is assigned to the enol-methyl protons by analogy with the corresponding assignment for acetylacetone.[4]

The fact that only two methyl resonances are observed, rather than one or three, suggests that the following rapid equilibrium exists and that the other



In methylene chloride solution the triplet to be expected from the methylene was not observed. The line at −2.348 p.p.m. was considered to be the only line of the methylene triplet which could be observed, the other two lines being buried under the band from the methyl resonance of the keto group. The center of the triplet was estimated to fall at −2.23 p.p.m., and the line at highest field at about −2.13 p.p.m. In Table I these two lines which were hypothesized are in parentheses.

To confirm the existence of this $-CH_2-$ triplet, spectra were recorded for the compound in chloroform and thiophene solutions. Table III gives a comparison of the chemical shifts obtained from these spectra. In the thiophene solution the resonance of the acetyl

(4) L. W. Reeves, *Can. J. Chem.*, **35**, 1351 (1957).

Table III

Comparison of Chemical Shifts[a] of 3,5-Diacetyl-2,6-heptanedione, M.p. 41.5–42.5°, in Chloroform and Thiophene

Concentration			
21% in $CHCl_3$, 3% TMS, p.p.m.	20% in thiophene, 3% TMS, p.p.m.	Δ, p.p.m.	Assignment
−2.238	−1.940	0.298	Keto CH_3
−2.170	−2.093	0.077	
−2.275	−2.198	0.077	Triplet $-CH_2-$
−2.383	−2.308	0.075	
	−2.407		Impurity
−3.593	−3.403	0.190	
−3.700	−3.512	0.188	Triplet $-CH$
−3.812	−3.623	0.189	

[a] Relative to TMS as internal standard.

chemical shift of the hydroxyl resonance when the concentration is changed from 8.5 to 1.7 mole %.

2. Compounds forming intermolecular hydrogen bonds (alcohols) show the following characteristics. (a) The hydroxyl resonance position is at about −4.2 to −5.0 p.p.m. (b) When the compounds are diluted from the pure state to 12.5 mole % in carbon tetrachloride, the chemical shift changed about 1.2 to 1.5 p.p.m.

3. Compounds forming intramolecular hydrogen bonds show the following characteristics. (a) For β-hydroxy ketones, the marked lowering of the position of the hydroxyl resonance found in the β-diketones and the β-hydroxylphenyl ketone does not occur, the chemical shift being very nearly the same as for the corresponding pure alcohols. (b) When the neat β-hydroxy ketones are diluted with carbon tetrachloride, the change in chemical shift for a 12.5 mole % solution

Table IV

Effect of Intramolecular Hydrogen Bonding on Methyl Resonance Positions[a] of $CH_3-\underset{|}{\overset{|}{C}}-OH$ Group

	Solvent				
		CCl_4, mole %		CH_2Cl_2, mole %	
	Neat	12.5	2.5	8.5	1.7
2-Pentanol	−1.128	−1.078	−1.065		
	−1.233	−1.183	−1.172		
	(av., −1.180)	(−1.130)	(−1.118)		
4-Hydroxy-2-pentanone	−1.093	−1.097	−1.065		
	−1.208	−1.205	−1.170		
	(av., −1.150)	(−1.150)	(−1.117)		
2-Methyl-2-pentanol	−1.142	−1.137	−1.158	−1.152	−1.165
4-Hydroxy-4-methyl-2-pentanone	−1.238	−1.192	−1.158	−1.208	−1.227

[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

group has been shifted far enough upfield so that the triplet of the methylene can be seen.

Spectra of Compounds with Hydrogen Bonding.—To aid in the assignment of the spectrum of 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone, the position of the hydroxyl resonance was determined in ten model compounds both neat (with 3% TMS added) and in various solvents in concentrations of, roughly, 15 and 3 w./v. % The actual concentrations in the methylene chloride solutions were 8.5 and 1.7 mole %, and in the carbon tetrachloride solutions, 12.5 and 2.5 mole %. These concentrations correspond to those used for the 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone.

The acetyl resonance positions were also measured in the model compounds and in 2-pentanone and 4-methyl-2-pentanone. In addition, the 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone itself was examined in several solvents at various concentrations.

The model compounds were chosen to cover four groups: (1) β-diketones, (2) *o*-hydroxyphenyl ketones, (3) alcohols, and (4) β-hydroxy ketones. The results are given in Tables II, IV, and V. For ease of comparison, the alcohols have been placed next to the β-hydroxy ketones to which they correspond.

1. Compounds forming conjugated chelates show the following characteristics. (a) For β-diketones, the hydroxyl resonance is between −15.0 and −16.7 p.p.m.; for an *o*-hydroxyphenyl ketone, it is about −12 p.p.m. (b) Both classes show very little change in

Table V

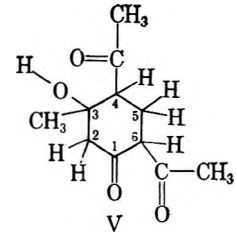
Effect of Intramolecular Hydrogen Bonding on Acetyl Resonance Positions[a]

	Solvent				
		CCl_4, mole %		CH_2Cl_2, mole %	
	Neat	12.5	2.5	8.5	1.7
2-Pentanone	−2.037	−2.097	−2.098		
4-Hydroxy-2-pentanone	−2.108	−2.168	−2.130		
4-Methyl-2-pentanone	−2.117	−2.088	−2.060	−2.073	−2.058
4-Hydroxy-4-methyl-2-pentanone	−2.225	−2.123	−2.122	−2.153	−2.147

[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

is about half as large as the change for the corresponding alcohols.

Spectrum of 4,6-Diacetyl-3-hydroxy-3-methylcyclohexanone (V).—The method of preparation indicated



V

TABLE VI

RESONANCE POSITIONS[a] OF 4,6-DIACETYL-3-HYDROXY-3-METHYLCYCLOHEXANONE IN VARIOUS SOLVENTS

	Concentration					
Band	20% in CH_2Cl_2, 3% TMS	20% in CH_3CN, 4% TMS	4% in CH_2Cl_2, 3% TMS	4% in CCl_4, 3% TMS	20% in CH_3CN, 4% TMS, 5% D_2O	20% in CH_3CN, 4% TMS, 20% D_2O; 0.3% HCl
A	−1.255	−1.215	−1.257	−1.223	−1.240	−1.265
B	−2.127	−2.113	−2.130	−2.092	−2.135	−2.143
C	−2.293	−2.243	−2.292	−2.253	−2.260	−2.278
D	−2.367	−2.348	−2.372	Shoulder	−2.372	−2.407
E	−2.583	−2.585	−2.577	−2.532	−2.597	−2.605
F	−3.522	−3.412	−3.473	−3.222	−3.743	None
G	−15.840	−15.888	Not measured	−15.690	−15.865	None
New band					−2.798	−4.443

[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

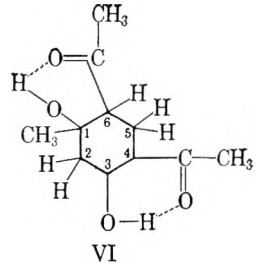
that this substance was 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone.[1]

Although several stereoisomers are possible which may have different axial and equatorial conformations, the sharpness of the melting point indicates the presence of only one. We cannot tell from the spectrum which it is.

The resonance positions for the n.m.r. spectrum of the compound in different solvents at various concentrations are given in Table VI, and a summary of the band assignments in Table VII. A summary of the acetyl and enol methyl resonance positions in a number of compounds is given in Table VIII for comparison.

The per cent of the keto form (structure V) present was determined from the relative areas of bands A, F, and G of Table VII. In a freshly prepared 20% methylene chloride solution, about 20% of the compound is in the keto form. Comparison of the areas of these bands, made on spectra recorded each day for several days after sample preparation, shows that at equilibrium the keto form approaches 10%. Since we used mainly 20% solutions for measuring the spectra, the contribution of the keto form would be negligible. The interpretation of the spectra will therefore be made in terms of the major portion (80–90%) of the compound.

Our data are compatible with either a 4-acetyl-3-hydroxy-6-(1-hydroxyethylidene)-3-methylcyclohexanone structure (III) or a 4,6-diacetyl-1-methyl-3-cyclohexene-1,3-diol structure (VI). Since there seems to be a slight preponderance of evidence in favor of III, we shall discuss the spectrum in terms of it, although we recognize that resonance forms and intramolecular hydrogen bonds diminish both the differences between III and VI and the differences one would expect in the n.m.r. spectra.



VI

The evidence for the exocyclic structure, III, is as follows. Examination of the first six compounds in Table VIII shows that the acetyl resonance positions vary from −2.285 to −2.158 p.p.m., while the enol methyl resonance positions vary from −2.155 to −2.000 p.p.m. From this it appears that 2-acetylcyclohexanone has an enol methyl and an exocyclic double bond at C-2. The groups in the 1- and 6-positions in 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone and the corresponding groups in 2-acetylcyclohexanone are very similar. The fact that one of the acetyls of the former falls in the acetyl methyl region, while the other falls in the enol methyl region, leads us to believe that the compound has the exocyclic structure with an enol methyl. The compound appears to be, then, a 1-hydroxyethylidene ketone, quite analogous to the hydroxymethylene ketones which Wheland discusses.[5]

TABLE VII

BAND ASSIGNMENT FOR 4,6-DIACETYL-3-HYDROXY-3-METHYLCYCLOHEXANONE[a]

Band	Chemical shift, p.p.m.	Relative areas	Structure	Assignment
A	−1.255	~3	Singlet	CH_3 at C-3
B	−2.127	~3	Singlet	CH_3CO at C-6
C	−2.293	~3	Singlet	CH_3CO at C-4
D	−2.367	~2	Singlet	CH_2 at 2
E	~−2.58	~3	ABC	CH_2 at 5
				CH at 4
F	−3.522	~1	Triplet	OH at C-3
G	−15.840	~1	Singlet	OH on ethylidene

[a] 20% in CH_2Cl_2, 3% TMS.

The reasons for the assignments of the various resonance positions will be evident mainly from the data in Tables VI–VIII. However, the following points should also be noted.

The assignment of the "singlet" at −2.367 p.p.m. (D-band) to the protons on C-2 is made by analogy with 2-acetylcyclohexanone, where the resonance of the corresponding protons falls at −2.300 p.p.m., in 20% solution in methylene chloride. This line is relatively broader than the three lines corresponding to the methyls, indicating some unresolved fine structure. Part of the broadening is from spin–spin splitting of the resonance of the protons on C-2 by the *hydroxyl* proton at C-3. Additional broadening would result if the rate of inversion of the cyclohexane ring is slowed enough by the bulky side groups to produce a slight nonequivalence of the axial and equatorial protons.

The multiplet designated E, which is overlapped on the high-field side by band D, seems to have about fifteen lines. It is probably an ABC spectrum arising from the protons at C-4 and C-5 in structure III.

(5) G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, pp. 685–687.

Table VIII

Acetyl and Enol Methyl Resonance Positions[a]

	Acetyl	Enol	State	Solvent: CCl_4, mole %	Solvent: CH_2Cl_2, mole %
Methyl isopropenyl ketone	−2.268		Neat		
3-Acetyl-3-penten-2-one	−2.285		Neat		
	−2.225				
3,5-Diacetyl-2,6-heptanedione, m.p. 41.5–42.5°	−2.188				8.5
3,5-Diacetyl-2,6-heptanedione, m.p. 55–56°	−2.193	−2.155			8.5
	−2.170	−2.130			2.9
3-Methyl-2,4-pentanedione	−2.162	−2.092	Neat		
	−2.160	−2.093			7.7
	−2.158	−2.120			1.6
Acetylacetone	−2.170	−2.000	Neat		
2-Acetylcyclohexanone		−2.092			8.5
		−2.062			1.7
		−2.043		2.5	
4,6-Diacetyl-3-hydroxy-3-methylcyclohexanone	−2.293	−2.128			5.6
	−2.292	−2.130			2.1
	−2.253	−2.092		2.5	

[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

The spectra of the compounds containing a hydrogen-bonded hydroxyl group indicate that the region −2.50 to −4.17 p.p.m. is the likely region for the hydrogen-bonded hydroxyl group formed by the hydroxyl at C-3 and the acetyl at C-4. The variation in position of the F-band in different solvents (Table VI) indicates that it is the hydroxyl at C-3. This was confirmed by deuteration carried out in a 20% solution of the compound in acetonitrile, both with and without catalyst (Table VI).

The new band at −2.798 p.p.m. which appeared with D_2O in acetonitrile solution in the absence of a catalyst is probably due to HOD. The new band appearing at −4.443 p.p.m. with D_2O in acetonitrile containing HCl as a catalyst is probably a hydroxyl resonance representing an average from the rapid exchange between HOD and the protons of the F- and G-bands.[6]

The triplet structure of the F-band in methylene chloride, which initially has a separation of 1.3 c.p.s., disappears gradually over a period of 2 weeks. During this time its position does not shift within the limits of the experimental error of our measurements. The rounded contour of the F-band after the disappearance of the fine structure is characteristic of bands in which there is fairly rapid proton exchange.[6] This led to the hypothesis that the change in band contour was due to the formation of hydrochloric acid from the methylene chloride, which catalyzes the proton exchange. A similar loss of fine structure with amines dissolved in chloroform has been observed.[7] Our hypothesis is strengthened by the fact that the irreversible disappearance of fine structure is greatly accelerated when the solution is heated or when HCl fumes are blown over the end of the sample tube.

That the triplet structure of this band is due to spin–spin coupling has been shown by measurements made at 40 Mc./sec.[8] The average of eleven determinations gives a splitting of 1.3 c.p.s., the band being symmetrical.

Since there are no protons on C-3, spin–spin splitting would have to be long range. Davis, *et al.*,[9] have reported long-range spin–spin coupling of H–H and H–F involving more than three consecutive single bonds. Holmes and Kivelson[10] have reported long-range coupling in acetone involving four σ-bonds. Coupling over four or more bonds, where at least one is unsaturated, has also been discovered.[11]

Spin–spin coupling of the protons of a methoxy group to ring protons through five bonds including part of a π-electron system has been reported by Forsen.[12] The magnitude of the coupling constant appears to depend on the exact conformation of the molecule. Similar long-range spin–spin coupling of an OH proton with a ring proton through five bonds, part of which involve π-electrons has been reported by Freeman.[13]

The determination of the protons which may be involved in long-range coupling with the hydroxyl proton on C-3 in the present case is complicated by the fact that the spin–spin splitting characteristic of the F-band is not found elsewhere in the spectrum. The most likely possibility appears to be long-range coupling through four σ-type bonds with the two protons on C-2. Equivalent or nearly equivalent coupling with each of these protons would account for the fact that the F-

(6) J. D. Roberts, "Nuclear Magnetic Resonance. Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 63–65.

(7) Professor David J. Wilson, University of Rochester, private communication.

(8) For these measurements, we are indebted to Dr. Wilson Goodlet and Mrs. Evelyn Simon, Tennessee Eastman Co., Kingsport, Tenn.

(9) D. R. Davis, R. P. Lutz, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 246 (1961).

(10) J. R. Holmes and D. Kivelson, *ibid.*, **83**, 2959 (1961).

(11) (a) E. B. Whipple, J. H. Goldstein, and W. E. Stewart, *ibid.*, **81**, 4761 (1959); (b) E. B. Whipple, J. H. Goldstein, and L. Mandell, *J. Chem. Phys.*, **30**, 1109 (1959); (c) R. R. Fraser, *Can. J. Chem.*, **38**, 549 (1960).

(12) S. Forsen, *J. Phys. Chem.*, **67**, 1740 (1963).

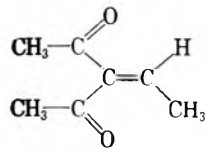
(13) R. Freeman, *Mol. Phys.*, **6**, 535 (1963).

band appears to be a symmetrical triplet. This spin–spin coupling would also explain the greater width of the D-band which we have assigned to the protons on C-2.

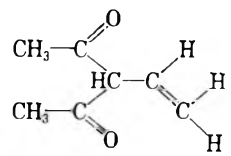
The structure on the F-band was clearly shown to be due to spin–spin coupling of the hydroxyl proton with the protons on C-2 by the application of "double resonance" methods.[14] When the F-band resonance was observed while the protons corresponding to the D-band were strongly irradiated, the fine structure of the F-band was removed and it became a single sharp peak. Conversely, when the D-band resonance was observed while the proton corresponding to the F-band was strongly irradiated, the D-band became somewhat sharper and its amplitude increased. These experiments establish that the protons corresponding to the D- and F-bands are spin–spin coupled.

Our interpretation of the spectrum of this substance on the basis that it is 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone is also in agreement with infrared data[15] showing two carbonyl bands, one at 1690 which could be characteristic of carbonyl in a β-hydroxy ketone, and the other at 1600 cm.$^{-1}$ which could occur only in a conjugated chelate.[3] An intense hydroxyl band at 3420 cm.$^{-1}$, characteristic of a β-hydroxy ketone, and a not very well defined band in the 2700–2500-cm.$^{-1}$ region, characteristic of the hydroxyl in a conjugated chelate, were also observed. These spectra were obtained both in KBr pellets and in methylene chloride solution.

Spectrum of 3-Acetyl-3-penten-2-one (3-Ethylidene-2,4-pentanedione).—The method of preparation of this compound 2,4-pentanedione and acetaldehyde[1] suggests either the 3-acetyl-3-penten-2-one (VII) or the 3-acetyl-4-penten-2-one structure (VIII).



VII



VIII

The resonance positions for the n.m.r. bands of the pure compound (with 3% TMS as internal reference) are given in Table IX. No band which could be ascribed to a vinyl group,[16] even as an impurity of 1–2%, was seen.

TABLE IX

CHEMICAL SHIFTS[a] AND SPIN–SPIN COUPLING CONSTANTS FOR 3-ACETYL-3-PENTEN-2-ONE

P.p.m.	Band contour	Relative intensities	J_{H,CH_3}, c.p.s.	Assignment
−1.848	Doublet	3	7.2	CH_3—C=C
−2.225	Singlet	3		Methyl at C-1′
−2.285	Singlet	3		Methyl at C-1
−6.915	Quartet	1	7.4	=CH

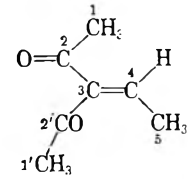
[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

The quartet and doublet with the same fine structure splitting, and the magnitude of this, 7.2–7.4 c.p.s., show conclusively that there are a *sib*[17] proton and a methyl group. The chemical shifts for these two groups also agree well with those for an ethylenic hydrogen and for a methyl attached to doubly bonded carbon.[11,18] The relative intensities of these two resonances are in the ratio 1:3. These features identify the compound as the ethylidene, rather than the vinyl, pentanedione.

The two singlets at −2.225 and −2.285 p.p.m. have been assigned to the methyls of the two acetyl groups. From both areas and peak heights, it is known that each corresponds to three hydrogens.

In the infrared region (smear on NaCl), two carbonyl bands, one at 1700 and the other at 1660 cm.$^{-1}$, are observed.[15] The latter is in the region characteristic of α,β-unsaturated ketones,[19] whereas the former is close to the region for saturated, open-chain ketones.[19a]

These n.m.r. and infrared data are consistent with the following hypothesis as to the conformation of the molecule. Fisher–Taylor–Hirschfelder and Courtauld models show a severe steric hindrance between the *gem*-diacetyls, which is not present between the *gem*-diacetyl groups of the heptanediones previously discussed. According to the models, conformation IX gives the least steric hindrance. In this conformation the carbonyl at C-2 is coplanar with the ethylenic carbons, whereas that at C-2′ is out of this plane.



IX

The carbonyl at C-2 then would have the frequency 1660 cm.$^{-1}$, agreeing with the broad carbonyl band at 1670–1660 cm.$^{-1}$ reported for *trans*-3-penten-2-one.[19b,c] The carbonyl at C-2′, which is out of the plane and therefore not conjugated, would have the frequency at 1700 cm.$^{-1}$.

Two effects cause the proton resonance of the methyl attached to the more conjugated carbonyl to occur at a lower field than that of the methyl attached at C-1′. The first is the greater electron withdrawal associated with the more conjugated carbonyl. The second is the fact that the model shows this methyl to be situated quite close to the transverse axis of the carbon–carbon

(14) L. F. Johnson, Varian Associates Publication No. 87-100-082, Palo Alto, Calif., August, 1962.

(15) For these measurements and for assistance with the interpretation, we are indebted to Miss Thelma Davis of these laboratories.

(16) (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 238–241; (b) R. W. Fessenden and J. S. Waugh, *J. Chem. Phys.*, **30**, 944 (1959).

(17) The term "*sib*" is proposed to describe a group which is attached to a given atom, but which differs in structure from the other groups attached to the same atom. The use of "*gem*" for this is etymologically unsound, since the Latin root of *gem* means twin, and is contrary to the accepted usage of *gem* in such phrases as "the *gem*-dimethyl grouping in camphor."

(18) (a) L. M. Jackman and R. H. Wiley, *Proc. Chem. Soc.*, 196 (1958); in the last line of the 2nd paragraph, read "*trans*" for "*cis*." (b) J. A. Elvidge, *J. Chem. Soc.*, 474 (1959).

(19) (a) Ref. 3b, pp. 132, 136; (b) R. Heilmann, D. de Gaudemaris, and P. Arnaud, *Compt. rend.*, **240**, 1995 (1955); (c) R. Heilmann, G. de Gaudemaris, and P. Arnaud, *Bull. soc. chim. France*, 119 (1957).

double bond. It will therefore be subjected to a negative (deshielding) effect from the anisotropy of this bond.[20] The resonance at −2.285 p.p.m. is therefore assigned to the methyl at C-1 and that at −2.225 p.p.m. to the methyl at C-1′.

Our ultraviolet spectral data in methanol solution agree with those of McEntee and Pinder.[21]

(20) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 124, 129.

(21) M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957).

Preparation of 1-Azabicycloalkanes by Reductive Cyclization

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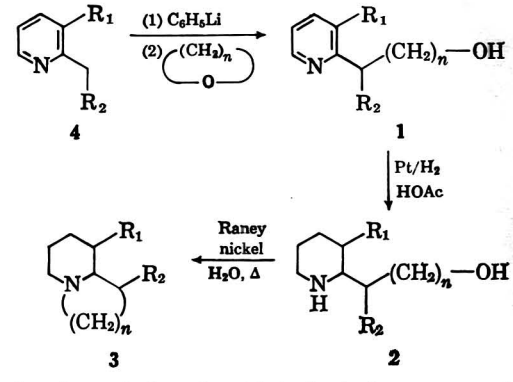
Indolizidine, quinolizidine, and several of their methyl derivatives have been prepared in 80–90% yield by the two-step reductive cyclization of readily available 2-pyridyl alcohols. Under similar conditions, the corresponding 3- and 4-pyridyl alcohols failed to undergo cyclization. The probable stereochemistry of the 8-methylindolizidines produced in this cyclization is discussed.

In connection with another problem in this laboratory we recently required substantial quantities of various indolizidines and quinolizidines. Although several methods for synthesizing compounds of this type had been reported in the literature,[2] for the most part these proceeded in low over-all yields from readily available starting materials. The most attractive method in this regard seemed to be the high-pressure, high-temperature, reductive cyclization of various 2-(3′-hydroxypropyl)pyridines such as **1a** to the corresponding indolizidines. In the case of indolizidine itself (**3a**) a 78% yield was reported[3] although with slightly more complex molecules it was much lower.[4] Repeated attempts to prepare indolizidine by this method in our laboratory, however, led only to complex mixtures containing, at best, 15% of the desired product.[5]

A related method which was considered was that of Lavagnino, *et al.*,[6] in which indolizidine (**3a**) was obtained in 73% yield by simply distilling an aqueous solution of 2-(3′-hydroxypropyl)piperidine (**2a**) from Raney nickel. Since the piperidine **2a** is easily prepared by catalytic reduction[3] of the commercially available pyridine **1a**, it appeared that this sequence of two reactions (reduction followed by cyclization) might be used for the preparation of the desired compounds. This paper reports the synthesis of a variety of indolizidines and quinolizidines in 80–90% over-all yield by this two-step reductive cyclization of readily available pyridyl alcohols of the type **1**.

Results and Discussion

The starting pyridyl alcohols **1** were obtained either commercially (**1a**), or by treatment of the appropriate alkylpyridyllithium reagent[7] with ethylene oxide[8] (**1c, 1e–g**) or propylene oxide[9] (**1b** and **1d**). Reduction of the pyridine ring of **1a–g** proceeded in 92–96% yield at room temperature and moderate pressure according to the method of Prelog.[10] The saturated alcohols **2a–g** produced in this reaction were partially esterified by the glacial acetic acid used as a solvent and therefore were saponified before isolation and purification. In those preparations where only the final quinolizidines or indolizidines were desired, the crude mixture of piperidyl alcohols **2a–g** and their acetate esters could be used without prior saponification since hydrolysis apparently took place under the conditions of the cyclization described below.



Cyclization of the piperidyl alcohols **2a–g** to the desired indolizidines and quinolizidines **3a–g** took place in high yield (85–95%) by a procedure very similar to that of Lavagnino, *et al.*[6] The 15% higher yields in our cyclizations may be due to the repeated use of the same portion of Raney nickel, since the ability of the catalyst to irreversibly adsorb either the reactants or the products[11] would be greatly reduced after the first prep-

(1) (a) Department of Chemistry, Texas Christian University, Fort Worth, Texas; (b) National Science Foundation Summer Teaching Fellow, 1963; National Institutes of Health Predoctoral Fellow in Chemistry, 1963–1964.

(2) For a recent summary of the syntheses of compounds with bridgehead nitrogen atoms, see W. L. Mosby, "The Chemistry of Heterocyclic Compounds," Vol. 15, parts 1 and 2, A. Weissburger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961.

(3) V. Boekelheide and S. Rothchild, *J. Am. Chem. Soc.*, **70**, 864 (1948).

(4) J. Sam. J. Plampin, and D. Alwani, *J. Org. Chem.*, **27**, 4543 (1962).

(5) The reason for the failure of this synthesis in our hands is not clear, although the exact nature of the Raney nickel catalyst used may be responsible. The identities of the products obtained from this attempted reductive cyclization are under investigation and will be reported elsewhere.

(6) E. R. Lavagnino, R. R. Chauvette, W. N. Cannon, and E. C. Kornfeld, *J. Am. Chem. Soc.*, **82**, 2609 (1960).

(7) The successful preparation of at least a 25% yield (see Table I) of the lithium reagent of 2-isopropylpyridine is surprising in view of the failure of C. Osuch and R. Levine [*J. Org. Chem.*, **21**, 1099 (1956)] and W. von E. Doering and V. Z. Pasternak [*J. Am. Chem. Soc.*, **72**, 143 (1950)] to metalate 2-isopropyl- and 2-*sec*-butylpyridine, respectively, with phenyllithum under essentially identical conditions (see Experimental).

(8) L. A. Walter, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 757.

(9) K. Winterfeld and W. Haring, *Arch. Pharm.*, **295**, 615 (1962).

(10) V. Prelog and O. Metzler, *Helv. Chim. Acta*, **29**, 1163 (1946).

(11) For examples of the irreversible adsorption of certain amines on Raney nickel, see (a) A. Bendich, P. Russell, Jr., and J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954); and (b) M. G. Reinecke and L. R. Kray, unpublished results.

aration. By cyclizing the crude mixtures of the piperidyl alcohols **2** and their corresponding acetates without saponification or purification (see above), the time and effort necessary to carry out the over-all conversion **1** → **3** was greatly reduced and the yield of final product (**3**) increased by about 5%. The yields of the various reactions discussed above are summarized in Table I.

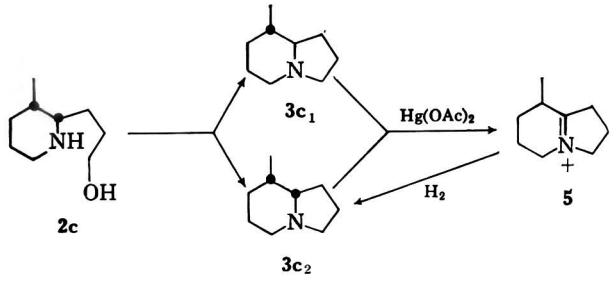
TABLE I

YIELDS OF 1-AZABICYCLOALKANES (**3**), 2-(ω-HYDROXYALKYL)-PIPERIDINES (**2**), AND 2-(ω-HYDROXYALKYL)PYRIDINES (**1**) OBTAINED FROM VARIOUS ALKYLPYRIDINES (**4**)

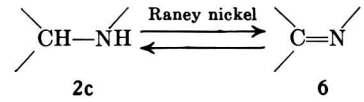
	Compounds			% yield in conversion of—		
	R_1	R_2	n	**4** → **1**	**1** → **2**	**2** → **3**
a	H	H	2	*a*	94	85
b	H	H	3	46	95	89
c	CH_3	H	2	63	92	85
d	CH_3	H	3	43	93	95
e	H	CH_3	2	39	96	92
f	CH_3	CH_3	2	35	92	92
g	H	$(CH_3)_2$	2	25	95	90

[a] 2-(3′-Hydroxypropyl)pyridine (**1a**) was obtained commercially.

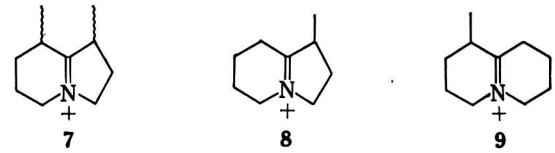
The 8-methylindolizidine (**3c**) produced by the above method proved to be a 5:1 mixture of the two possible diastereoisomers ($3c_1$ and $3c_2$) that could be readily separated by preparative vapor phase chromatography. The diastereoisomeric relationship of these two compounds was indicated by the similarity of their analyses and infrared spectra and proven by the mercuric acetate oxidation[12] of their mixture to a single quaternary immonium salt (**5**) which on catalytic reduction produced only that isomer which had been obtained in lesser amount from the original cyclization reaction



If preferential *cis* hydrogenation from the least-hindered side of the immonium salt **5** is assumed,[13] then the stereochemical assignment which logically follows indicates that the major product of the cyclization of the piperidyl alcohol **2c** is $3c_1$ and the minor product $3c_2$. This assignment is not necessarily inconsistent with the expected[14] predominantly *cis* orientation of the alkyl groups in the piperidyl alcohol **2c**, since epimerization at C-2 could occur under the conditions of the cyclization by means of a reversible dehydrogenation to the imine **6**.[15]

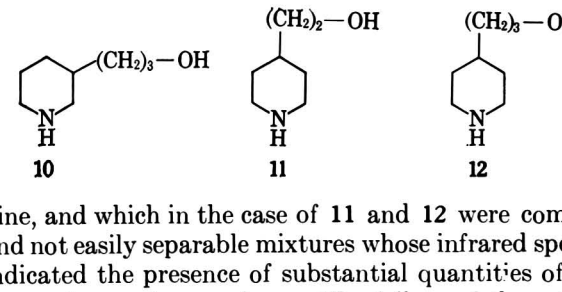


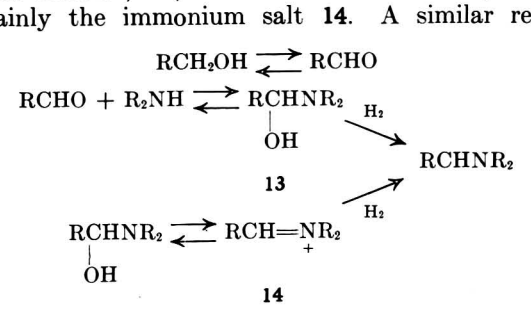
Cyclization of the piperidyl alcohol **1f** also led to a mixture which according to a vapor phase chromatogram contained only two of four possible diastereoisomers of 1,8-dimethylindolizidine, $3f_1$ and $3f_2$, in a ratio of 7:3, respectively. Oxidation of this mixture with mercuric acetate[12] produced the immonium salt **7** which on catalytic reduction gave predominantly a single isomer of 1,8-dimethylindolizidine ($3f_3$) different from the two products of cyclization. At present, insufficient evidence is available for the assignment of the relative stereochemistry of these isomers.



Vapor phase chromatography indicated that 1-methylindolizidine (**3e**) and 1-methylquinolizidine (**3d**) also were obtained as diastereoisomeric mixtures from the cyclization reaction. In these cases, however, no separation was attempted since the properties of these mixtures agreed with those reported in the literature, and in both cases single quaternary immonium salts (**8** and **9**, respectively) were obtained upon oxidation with mercuric acetate.[12]

The 3- and 4-substituted piperidyl alcohols **10**, **11**, and **12** were prepared by catalytic reduction of the corresponding commercially available pyridyl alcohols. Attempted cyclization by the procedure employed for the 2-substituted isomers (**2**) gave only small amounts of volatile material which in the case of **10** was wholly the dehydroxymethylation product,[16] 3-ethylpiperidine, and which in the case of **11** and **12** were complex and not easily separable mixtures whose infrared spectra indicated the presence of substantial quantities of olefins and secondary amines. The failure of these three piperidyl alcohols to cyclize to the expected bridged bicyclic tertiary amines is probably due to prohibitive strain in one or more of the proposed[17] intermediates of this reaction, *i.e.*, the carbinolamine **13** and/or most certainly the immonium salt **14**. A similar reason





(12) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**439 (1955).

(13) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *ibid.*, **64**, 1985 (1942).

(14) Catalytic reduction of 1,2-dialkylbenzenes gives predominantly *cis* products at room temperature: see R. L. Burwell, *Chem. Rev.*, **57**, 895 (1957).

(15) K. Kindler, G. Melamed, and D. Matthies, *Ann.*, **644**, 23 (1961).

(16) Dehydroxymethylation is also the primary process which occurs during the attempted cyclization[6] of 2-(2′-hydroxyethyl)piperidine.

(17) R. G. Rice and E. J. Kohn, *J. Am. Chem. Soc.*, **77**, 4052 (1955).

doubtless accounts for the failure of 2-(2′-hydroxyethyl)piperidine to cyclize under these conditions.[6]

Experimental[18]

Preparation of Pyridyl Alcohols Ib–g. General Procedure.[8,9]—To 6 g. of finely cut lithium wire and 400 ml. of anhydrous ether under nitrogen in a 2-l. Morton flask equipped with a reflux condenser, dropping funnel, and mechanical stirrer was added 68.2 g of freshly distilled bromobenzene over a period of 20 min. with rapid stirring. After all the lithium had dissolved (2 hr.), 0.43 mole of the freshly distilled alkylpyridine[19] was added in a 30-min. period and the resulting red-brown solution stirred at room temperature for an additional hour at which time the flask was cooled in an ice bath and 0.43 mole of ethylene oxide or propylene oxide in 75 ml. of ether was slowly added. The pale yellow solution thus formed was stirred for an hour, 200 ml. of 6 *M* hydrochloric acid added, and the aqueous layer separated, made basic with a solution of 111 g. of sodium carbonate in 150 ml. of water, and extracted with four 100-ml. portions of chloroform. After the chloroform extracts were dried over anhydrous potassium carbonate, the chloroform was removed by distillation and the remaining oil distilled through a small Vigreux column under reduced pressure.

The pyridyl alcohols obtained in this way were generally viscous, colorless to pale yellow oils which darkened on standing and gave poor analytical results. In most cases the only satisfactory derivatives were the **2,4,6-trinitrobenzenesulfonates (TNBS)** which were prepared as sharp-melting, pale yellow to white, crystalline solids by the dropwise addition of an ethanol solution of the free base to an ethanol solution of 2,4,6-trinitrobenzenesulfonic acid,[22] followed by precipitation with ether and recrystallization from ethanol–ether.

The properties of the pyridyl alcohols **Ib–g** and their derivatives are summarized in Table II.

TABLE II

PROPERTIES OF PYRIDYL ALCOHOLS AND THEIR DERIVATIVES

Compound	M.p. or b.p. (mm.), °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1b	98–100 (0.05)[a]				
1b·CH_3I	98–99[b]				
1c	125–126 (0.2)				
1c·TNBS	150–151	40.54	3.63	40.74	3.96
1d	152–153 (0.5)				
1d·TNBS	135–136	41.92	3.95	42.29	3.80
1e	112–113 (0.09)	71.48	8.66	71.19	8.69
1e·TNBS	137–138	40.54	3.63	40.17	3.77
1f	128–130 (0.09)				
1f·TNBS	138–139	41.92	3.95	41.61	3.61
1g	123–125 (0.1)				
1g·TNBS	146–148	41.92	3.95	42.00	4.24

[a] Lit.[9] b.p. 98–100° (0.04). [b] Lit.[9] m.p. 98–99°.

Preparation of Piperidyl Alcohols 2a–g, 10, 11, and 12. General Procedure.—A solution of 0.12–0.17 mole of the appropriate pyridyl alcohol[23] in 150 ml. of glacial acetic acid containing 0.4–0.5 g. of platinum oxide was hydrogenated in a medium-pressure Paar apparatus with an initial pressure of *ca.* 60 p.s.i. After the theoretical pressure drop had been realized (15–20 hr.), the catalyst was removed by filtration and the solvent evaporated at reduced pressure with a rotary evaporator. A vapor phase chromatogram of the remaining residue displayed two peaks of varying proportions depending on the particular pyridyl alcohol being reduced. Infrared spectra indicated that the material of higher retention time contained ester carbonyl (1746 cm.$^{-1}$) and NH (3100 cm.$^{-1}$, broad) groups while that of lower retention time contained only the latter. In those preparations where only the final 1-azabicycloalkanes were desired, this mixture could be used directly in the cyclization reaction (*vide infra*); if the pure piperidyl alcohol was to be isolated, however, this mixture was heated until reflux with 100 ml. of a 25% sodium hydroxide solution for 2–3 hr. and the resulting mixture saturated with potassium carbonate and extracted with three 100-ml. portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate, the ether removed by distillation, and the remaining oil distilled under nitrogen at reduced pressure.

The piperidyl alcohols prepared in this manner were viscous, colorless oils some of which darkened on standing and gave poor analyses. Once again the most satisfactory derivatives were the 2,4,6-trinitrobenzenesulfonates.

The properties of the piperidyl alcohols **2a–g, 10, 11,** and 12 and their derivatives are summarized in Table III.

TABLE III

PROPERTIES OF PIPERIDYL ALCOHOLS AND THEIR DERIVATIVES

Compound	M.p. or b.p. (mm.), °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2a	94–95 (0.6)[a,b]				
2a·HCl	128–129[c]				
2b	46–48[d] / 92–93 (0.1)[e]				
2c	112–113 (2.0)	68.74	12.10	69.14	12.17
2c·TNBS	134–135	39.99	4.92	39.98	5.09
2d	104–105 (0.6)				
2d·TNBS	147–148	41.37	5.21	41.43	5.02
2e	110–111 (0.05)				
2e·TNBS	164–165	39.99	4.92	40.28	4.83
2f	113–115 (0.05)				
2f·TNBS	201–203 dec.	41.37	5.21	41.72	5.33
2g	111–112 (0.05)				
2g·TNBS	200–202 dec.	41.37	5.21	41.16	5.25
10	107–108 (0.04)				
10·TNBS	166–167	38.51	4.58	38.93	4.88
11	99–100 (0.06)[f,g]				
12	64–65 / 109–110 (0.06)				
12·TNBS	184–185	38.51	4.58	38.35	4.90

[a] Lit.[3] 101–102° (3.0). [b] Observed $n^{25}D$ 1.4880, lit.[3] $n^{21.5}D$ 1.4882. [c] Lit.[3] 128–129°. [d] Lit.[9] 47–49°. [e] Lit.[9] 90–92° (0.1). [f] J. Meisenheimer, J. Neresheimer, O. Finn, and W. Schneider, [*Ann.*, **420**, 190 (1920)] give b.p. 140–141° (13 mm.). [g] Observed $n^{23.8}D$ 1.4903; S. Wawzonek, M. F. Nelson, Jr., and P. S. Thelen [*J. Am. Chem. Soc.*, **74**, 2894 (1952)] give $n^{23}D$ 1.4902.

Preparation of 1-Azabicycloalkanes 3a–g. General Procedure—A mixture of 500 ml of water, 60 g. of wet, W-5 Raney nickel,[24] and 25 g. of the piperidyl alcohol **2**, either pure or as originally obtained from the reduction of the corresponding pyridyl alcohol **1** (*i.e.*, contaminated with the acetate ester of **2**), was placed in a 1-l., three-necked flask equipped with a mechanical stirrer, dropping funnel, Claisen head, with condenser arranged for distillation. The reaction mixture was heated to boiling with stirring and water added from the dropping funnel to keep the level of liquid in the flask constant. When the distillate was no longer strongly basic to pH paper, the heating was stopped (about 500–800 ml. of distillate had been collected at this point) and the distillate saturated with potassium carbonate and extracted with three 100-ml. portions of ether. The combined ether extracts were dried over potassium carbonate, the ether removed by distillation, and the remaining colorless oil distilled through a Vigreux

(18) All melting points and boiling points are corrected; analyses were performed by Mr. C. F. Geiger of Ontario, Calif.

(19) All the alkyl pyridines were obtained commercially with the exception of 2-ethyl-3-methylpyridine[20] and 2-isopropylpyridine[21] which were prepared in 49% yields from 2,3-dimethylpyridine and 2-ethylpyridine, respectively, by a procedure identical with that described above for the preparation of the pyridyl alcohols **1b–g** except that methyl iodide was used in place of the ethylene or propylene oxides.

(20) H. L. Lochte and T. H. Cheavens, *J. Am. Chem. Soc.*, **79**, 1667 (1957).

(21) H. C. Brown and W. A. Murphey, *ibid.*, **73**, 3308 (1951).

(22) D. J. Pettitt and C. K. Helmkamp, *J. Org. Chem.*, **28**, 2939 (1963).

(23) The pyridyl alcohols used in addition to those (**1a–g**) prepared above were 2-(3′-hydroxypropyl)pyridine (**1a**), 3-(3′-hydroxypropyl)pyridine, 4-(3′-hydroxypropyl)pyridine, and 4-(2′-hydroxyethyl)pyridine which were obtained from Reilly Tar and Chemical Co., Indianapolis, Ind.

(24) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 176.

TABLE IV

PROPERTIES OF 1-AZABICYCLOALKANES AND THEIR DERIVATIVES

Compound	M.p. or b.p. (mm.), °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
3a	156–157 (745)[a]				
3a·picrate	230–231[b]				
3a·H_2PtCl_6	218–219[c]				
3b	164.5 (735)[d,e]				
3b·picrate	199–200[f]				
3b·$HClO_4$	149–150[g]				
3c$_1$	179 (733)[d]				
3c$_1$·picrate	218–219	48.91	5.47	49.07	5.73
3c$_2$	175 (733)[d]				
3c$_2$·picrate	203–204	48.91	5.47	48.82	5.65
3c$_2$·$HClO_4$	154–155	45.07	7.56	45.39	7.56
3d	193.5 (735)[d]				
3d·picrate	170–172[h]				
3e	175.5 (735)[d]				
3e·picrate	192–193[i]				
3f$_1$	188.0 (736)[d]				
3f$_1$·picrate	187–189 dec.	50.13	5.75	49.88	5.85
3f$_2$	195.0 (736)[d]				
3f$_2$·picrate	230–234 dec.	50.13	5.75	50.42	5.73
3f$_3$[j]	187.5 (737.6)[d]				
3f$_3$·picrate	197–198 dec.	50.13	5.75	50.38	5.88
3f$_3$·$HClO_4$	162–163	47.39	7.89	47.48	7.78
3g	178.5 (735)[d]				
3g·picrate	191–192	50.13	5.75	50.35	5.91
3g·$HClO_4$	209–210	47.39	7.89	47.49	8.17

[a] C. W. Tullock and S. M. McElvain [*J. Am. Chem. Soc.*, **61**, 961 (1939)] report b.p. 156–158°. [b] Lit.[3] 228–229. [c] E. Ochiai and K. Tsuda [*Chem. Ber.*, **67**, 1011 (1934)] report m.p. 215°. [d] Microboiling point determination (R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., **1956**, p. 32). [e] N. J. Leonard and W. E. Goode [*J. Am. Chem. Soc.*, **72**, 5404 (1950)] report b.p. 165–169° (748 mm.). [f] G. R. Clemo, G. R. Ramage, and R. Raper [*J. Chem. Soc.*, 2959 (1932)] report m.p. 199–200°. [g] Lit.[12] 149–150°. [h] N. J. Leonard, R. W. Fulmer, and A. S. Hay [*J. Am. Chem. Soc.*, **78**, 3457 (1956)] report m.p. 171.5–172.5°. [i] G. R. Clemo and T. P. Metcalfe [*J. Chem. Soc.*, 1518 (1937)] report m.p. 191° dec. [j] Obtained by catalytic hydrogenation of **7** (*vide infra*).

column. The Raney nickel was recovered from the distillation pot, washed thoroughly with distilled water, and used for subsequent cyclizations.

Vapor phase chromatograms indicated that **3d**, **3e**, **3f**, and **3g** each consisted of two substances, presumably diastereoisomers. In the case of **3d** and **3e** separation was neither feasible nor necessary, since the physical properties of these mixtures and their derivatives had been reported previously (see Table IV). The mixtures of **3c** and **3f**, however, were easily separated by preparative v.p.c. into **3c**$_1$ and **3c**$_2$ (5:1) and **3f**$_1$ and **3f**$_2$ (7:3), each of which was characterized.

The physical properties of the 1-azabicycloalkanes **3a–g** and their derivatives are summarized in Table IV.

Mercuric Acetate Oxidation of Stereoisomeric Mixtures of 1-Azabicycloalkanes 3d, 3e, 3f, and 3g. General Procedure.[12]—In a 500-ml., three-necked flask fitted with an efficient mechanical stirrer, gas inlet valve, and a serum cap was placed 50 g. (0.38 mole) of mercuric acetate and 200 ml. of 5% aqueous acetic acid. After the apparatus had been evacuated and refilled with nitrogen several times, it was placed on a steam bath until all of the mercuric acetate had dissolved. Upon addition of 0.036 mole of the stereoisomeric 1-azabicycloalkane mixture through the serum cap by means of a syringe, an immediate precipitate of mercurous acetate formed. The reaction mixture was stirred on the steam bath for an hour, cooled, and the mercurous acetate removed by filtration. The filtrate was saturated with hydrogen sulfide and the resulting black precipitate removed by centrifugation. The resulting clear centrifugate was treated with sodium hydroxide, saturated with potassium carbonate, and extracted with three 100-ml. portions of ether which were dried over anhydrous potassium carbonate. After the drying agent had been removed by filtration, the ether extracts were concentrated to 100 ml. on a rotary evaporator, diluted with 50 ml. of absolute ethanol, and acidified (to litmus) with a 50% (v./v.) solution of 70% perchloric acid in absolute ethanol. The precipitated immonium perchlorate salt was recrystallized from ethanol–ether with the aid of some Norit.

The yields, properties, and analyses of these immonium salts are summarized in Table V.

TABLE V

PROPERTIES AND YIELDS OF IMMONIUM PERCHLORATES FROM MERCURIC ACETATE OXIDATION OF MIXTURES OF STEREOISOMERIC 1-AZABICYCLOALKANES **3d–g**

Compound	Yield, %	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
5	53	258–260 dec.	45.48	6.78	45.20	6.68
7	54	238–239 dec.	47.72	7.16	47.57	7.12
8	62	235–237 dec.	45.48	6.78	45.65	6.56
9	49	253–255[a]				

[a] N. J. Leonard, R. W. Fulmer, and A. S. Hay [*J. Am. Chem. Soc.*, **78**, 3457 (1956)] report m.p. 252–253°.

Catalytic Reduction of the Immonium Perchlorates 5 and 7. A. 8-Methyl-$\Delta^{4(9)}$-dehydroindolizidinium Perchlorate (5).—A methanol solution of 1 g. of the immonium salt **5** was hydrogenated at atmospheric pressure and room temperature in the presence of about 10 mg. of platinum oxide catalyst. After 1 equivalent of hydrogen had been taken up (10 min.), the reaction was stopped, the catalyst removed by filtration, and the solvent evaporated at reduced pressure to leave 1.0 g. of a white crystalline solid, m.p. 150–153° (153–155° after recrystallization from ethanol–ether), which on treatment with base and ether extraction gave 0.5 g. of a colorless oil whose vapor phase chromatogram gave a single peak with a retention time identical with that of **3c**$_2$.

B. 1,8-Dimethyl-$\Delta^{4(9)}$-dehydroindolizidinium Perchlorate (7).—A vapor phase chromatogram of the colorless oil obtained by reduction and work-up of **7** in the same manner as employed for **5**, showed the presence of three substances. Separation of the major component (80–90%) by preparative v.p.c. gave a colorless oil (**3f**$_3$) whose infrared spectrum, boiling point, and the melting point of its picrate (see Table IV) indicated that it was different from **3f**$_2$ and **3f**$_1$.

Attempted Cyclization of 3-(3′-Hydroxypropyl)piperidine (10).—Treatment of 8 g. of the piperidyl alcohol **10** by the general procedure described above led to 1 l. of aqueous distillate which after the usual work-up yielded 0.5 g. of a colorless oil, identified as 3-ethylpiperidine by its b.p. 152° (745 mm.) (lit.[25] b.p. 154–155°), and by the melting points of its picrate, m.p. 62–63° (lit.[25] m.p. 63°), and chloroplatinate, m.p. 182–183° (lit.[25] m.p. 181°).

Attempted Cyclization of 4-(2′-Hydroxyethyl)piperidine (11).—Treatment of 9 g. of the piperidyl alcohol **11** in the same manner as above gave about 1 g. of an oil whose vapor phase chromatogram indicated the presence of at least five components and whose infrared spectrum showed strong absorption in the N–H,O–H and C=O regions. The distillation pot residue was filtered, saturated with sodium carbonate, and extracted with three 50-ml. portions of chloroform. After being dried over anhydrous potassium carbonate, the combined chloroform extracts were freed of chloroform by distillation through a Vigreux column to leave 4 g. of an oily residue whose vapor phase chromatogram and infrared spectrum were as complex as those of the oil which had distilled over during the attempted cyclization.

Attempted Cyclization of 4-(3′-Hydroxypropyl)piperidine (12).—Treatment of 9 g. of the piperidyl alcohol **12** in the same manner as above gave about 0.5 g. of an oil whose vapor phase chromatogram indicated the presence of at least three components and whose infrared spectrum showed strong absorption in the NH,OH and C=C regions. In the same way as above, the distillation pot residue yielded 6 g. of an oil whose infrared spectrum was quite similar to that of the starting piperidyl alcohol **12**.

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Studies on the Pyrimidine Derivatives. XXIX.[1,2] Reactions of 3-Ethoxy-2-methoxymethylenepropionitrile and 3-Ethoxy-2-ethoxymethoxymethylpropionitrile with Urea and Thiourea Derivatives

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3-Ethoxy-2-methoxymethylenepropionitrile (I) or its acetal (II) undergo condensation with urea, N-substituted ureas, thiourea, and N-substituted thiourea. The condensation has been carried out by heating the enol ether propionitrile (I) or acetal propionitrile (II) in ethanol solution, in the presence of hydrochloric acid, with urea to obtain directly 5-cyano-2-oxo-1,2,3,4-tetrahydropyrimidine (III), with N,N'-dimethylurea to yield 5-cyano-1,3-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine (IX), with N-methylurea to give a mixture of 5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (X) and its isomeric 3-methyl compound (XI), which was separated into each isomer, and with N-phenylurea to obtain exclusively the 1-phenyl compound (XV). Further dehydrogenation of these compounds made possible a new synthetic route to pyrimidines. The condensation was also carried out with thiourea and I or II in alcoholic solution in the presence of hydrochloric acid to obtain 5-cyano-2-oxo-6H-2,3-dihydro-1,3-thiazine (XVIII) and with N-phenylthiourea to give XVIII and aniline. Elucidation of the structures of these compounds is described.

We have previously reported the reaction of acetamidine[3] and related amidines[4] with 3-ethoxy-2-methoxymethylenepropionitrile (I) to give 2-substituted 4-amino-5-ethoxymethylpyrimidines, and with 3-ethoxy-2-ethoxymethoxymethylpropionitrile (II) to yield 2,7-disubstituted 5,6-dihydropyrimido[4,5-*d*]pyrimidines.[3,4] This paper deals with the reaction of I or II with urea, N-substituted ureas, thiourea, and N-substituted thiourea (see Scheme I).

Reaction of I, a mixture of geometrical isomers,[5] with urea was carried out in ethanol solution in the presence of hydrochloric acid. The base-catalyzed condensation of aldehyde nitrile derivatives with urea is a standard synthesis of cytosine derivatives.[6] However, in this case a product III, $C_5H_5N_3O$, was obtained in 42.6% yield by acid-catalyzed reaction, and no evidence for the formation of other products was shown by thin-layer chromatography of the filtrate. The infrared spectrum of III shows NH bands, a conjugated C≡N band, and an amide I band. Hydrolysis of III in concentrated hydrochloric acid gave the amide IV. Acetylation with acetic anhydride afforded the diacetate V. The proton magnetic resonance spectrum[7] of V (Table I) shows two singlet signals (3H) at τ 7.32 and 7.40 arising from the protons of 1- and 3-N-acetyl groups, respectively. The signals of the protons of C-4 methylene and C-6 methylidyne groups appear at τ 5.56 (2H) and 2.05 (1H), respectively; the former is split into a doublet and the latter into a triplet due to the spin coupling (J = 1.0 c.p.s.) with each other. These results indicate that III can be formulated as 5-cyano-2-oxo-1,2,3,4-tetrahydropyrimidine. By the action of bromine in acetic acid solution, III was dehydrogenated to give 5-cyano-2-oxo-1,2-dihydropyrimidine (VI), which was converted into 5-cyano-2-chloropyrimidine (VII) on treatment with phosphorus oxychloride. Amination of VII gave the 2-amino derivative VIII. This compound VIII was identified as 2-amino-5-cyanopyrimidine by comparison of its infrared and ultraviolet spectra with those of an authentic sample.[8] Thus the structure of III was established. It should be noted that this synthesis is useful in obtaining 2-substituted 5-cyanopyrimidines.

Reaction of I with N,N'-dimethylurea in ethanol solution in the presence of hydrochloric acid gave a product IX, $C_7H_9N_3O$, in 56.3% yield. Infrared spectrum of IX shows a conjugated C≡N band and C=O band, but no NH band is shown. The n.m.r. spectrum of IX exhibits the signals of the protons of two N-methyl, C-4 methylene, and C-6 methylidyne groups as shown in Table I. Thus IX is formulated as 5-cyano-1,3-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine.

Reaction of I with N-methylurea in ethanol solution in the presence of hydrochloric acid afforded a product of m.p. 187–188°, $C_6H_7N_3O$, which showed two spots on a thin-layer chromatogram and which could be converted into a mixture of acetates. The n.m.r. spectrum of this mixture of acetates consists of four pairs of signals of N-acetyl, N-methyl, C-4 methylene, and C-6 methylidyne protons whose respective relative integrated intensities are about 3:2. Thus, this product was revealed to be a mixture of 3-acetyl-5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XII) and the 3-methyl isomer XIII in a ratio of 3:2. This mixture was subjected to column chromatography on alumina and two crystalline products of m.p. 94° (XII) and m.p. 118° (XIII) were obtained separately. The assignment of the structures of these compounds was made as follows. The n.m.r. spectrum of N,N'-diacetyl compound V shows the signals of C-4 methylene and C-6 methylidyne protons at lower fields than those of the protons of N,N'-dimethyl compound IX (see Table I). Therefore, in XII and XIII these protons resonating at lower fields will be situated at positions adjacent to the N-acetyl group. The spectrum of XII shows the signals of the N-acetyl and C-6

(1) A part of this paper has been delivered at the 19th congress of I.U.P.A.C., London, July 10–17, 1963.

(2) Part XXVIII: *Chem. Pharm. Bull.* (Tokyo), **12**, 398 (1964).

(3) A. Takamizawa, K. Ikawa, and K. Tori, *Yakugaku Zasshi*, **78**, 647 (1958); A. Takamizawa, K. Tokuyama, and K. Tori, *Bull. Chem. Soc. Japan*, **32**, 188 (1959).

(4) A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.* (Tokyo), **12**, 393 (1964).

(5) A. Takamizawa, K. Hirai, and K. Tori, *ibid.*, **11**, 1212 (1963).

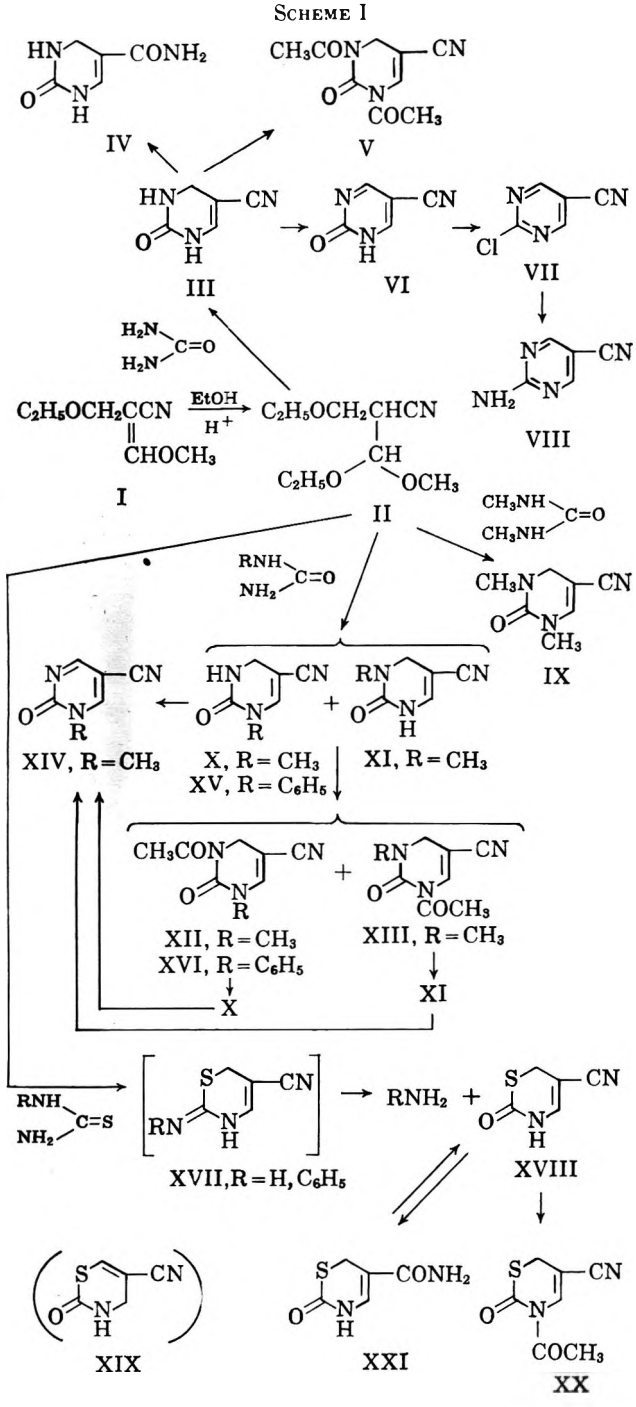
(6) D. J. Brown, "The Pyrimidines," John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 59–61.

(7) All the n.m.r. spectra were taken with a Varian A-60 spectrometer on about 10% solution in deuteriochloroform containing about 1% tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed in τ-values and coupling constants are in c.p.s. Accuracy limits are about τ ±0.02 for chemical shifts and about ±0.3 c.p.s. for coupling constants.

(8) J. P. English, J. H. Clark, R. G. Shepard, H. W. Marson, J. Krapcho, and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **68**, 1039 (1946).

(9) T.l.c.: alumina plate, ethyl acetate solvent, detected by iodine vapor.

SCHEME I



methylidyne protons at higher fields and those of the N-methyl and C-4 methylene protons at lower fields than does that of XIII. Accordingly, the C-4 methylene in XII should be situated at a position adjacent to to the N-acetyl group. Therefore, XII can be formulated as 3-acetyl-5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine. Conversely, XIII can be formulated as the 3-methyl isomer. Hydrolyses of XII and XIII gave 5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (X) and the 3-methyl isomer XI, respectively. A mixture of X and XI was dehydrogenated by the action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane solution to give 5-cyano-1-methyl-2-oxo-1,2-dihydropyrimidine (XIV) in good yield. It should be noted that this synthesis is a useful method for obtaining new N-substituted 5-cyano-2-oxopyrimidines. The dehydrogenation of X and XI was made separately to yield the same product XIV.

N-Phenylurea reacted with I in ethanol solution in the presence of hydrochloric acid to give the product XV, $C_{11}H_9N_3O$, in 42.6% yield. The n.m.r. spectrum of the acetate of XV shows that this product is not a mixture and that the acetate XVI can be formulated as 3-acetyl-5-cyano-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine. In this reaction the 3-phenyl isomer was not obtained.

Reaction of I with thiourea was also carried out in ethanol solution in the presence of hydrochloric acid and the product XVIII, $C_5H_4N_2OS$, and ammonium chloride were obtained. This product XVIII was hydrolyzed in concentrated hydrochloric acid to give the amide XXI which was converted into the original XVIII by the action of phosphorus oxychloride. Acetylation of XVIII gave monoacetate XX. These facts suggest that this compound XVIII is 5-cyano-2-oxo-6H-2,3-dihydro-1,3-thiazine or its isomeric structure XIX. The n.m.r. spectrum of XX shows a singlet (3H) at τ 7.38 due to the N-acetyl group, a doublet (2H, J = 0.8 c.p.s.) at τ 6.23 due to the C-6 methylene protons, and a triplet (1H, J = 0.8 c.p.s.) at τ 2.07 due to the C-4 methylidyne proton. The spectrum of XVIII shows a doublet (J = 0.8 c.p.s.) at τ 6.26, and a doubling triplet (J = 6.5, 0.8 c.p.s.) at τ 3.11, which changes into a triplet by the addition of a small amount of deuterium oxide to the solution examined.[10,11] These facts imply that the NH group is situated at a position adjacent to the C-4 methylidyne group. From all of these observations, XVIII was elucidated to be 5-cyano-2-oxo-6H-2,3-dihydro-1,3-thiazine. Similarly, the reaction of I with N-phenylthiourea in ethanol solution in the presence of hydrochloric acid gave XVIII and aniline hydrochloride. These products would result from hydrolysis of the probable 2-imino intermediate.

In a previous paper,[12] acid treatment of the enol ether nitrile I in ethanol was reported to give its acetal II. In the present cases, it is reasonable to assume that II is an intermediate in the reaction of I with ureas or thioureas in ethanol in the presence of hydrochloric acid. This assumption was supported by the facts that II reacted with urea, N,N'-dimethylurea, and thiourea to afford III, IX, and XVIII in 46.7, 56.3, and 24.3% yield, respectively. However, the possibility that a part of the nitrile I can directly react with these reagents to give products analogous to those obtained from the reaction with amidines cannot be excluded at this point.

It should be noted that the cyano group in I or II did not participate in the cyclization reaction with urea, in contrast to reaction with amidines.[3] Of much interest is the fact that the sulfur atom participated preferentially, probably in a thiol form, in the cyclization reaction

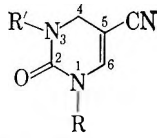
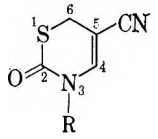
(10) This decoupling results from the proton exchanging of the N-H group [refer to H. M. Fales and A. T. Robertson, *Tetrahedron Letters*, No. 3, 111 (1962)].

(11) Spin coupling between -CH and -CONH- protons has frequently been reported [H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1959); G. V. D. Tiers and F. A. Bovey, *J. Phys. Chem.*, **63**, 302 (1957); K. Tori, *Ann. Rept. Shionogi Res. Lab.*, **12**, 114 (1962); and K. Tori and K. Kuriyama, *Chem. Ind.* (London), 1525 (1963)]. However, it is of considerable interest to note that =CH proton appreciably couples with a CONH proton.

(12) A. Takamizawa, K. Ikawa, and M. Narisada, *Yakugaku Zasshi*, **78**, 637 (1958).

TABLE I

N.M.R. SPECTRAL DATA IN DEUTERIOCHLOROFORM (10%)[a]

Compound	Chemical shift (τ) N-1-CH_3	N-3-CH_3	N-1-$COCH_3$	N-3-$COCH_3$	C-4-H[b]	C-6-H[b]
						
V, R = R′ = $COCH_3$			7.32	7.40	5.56 (d)	2.05 (t)
IX, R = R′ = CH_3	6.87	7.07			5.93 (d)	3.17 (t)
X, R = CH_3; R′ = H	6.88				5.87 (d)	3.20 (t)
XI, R = H; R′ = CH_3		7.08			5.95 (d)	3.15 (m)
XII, R = CH_3; R′ = $COCH_3$	6.77			7.46	5.57 (d)	3.08 (t)
XIII, R = $COCH_3$; R′ = CH_3		6.97	7.37		5.92 (d)	2.07 (t)
XVI, R = C_6H_5; R′ = $COCH_3$				7.42	5.43 (d)	2.95 (t)
						
XVIII,[c] R = H					3.11 (d-t)	6.26 (d)
XX, R = $COCH_3$				7.38	2.07 (t)	6.23 (d)

[a] Peak multiplicities are represented by d (doublet), t (triplet), m (multiplet), and d-t (doubling triplet). All methyl peaks are sharp singlets. [b] $J_{4,6}$ = 1.0 c.p.s. [c] Observed on a saturated solution.

of thioureas with I or II, and the expected product,[6] 4-amino-5-ethoxymethyl-2-mercaptopyrimidine, was not obtained.

Experimental

5-Cyano-2-oxo-1,2,3,4-tetrahydropyrimidine (III). A.—3-Ethoxy-2-methoxymethylenepropionitrile (I, 2.8 g.) and 1.2 g. of urea were added to a solution of 200 ml. of ethanol and 4 ml. of concentrated hydrochloric acid. The mixture was refluxed for 15 hr. and the product was collected after cooling, yielding 1.35 g. Recrystallization from water afforded 1.05 g. (42.6%) of colorless prisms, m.p. >300°, insoluble or slightly soluble in ether, ethyl acetate, chloroform, acetone, and ethanol; infrared spectrum (Nujol mull), 3250, 3100 (NH), 2230 (C≡N), and 1670 $cm.^{-1}$ (amide I); ultraviolet spectrum, $\lambda_{max}^{EtOH\ suspension}$ 276 mμ.

Anal. Calcd. for $C_5H_3N_3O$: C, 48.77; H, 4.10; N, 34.14. Found: C, 48.76; H, 4.41; N, 34.12.

B.—A solution of 1.2 g. of urea, 3.8 g. of II, and 4 ml. of concentrated hydrochloric acid in 200 ml. of ethanol was refluxed for 19 hr. as described above. The product (1.55 g.) was recrystallized from water to afford 1.15 g. (46.7%) of III.

5-Carboxamido-2-oxo-1,2,3,4-tetrahydropyrimidine (IV).—One gram of III was dissolved in 20 ml. of concentrated hydrochloric acid with slight warming and allowed to stand overnight at room temperature. The product was collected and recrystallized from water to afford 0.7 g. (61.1%) of colorless needles, m.p. 286–289° dec.; infrared spectrum shows no C≡N band; ultraviolet spectrum, λ_{max}^{EtOH} 240 mμ (log ε 4.38), 276 mμ (log ε 4.38).

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.56; H, 5.00; N, 29.78. Found: C, 42.47; H, 5.03; N, 29.82.

5-Cyano-1,3-diacetyl-2-oxo-1,2,3,4-tetrahydropyrimidine (V).—A mixture of 0.5 g. of III and 5 ml. of acetic anhydride was refluxed for 8 hr. The excess reagent was removed under reduced pressure and the residue was solidified on trituration with petroleum ether. Recrystallization from a mixture of ether and petroleum ether afforded 0.5 g. (61.4%) of colorless needles, m.p. 79–81°; infrared spectrum shows no NH band; ultraviolet spectrum, λ_{max}^{EtOH} 235 mμ (log ε 4.11).

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.36; N, 20.28. Found: C, 52.61; H, 4.59; N, 19.23.

5-Cyano-2-oxo-1,2-dihydropyrimidine (VI).—A mixture of 0.5 g. of III and 10 ml. of glacial acetic acid was heated and a solution of 0.65 g. of bromine in 2 ml. of glacial acetic acid was added to the mixture. The solution was refluxed for 3 hr., the product was collected and recrystallized from ethanol to afford 0.4 g. (80.3%) of colorless prisms, m.p. 260–262°; ultraviolet spectrum, λ_{max}^{EtOH} 257 mμ (log ε 4.40), 300 mμ (shoulder, log ε 2.97).

Anal. Calcd. for $C_5H_3N_3O$: C, 49.59; H, 2.50; N, 34.70. Found: C, 49.33; H, 2.69; N, 33.93.

2-Chloro-5-cyanopyrimidine (VII).—A mixture of 0.4 g. of VI, 4 ml. of phosphorus oxychloride, and 0.2 ml. of dimethylaniline was refluxed for 1 hr. The excess reagent was removed under reduced pressure, ice–water was added to the residue, and the mixture was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate, the ether was removed, and the residue was recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°) to afford 0.3 g. (65.2%) of pale yellow needles, m.p. 130–132°; ultraviolet spectrum, λ_{max}^{EtOH} 228 mμ (log ε 4.10), 260 mμ (log ε 3.39).

Anal. Calcd. for $C_5H_2N_3Cl$: C, 43.05; H, 1.45; N, 30.17; Cl, 25.42. Found: C, 43.35; H, 1.81; N, 30.38; Cl, 25.44.

2-Amino-5-cyanopyrimidine (VIII).—A suspension of 0.5 g. of VII in 40 ml. of ethanol saturated with NH_3 was heated at 100° for 2 hr. On cooling, the product was collected and recrystallized from ethanol to afford 0.3 g. (69.7%) of colorless prisms, d.p. *ca.* 260°, lit.[5] d.p. 300–310°; infrared spectrum (Nujol mull), 3100, 2220, 1677, 1597, 1525, 1385, 1235, 1070, 969, 803, and 659 $cm.^{-1}$; ultraviolet spectrum, λ_{max}^{EtOH} 257 mμ (log ε 4.46), 296 mμ (log ε 3.54).

Anal. Calcd. for $C_5H_4N_4$: C, 50.00; H, 3.36; N, 46.65. Found: C, 50.08; H, 3.49; N, 46.09.

The infrared and ultraviolet spectra were identical with those of an authentic sample prepared by the method of English, *et al.*,[8] from 2-aminopyrimidine by bromination and subsequent cyanation.

5-Cyano-1,3-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine (IX). A.—A solution of 0.88 g. of N,N′-dimethylurea, 1.4 g. of I, and 2 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 12 hr. The solution was concentrated *in vacuo*, neutralized with sodium bicarbonate solution, and extracted with chloroform. The chloroform extract, after drying over anhydrous magnesium sulfate, was evaporated to give the product which on recrystallization from a mixture of benzene and petroleum ether gave 0.85 g. (56.3%) of colorless pillars, m.p. 109°; infrared spectrum (Nujol mull), 2220 $cm.^{-1}$ (C≡N) and no NH band; ultraviolet spectrum, λ_{max}^{EtOH} 219 mμ (log ε 3.93). 290 mμ (log ε 3.92).

Anal. Calcd. for $C_7H_9N_3O$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.36; H, 6.16; N, 27.60.

B.—The solution of 0.88 g. of N,N′-dimethylurea, 1.9 g. of II, and 2 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 6 hr. as described above and 0.85 g. (56.3%) of IX was obtained.

Reaction of I and N-Methylurea.—A solution of 2.82 g. of I, 1.48 g. of N-methylurea, and 2 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 12 hr. It then was con-

centrated *in vacuo*, water was added to the residue, and the product was collected, yielding 1.6 g. (54.5%). Recrystallization from ethanol gave 1.25 g. (42.5%) of colorless prisms, m.p. 187–189°; t.l.c., R_f 0.33, 0.26.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.67; H, 5.41; N, 30.35.

3-Acetyl-5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XII) and 1-Acetyl-5-cyano-3-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XIII).—A mixture of 4.5 g. of the product obtained above and 45 ml. of acetic anhydride was refluxed for 5 hr. After removing excess reagent, the residue was recrystallized from a mixture of benzene and petroleum ether to give 4.66 g. (85.0%) of colorless prisms, m.p. 75–78°.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.88; H, 5.25; N, 22.95.

This product (2.4 g.) was chromatographed on alumina. Chloroform eluates yielded 1.0 g. of a compound, m.p. 205–206°, which was acetylated again with 10 ml. of acetic anhydride to give 1.0 g. of colorless needles, m.p. 94° (recrystallized from a mixture of benzene and petroleum ether); n.m.r. spectrum (Table I) shows that these crystals are XII. Ethanol elution yielded 0.4 g. of the product, m.p. 182–183°, which was acetylated again with 4 ml. of acetic anhydride to give 0.4 g. of colorless needles, m.p. 118° (recrystallized from a mixture of benzene and petroleum ether); n.m.r. spectrum (Table I) shows that these crystals are XIII.

5-Cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (X).—A mixture of 0.6 g. of XII and 6 ml. of 5% potassium hydroxide–ethanol was allowed to stand overnight at room temperature. The solution was concentrated *in vacuo*, water was added to the residue, and the product was collected and recrystallized from ethanol to give 0.35 g. of colorless pillars, m.p. 205–206°; t.l.c., R_f 0.33; ultraviolet spectrum, λ_{max}^{EtOH} 213 mμ (log ε 3.92), 286 mμ (log ε 3.97).

Anal. Found: C, 52.21; H, 5.46; N, 30.64.

5-Cyano-3-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XI).—A mixture of 0.4 g. of XIII and 4 ml. of 5% potassium hydroxide and 4 ml. of ethanol was allowed to stand overnight at room temperature, and concentrated *in vacuo*. Water was added to the residue and the product was recrystallized from ethanol to give 0.15 g. of colorless rhombics, m.p. 182–183°; t.l.c., R_f 0.25; ultraviolet spectrum, λ_{max}^{EtOH} 217 mμ (log ε 3.96), 278.5 mμ (log ε 3.90).

Anal. Found: C, 52.64; H, 5.37; N, 30.28.

5-Cyano-1-methyl-2-oxo-1,2-dihydropyrimidine (XIV). A.—A solution of 0.757 g. of DDQ in 10 ml. of dioxane was added to the solution of 0.457 g. of the mixture of X and XI in 10 ml. of dioxane and refluxed for 1 hr. The separated crystals were filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from a mixture of methanol and ethyl acetate to give 0.216 g. of colorless prisms, m.p. 233–234°; the filtrate was concentrated and the residue was purified by alumina chromatography to afford 0.08 g. of the crystals. Both crystals were found to be identical by infrared spectra; t.l.c., R_f 0.15; ultraviolet spectrum, 262 mμ (log ε 4.04), 312 mμ (log ε 2.75); infrared spectrum (Nujol mull), 2255 (C≡N), 1670–1680 cm.$^{-1}$ (C=O, C=N), no NH band.

Anal. Calcd. for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.02; H, 3.91; N, 30.82.

B.—A solution of 0.137 g. of X and 0.227 g. of DDQ in 6 ml. of dioxane was refluxed for 1 hr. as described above and 0.106 g. (78.5%) of XIV was obtained.

C.—A solution of 0.044 g. of XI and 0.073 g. of DDQ in 6 ml. of dioxane was refluxed for 1 hr. as above, and 0.03 g. (69.2%) of XIV was obtained.

5-Cyano-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine (XV).—A solution of 5 g. of I, 4.8 g. of N-phenylurea, and 14 ml. of concentrated hydrochloric acid in 37 ml. of ethanol was refluxed for 5 hr. The product was collected, washed with water, and dried, yielding 4.2 g. (60%), m.p. 218–221° dec. Recrystallization from methanol gave 3.0 g. (42.6%) of colorless prisms, m.p. 220–221° dec.; ultraviolet spectrum, λ_{max}^{EtOH} 286.5 mμ (log ε 4.01).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.56; N, 21.10. Found: C, 66.18; H, 4.74; N, 20.57.

3-Acetyl-5-cyano-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine (XVI).—A mixture of 0.6 g. of XV and 6 ml. of acetic anhydride was refluxed for 7 hr. After removing excess reagent, the residue was recrystallized from a mixture of benzene and petroleum ether to afford 0.7 g. (96.3%) of colorless needles, m.p. 160–163°; ultraviolet spectrum, λ_{max}^{EtOH} 283 mμ (log ε 3.99).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.43. Found: C, 64.71; H, 4.72; N, 17.04.

5-Cyano-2-oxo-2,3-dihydro-6H-1,3-thiazine (XVIII). A.—A solution of 7 g. of thiourea, 13.2 g. of I, and 35 ml. of concentrated hydrochloric acid in 700 ml. of ethanol was refluxed for 25 hr. After concentration, chloroform was added to the residue and separated ammonium chloride was filtered off. The filtrate was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residual solid was treated with charcoal and recrystallized from water to afford 4.1 g. (31.8%) of colorless pillars, m.p. 120–122°; infrared spectrum (Nujol mull), 3220 (NH), 2220 (C≡N), 1680 and 1630 cm.$^{-1}$ (amide I and conjugated C=C); ultraviolet spectrum, λ_{max}^{EtOH} 241 mμ (log ε 3.75), 285 mμ (log ε 3.74); t.l.c, R_f 0.51.

Anal. Calcd. for $C_5H_4N_2OS$: C, 42.85; H, 2.85; N, 20.00; S, 22.86. Found: C, 43.03; H, 2.98; N, 19.89; S, 23.04.

B.—A solution of 1.52 g. of thiourea, 3.8 g. of II, and 4 ml. of concentrated hydrochloric acid in 200 ml. of ethanol was refluxed for 22 hr., and treated as described above to afford 0.684 g. (24.6%) of XVIII.

5-Carboxamido-2-oxo-2,3-dihydro-6H-1,3-thiazine (XXI).—To 20 ml. of concentrated hydrochloric acid, 0.4 g. of XVIII was added and allowed to stand overnight at room temperature. Crystals were collected and recrystallized from ethanol to give 0.25 g. (55.5%) of colorless needles, m.p. 205° dec.; infrared spectrum, no C≡N band.

Anal. Calcd. for $C_5H_6N_2O_2S$: C, 37.98; H, 3.83; N, 17.72. Found; C, 38.33; H, 3.99; N, 17.79.

A mixture of 0.2 g. of XXI and 1.5 ml. of phosphorus oxychloride was refluxed for 1 hr. After evaporation of the reagent under reduced pressure, ice–water was added to the residue and the product was collected. Recrystallization from a mixture of ethyl acetate and petroleum ether gave 0.1 g. of XVIII.

3-Acetyl-5-cyano-2-oxo-2,3-dihydro-6H-1,3-thiazine (XX).—A mixture of 0.1 g. of XVIII and 2 ml. of acetic anhydride was refluxed for 6 hr. After evaporation, the residue was recrystallized from a mixture of benzene and petroleum ether to afford 0.11 g. (84.7%) of colorless needles, m.p. 107–108°; infrared spectrum, no NH band; ultraviolet spectrum, λ_{max}^{EtOH} 233 mμ (log ε 4.09).

Anal. Calcd. for $C_7H_6N_2O_2S$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.18; H, 3.55; N, 15.38.

Reaction of I with N-Phenylthiourea.—A solution of 1.4 g. of I, 1.5 g. of N-phenylthiourea, and 2 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 12 hr. and evaporated *in vacuo*. Chloroform was added to the residue and aniline hydrochloride (0.4 g., 44.4%) was filtered off. The filtrate was evaporated and the residue was treated with charcoal, and recrystallized from water to afford 0.3 g. (21.4%) of XVIII.

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Deoxygenation of Pyridine N-Oxide[1]

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The deoxygenation of pyridine, 2-picoline, and 2,6-lutidine N-oxides employing 9-diazofluorene (I) is described. The mechanisms of the reaction and the formation of fluorenone ketazine (VI) are discussed.

Numerous methods have been found for deoxygenating pyridine N-oxides.[2,3] In a previous paper[3] we have shown that dichlorocarbene deoxygenates pyridine N-oxide. However, relatively high conversions of pyridine N-oxide to pyridine were difficult to achieve unless high pyridine N-oxide to halocarbene precursor ratios were maintained. In an effort to achieve a deoxygenation procedure with greater synthetic utility our attention was turned to nonhalocarbene precursors. Fluorene carbene (II) has been postulated to exist in the photochemical[4] and thermal[5] decomposition of 9-diazofluorene (9-DAF, I). The 9-DAF (I) may be prepared in high yield[6] from readily available starting materials and stored under ordinary conditions for extended periods of time.

Table I gives the yields of pyridines obtained when the corresponding pyridine N-oxides were allowed to react with I in benzene or dimethyldiethylene glycol (diglyme) solvent. Yields of the pyridines ranged from 45 to 66% when the I to N-oxide ratio was 4 to 1. These results were obtained by allowing the pyridines formed to distil as I was added; this technique was necessary in order to suppress the side reaction which gave fluorenone ketazine (VI).

TABLE I

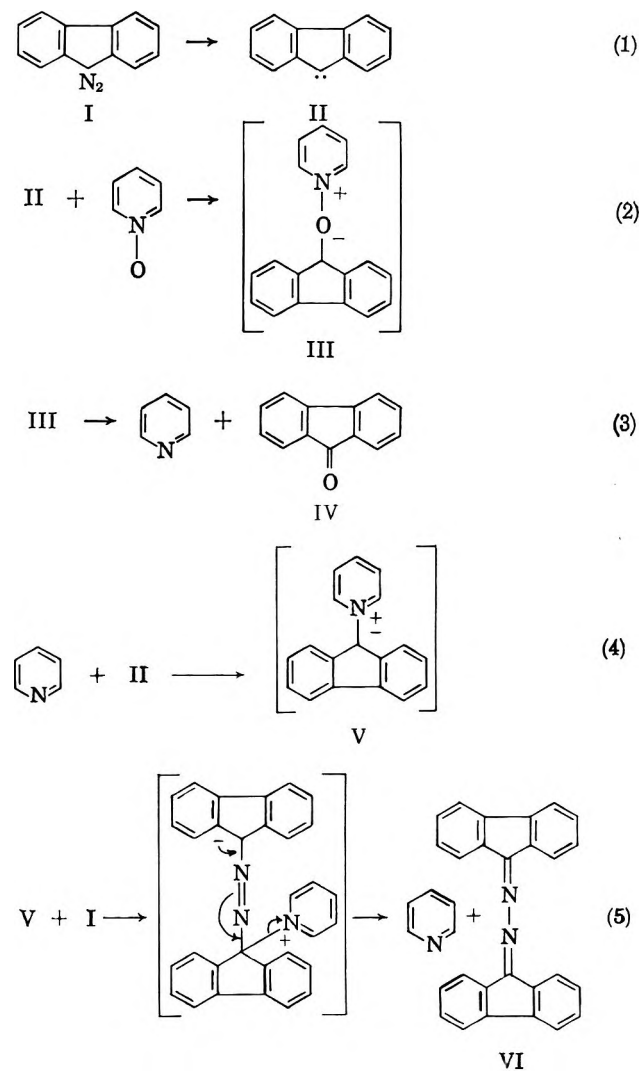
N-oxides	Mole ratio of 9-DAF–N-oxide	Solvent	Time, hr.	% yield of pyridines
Pyridine	1	Benzene	72	16[a]
Pyridine	1.5	Benzene	65	28[a]
Pyridine	2.0	Diglyme	2	39[b]
Pyridine	4.0	Diglyme	2	66[b]
2-Picoline	4.0	Diglyme	2	45[b]
2,6-Lutidine	4.0	Diglyme	2	62[b]

[a] Isolated. [b] Determined as picrate.

Staudinger and Kupfer[7] had previously shown that on decomposing I in refluxing benzene, bifluorene was the only product obtained. On repeating this reaction we obtained 91% bifluorene and 4% of the previously unreported ketazine (VI). A similar reaction using pyridine as the solvent gave 5% of bifluorene and 92% of VI (Table II). When equimolar quantities of I and 2,6-lutidine were allowed to react in benzene, the bifluorene to ketazine VI ratio was 54 to 42%, whereas, in an identical experiment, substituting pyridine for the 2,6-lutidine, the ratio of bifluorene to VI was 28 to 68%. The following mechanism is postulated for the deoxygenation of pyridine N-oxide and for the formation of VI.

TABLE II

Benzene, ml.	Base	9-DAF (I), mole	Bifluorene, %	Fluorenone ketazine (VI), %
15		0.0078	91	4
	Pyridine (20 ml.)	0.0107	5	92
4	Pyridine (0.0021 mole)	0.0021	28	68
4	2,6-Lutidine (0.0021 mole)	0.0021	54	42



A decreased yield of the ketazine (VI) and an increased yield of bifluorene on using 2,6-lutidine instead of pyridine as the precursor for the ylid of type V (Table

(1) Acknowledgment is made of support from the University of Delaware Research Foundation.

(2) (a) T. R. Emerson and C. W. Rees, *J. Chem. Soc.*, 1917 (1962); (b) D. I. Relyea, P. O. Tawney, and A. R. Williams, *J. Org. Chem.*, **27**, 477 (1962), and references cited therein.

(3) E. E. Schweizer and G. J. O'Neill, *ibid.*, **28**, 2460 (1963).

(4) W. von E. Doering and M. Jones, Jr., *Tetrahedron Letters*, **No. 12**, 791 (1963).

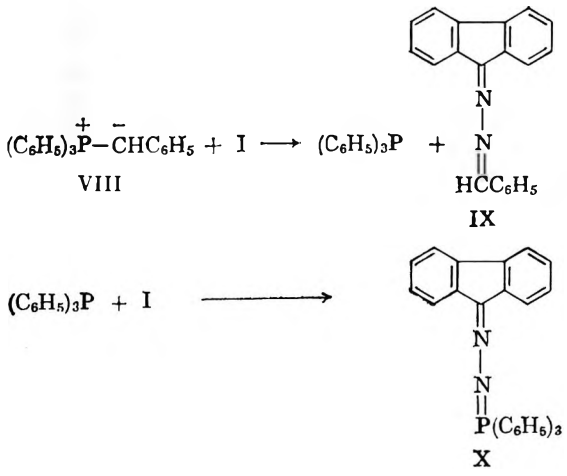
(5) (a) W. E. Parham, H. G. Braxton, Jr., and D. R. Theissen, *J. Org. Chem.*, **27**, 2632 (1962); (b) A. Schonberg, A. Mustafa, and M. Latif, *J. Am. Chem. Soc.*, **75**, 2267 (1953); (c) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4675 (1952).

(6) C. D. Nenitzescu and E. Solomonica, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 496.

(7) H. Staudinger and O. Kupfer, *Ber.*, **44**, 2197 (1911).

II) supports the postulation of the 1-(9-fluorenyl)-pyridinium ylid (V) as an intermediate, because one would expect that steric hindrance in the lutidine reaction would enhance the formation of bifluorene owing to the slowing down of the ylid V formation.[8] The postulation of V as an intermediate is further supported by the following facts: Pinck and Hilbert[9] suggested the formation of V as an intermediate when 1-(9-fluorenyl)pyridinium bromide (VII) is treated with 10% aqueous sodium hydroxide in ethanol. On treating essentially equimolar portions of VII and 9-DAF (I) with base, in the manner described by Pinck and Hilbert, at room temperature, an 87% yield of VI was obtained.

Benzylidenetriphenylphosphorane[10] (VIII) was allowed to react with I in an attempt to show similarities between this reaction and that described by Markl,[11] who demonstrated that aliphatic diazo ketones will form ketazines on reaction with phosphine methylenes. On allowing VIII to react with I, a 22% yield of the



expected[11] fluorenonebenzal hydrazone (IX) was obtained. A 26% yield of the expected[11] triphenylphosphine fluorenone azine (X) from the reaction of triphenylphosphorus and I was also found. Thus I in the presence of pyridine bases undergoes reactions which are characteristic for I and phosphorus ylids.

As shown by our suggested mechanistic scheme (1–5) fluorenone (IV) must be a major by-product of the deoxygenation of pyridine N-oxides by this procedure. Under suitable reaction conditions pyridine N-oxide can serve as a useful species for donating oxygen to a carbene[3]; a maximum yield of 69% of IV was isolated (see Table III).

TABLE III

9-DAF (I), mole	Pyridine N-oxide, mole	Benzene, ml.	Fluorenone (IV), %	Ketazine (VI), %
0.0156	0.250	0	33	57
0.0156	0.250	30	55	41
0.0156	0.250	60	69	23

(8) The authors recognize the possibility of forming intermediates III and V by direct displacement of the nitrogen from 9-DAF (I) by the oxygen of pyridine N-oxide or the nitrogen of pyridine, respectively; however, they favor initial carbene formation.[4,5]

(9) L. A. Pinck and G. E. Hilbert, *J. Am. Chem. Soc.*, **68**, 2011 (1946).

(10) G. Markl, *Tetrahedron Letters*, **No. 22**, 1027 (1692).

(11) G. Markl, *ibid.*, **No. 22**, 811 (1961).

Experimental[12]

Materials.—9-Diazofluorene (I) was prepared according to the method described by Nenitzescu and Solomonica.[6] The N-oxides[13] were distilled *in vacuo* under a nitrogen atmosphere prior to use. Fluorenone ketazine (VI) was prepared according to Arcus and Barrett.[14] The benzene used was anhydrous and thiophene free. The alumina used for chromatography was powdered, catalyst grade AL-0102-P, obtained from the Harshaw Chemical Co., Cleveland, Ohio.

Deoxygenation of Pyridine N-Oxides (Table I). A. In Benzene.—A mixture of 14.3 g. (0.074 mole) of 9-diazofluorene (I), 4.7 g. (0.050 mole) of pyridine N-oxide, and 95 ml. of benzene was refluxed for 65 hr. The mixture was chilled with an ice–water bath and 7.0 g. of fluorenone ketazine (VI), m.p. 273–274°, lit.[14] m.p. 273–274°, was filtered off.

The filtrate was extracted with three 20-ml. portions of 10% hydrochloric acid and the combined aqueous layers were saturated with potassium hydroxide pellets. This strongly basic solution was extracted with three 20-ml. portions of ether which were fractionally distilled to give 1.10 g. (28%) of pyridine, b.p. 114–116°, $n^{25}D$ 1.5076. Infrared spectrum, melting point, and mixture melting point of the picrate were identical with those of an authentic sample.

B. In Diglyme.—The following method is the general deoxygenation method using 4:1 molar ratio of 9-diazofluorene (I) to the N-oxide.

Into a 100-ml., three-necked flask equipped with a thermometer and a Vigreux column (77 × 12 mm.) with distilling head and condenser were placed 0.0204–0.0210 mole of the N-oxide and 25 ml. of anhydrous diglyme. The mixture was heated until distillation of diglyme (162–163°) occurred. After approximately 5 ml. of diglyme had been distilled, a solution of 16 g. (0.0834 mole) of 9-diazofluorene (I) in 120 ml. of diglyme was added dropwise concurrent with distillation. When a few drops of the distillate no longer gave a precipitate when treated with a saturated solution of picric acid in ether, the reaction was considered to be complete.

The calculation of the yield and the analysis of 2,6-lutidine picrate from 0.0204 mole of lutidine N-oxide are the same for all the N-oxides. An aliquot (7.01 g.) of the diglyme distillate (88.25 g.) was treated with a saturated solution of picric acid in ether. The resulting dry picrate (melting point and mixture melting point identical with an authentic sample and the infrared spectrum was superimposable on the spectrum of an authentic sample) weighed 0.341 g. The total yield of 2,6-lutidine picrate, 4.28 g. (62.3%), was calculated accordingly and is listed in Table I (see p. 1744): (wt. of picrate)/(wt. of aliquot) × (total wt. of distillate) = (total wt. of picrate).

9-Diazofluorene (I) in Refluxing Benzene[7] (Table II).—A solution of 1.5 g. (0.0078 mole) of 9-diazofluorene (I) and 15 ml. of benzene was refluxed for 48 hr. with stirring. The solution was taken to dryness on a steam bath and petroleum ether (b.p. 30–60°) was added to the residue. Column chromatography of the petroleum ether solution on 200 g. of alumina gave 1.18 g. (91%) bifluorene, m.p. 190–192° (lit.[6] m.p. 187–188°), with petroleum ether eluent, and 0.055 g. (4%) of fluorenone ketazine (I), m.p. 276–277° (lit.[14] m.p. 273–274°), with benzene as an eluent.

9-Diazofluorene (I) and Pyridine in Benzene (Table II).—A solution of 0.41 g. (0.0021 mole) of 9-diazofluorene (I), 0.168 g. (0.0021 mole) of pyridine, and 4 ml. of benzene was refluxed for 72 hr., cooled, and diluted with petroleum ether. A residue of 0.225 g. of fluorenone ketazine (VI) was recovered by filtration and the petroleum ether–benzene filtrate was chromatographed on 70 g. of alumina to give 0.10 g. (28%) of bifluorene (melting point and mixture melting point identical with authentic sample) with petroleum ether eluent. An additional 0.035 g. of fluorenone ketazine (VI) was also obtained. Total yield of azine is 0.26 g. (68%), melting point and mixture melting point identical with that of an authentic sample.

9-Diazofluorene (I) and 1-(9-Fluorenyl)pyridinium Bromide.—To a solution of 0.81 g. (0.0025 mole) of 1-(9-fluorenyl)pyridin-

(12) All melting points and boiling points are uncorrected. The infrared spectra were obtained with a Perkin-Elmer spectrophotometer, Model 137.

(13) Reilly Tar and Chemical Corporation, Indianapolis 4, Ind.

(14) C. L. Arcus and G. C. Barrett, *J. Chem. Soc.*, 2098 (1960).

ium bromide (VII) prepared according to Pinck and Hilbert[9] and 0.50 g. (0.0026 mole) of 9-diazofluorene (I) dissolved in 30 ml. of ethanol was added dropwise with swirling approximately 2 ml. of aqueous 10% sodium hydroxide. A dark blue color characteristic of 1-(9-fluorenyl)pyridinium ylid (V)[9] appeared with the addition of each drop of base, and gradually changed to colorless upon swirling. Addition of the base required approximately 0.5 hr. and the mixture was allowed to stand for 15 min. before 0.81 g. (0.0023 mole, 87.4% yield) of fluorenone ketazine (VI, melting point and mixture melting point checked with an authentic sample) was recovered by filtration.

9-Diazofluorene (I) and Benzylidine Triphenylphosphorane (VIII).—To a stirred mixture of benzyltriphenylphosphonium bromide (10.8 g.) and 125 ml. of anhydrous benzene was added 10.6 g. of 14.98% by weight of butyllithium in hexane. A deep red color, characteristic of triphenylphosphorus ylids, developed immediately. This mixture was stirred for 15 min. and then 9-diazofluorene (I, 3.68 g.) was added. Stirring was continued overnight during which time the color changed from deep red to golden yellow. The reaction mixture was heated until it boiled and filtered hot, and 200 ml. of petroleum ether was added to the cooled benzene filtrate. A golden yellow precipitate of triphenylphosphine fluorenone azine (X) was filtered off, 2.3 g. (26.5%), m.p. 210–215°, lit.[15] m.p. 209–210°. Recrystallization from benzene gave an analytically pure sample which had m.p. 210–215°.

Anal. Calcd. for $C_{31}H_{23}N_2P$: C, 81.77; H, 5.06; N, 6.16; P, 6.88. Found: C, 81.68; H, 5.09; N, 6.26; P, 6.48.

The infrared spectrum was identical with that of an authentic sample.

The benzene–petroleum ether filtrate was reduced on a steam bath to a red oil which gave an orange-yellow solid upon being chilled in an ice–water bath. Recrystallization once from ethanol gave 1.2 g. (22.2%) of fluorenone benzalhydrazone (IX), m.p. 91–94°, lit.[16] m.p. 91–94°, mixture melting point with that of an authentic sample prepared according to Curtius and Kof[16] was undepressed.

9-Diazofluorene (I) and Pyridine N-Oxide (Table III).—A mixture of 3.00 g. (0.0156 mole) of 9-diazofluorene (I), 24 g. (0.25 mole) of pyridine N-oxide, and 30 ml. (or 60 ml.) of benzene was refluxed for 5 days. The reaction mixture was extracted with two 100-ml. portions of distilled water and two 15-ml. portions of 10% hydrochloric acid. The benzene layer (when applicable) was added to a suitable volumetric flask and diluted to the mark. An aliquot was then taken and evaporated to dryness on a steam bath under a stream of air. The ether-insoluble residue, fluorenone ketazine (VI, melting point and mixture melting point checked with an authentic sample), was recovered and the filtrate was evaporated to dryness in a sublimation apparatus. The residue was sublimed at a bath temperature of 85° (2–3 mm.) overnight to give fluorenone (IV, melting point and mixture melting point checked with an authentic sample). The total yield of fluorenone (IV) was calculated according to the following equation and is given in Table III: total volume of benzene solution in volumetric flask/ml. of aliquot × wt. of fluorenone sublimed = total wt. of fluorenone.

(15) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 627 (1919).

(16) T. Curtius and K. Kof, *J. prakt. Chem.*, **86**, 113 (1912).

Phosphonium Salts. II. 2-Bromophenetole and Triphenylphosphorus as Novel Phosphonioethylation Precursors

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Triphenylphosphorus (I) and β-bromophenetole (II) in alcohol solvents gave high yields (45–88%) of the alkoxyethyltriphenylphosphonium bromides (IV). In nonhydroxylic solvents (and *t*-butyl alcohol) 1,2-ethylenebis(triphenylphosphonium bromide) (III) was obtained. Vinyltriphenylphosphonium bromide (V) was isolated (92%) and allowed to react with ROH, –SH, and –NH substrates.

Anionic, or Michael-type additions, have been observed with vinylsulfonium salts[1] and vinyldiphenylphosphine oxide.[2] Grayson and Keough[3] have recently shown that base-catalyzed reactions of vinyltributylphosphonium salts with compounds containing active hydrogens also undergo Michael-type additions (phosphonioethylations[3]) to give 2-substituted ethyl phosphonium salts. Wittig and Duffner[4] proposed vinyltriphenylphosphonium bromide (V) as an intermediate in the reaction of 1,2-ethylenebis(triphenylphosphonium bromide) (III) with lithium piperidide to give triphenyl(β-N-piperidinoethyl)phosphonium bromide, although the vinyl salt V was not isolated.

Pursuing our interest in the Wittig reaction,[5] we were led to undertake a study of the preparation of phosphorus salts of 2-substituted 1-bromoalkanes. The results of our studies of the reaction of triphenylphosphorus (I) with β-bromophenetole (II) in a variety of solvents showed this system to be a unique phosphonioethylation[3] precursor.

The preparation of 2-phenoxyethyltriphenylphosphonium bromide (IVf) was attempted by allowing triphenylphosphorus (I) and 2-bromophenetole (II) to react in a variety of nonprotonic solvents (Table I). The only products that were identifiable in these (and simple fusion) reactions were the unexpected 1,2-ethylenebis(triphenylphosphonium bromide) (III) and phenol.

$$\underset{\text{I}}{(C_6H_5)P} + \underset{\text{II}}{C_6H_5OCH_2CH_2Br} \xrightarrow[\text{and fusion}]{\text{nonprotonic solvents}} \underset{\text{III}}{Br^-(C_6H_5)_3\overset{+}{P}CH_2CH_2\overset{+}{P}(C_6H_5)_3Br^-} + C_6H_5OH \quad (1)$$

On employing methanol, ethanol, 1-butanol, benzyl alcohol, 2-propanol, or phenol as the solvent in the reaction of triphenylphosphorus (I) with 2-bromophenetole (II), the corresponding 2-alkoxy- or 2-phenoxyethyltriphenylphosphonium bromide (IV) was obtained in high yield (Table II).

The 2-phenoxyethylphosphonium bromide (IVf) decomposed readily, on heating in ethyl acetate (or ben-

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(2) M. I. Kabachnik, T. Y. Medved, Y. M. Polikarpov, and K. S. Yudena, *Izv. Akad. Nauk. SSSR Otd. Khim. Nauk*, **9**, 1584 (1962).

(3) M. Grayson and P. T. Keough, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 640.

(4) G. Wittig, H. Eggers, and P. Duffner, *Ann.*, **619**, 10 (1958).

(5) Paper I: E. E. Schweizer and R. Schepers, *Tetrahedron Letters*, **15**, 979 (1963).

TABLE I

REACTIONS YIELDING DISALT

$Br^-(C_6H_5)_3\overset{+}{P}CH_2CH_2\overset{+}{P}(C_6H_5)_3Br^-$ (III)

Precursors (mole)	Solvent	Reflux time, days	Yield of disalt III, %
1, $BrCH_2CH_2Br$ (0.09) + $(C_6H_5)_3P$ (0.018)	Ethanol (50 ml.)	1	94[a]
2, $CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3Br^-$ (0.003) + $(C_6H_5)_3P\cdot HBr$ (0.003)	Fuse at 120°	1.67	100
3, Same as 2	Ethyl acetate (25 ml.)	5	88
4, Same as 2	Chloroform (25 ml.)	5	100[b]
5, $C_6H_5OCH_2CH_2Br$ (0.1) + $(C_6H_5)_3P$ (0.1)	Fuse at 120°	2	28
6, $C_6H_5OCH_2CH_2Br$ (0.15) + $(C_6H_5)_3P$ (0.15)	Ethyl acetate[d] (200 ml.)	2	29
7, $C_6H_5OCH_2CH_2Br$ (0.05) + $(C_6H_5)_3P$ (0.05)	*t*-Butyl alcohol[d] (50 ml.)	2.5	24[c]
8, Same as 7	Benzene (150 g.)[e] + $C_6H_5OCH{=}CH_2$ (1.5 g.)	3	9
9, $C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^-$ (0.003) + $(C_6H_5)_3P$ (0.003)	Benzene[d] (25 ml.)	2	Low
10, $C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^-$ (0.003) + $(C_6H_5)_3P\cdot HBr$ (0.003)	Ethyl acetate (25 ml.)	5	63
11, $C_6H_5OCH_2CH_2Br$ (0.05) + $(C_6H_5)_3P$ (0.05) + $(C_6H_5)_3P\cdot HBr$ (0.05)	Ethyl acetate (150 ml.)	5	62[f]

[a] M.p. 297–300°, lit.[4] m.p. 308–315°. *Anal.* Calcd. for $C_{38}H_{34}Br_2P_2$: C, 64.06; H, 4.82. Found: C, 64.22; H, 4.66. [b] M.p. 305–315°. [c] Intractable residue also obtained. [d] No phenyl vinyl ether observed in the gas chromatographic analysis of the filtrate. [e] Gas chromatographic analysis of solvent system before and after reaction showed that the ratio of phenyl vinyl ether (VII) to benzene remained unchanged. [f] 76% based on recovered starting material.

$$(C_6H_5)_3P + C_6H_5OCH_2CH_2Br + ROH \xrightarrow{\text{solvent}}$$
(I) (II)

$$ROCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^- \quad (2)$$
IVa, R = CH_3
b, R = C_2H_5
c, R = $CH_2(CH_2)_2CH_3$
d, R = $C_6H_5CH_2$
e, R = $CH(CH_3)_2$
f, R = C_6H_5

zene) solvent, to give better than 90% yield of vinyltriphenylphosphonium bromide (V). The salt (V) has recently been prepared and isolated (no yield given) by a unique route.[6]

$$C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^- \xrightarrow{\text{nonhydroxylic solvent}}$$
(IVf)

$$CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3Br^- + C_6H_5OH \quad (3)$$
(V)

The phenoxyethylphosphonium salt (IVf) and the vinylphosphonium salt (V) both reacted readily on heating in alcohols to give the corresponding alkoxyethylphosphonium salts (IV). No basic catalysts were needed for any of the above mentioned reactions although reaction 4 was found to give higher yields when a catalytic amount of triphenylphosphorus (I) was present. The vinyl salt (V) gave essentially quantitative yields of the disalt (III, reaction 6) with triphenylphosphorus hydrobromide (VI).

$$C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^- + ROH \longrightarrow$$
(IVf)

$$ROCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^- + C_6H_5OH \quad (4)$$
(IVb,c)

$$CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3Br^- + ROH \longrightarrow IVa,e \quad (5)$$
(V)

$$CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3Br^- + (C_6H_5)_3P\cdot HBr \longrightarrow III \quad (6)$$
(V) (VI)

One of the mechanisms considered possible for the formation of the disalt III, from β-bromophenetole (II) and triphenylphosphorus (I) involves a decomposition of β-bromophenetole (II) under the influence of triphenylphosphorus to phenyl vinyl ether (VII) and triphenylphosphorus hydrobromide (VI) followed by the reaction (6) to give the disalt III. However the following series of experiments do not support this reasoning.

(a) Phenyl vinyl ether (VII) was recovered unchanged when it was allowed to be present during the formation of the disalt from reaction 1 in benzene.

(b) No phenyl vinyl ether (VII) was observed as a product in the gas chromatograms of the solvents used in reactions 1, 2, or 4.

(c) Phenyl vinyl ether (VII) reacts rapidly with triphenylphosphorus hydrobromide (VI) giving 1-phenoxyethyltriphenylphosphonium bromide (VIII). The latter salt (VIII) does not yield the bisphosphonium salt (III) on heating with the hydrobromide VI in a solvent, although the comparable reaction with 2-phenoxyethyltriphenylphosphonium bromide (IVf) readily gives the disalt III, in good yield (see Table I). The 1-phenoxyethyl salt (VIII) also does not give 2-ethoxyethyltriphenylphosphonium bromide (IVb) when allowed to react in ethanol.

$$C_6H_5OCH{=}CH_2 + (C_6H_5)_3P\cdot HBr \longrightarrow$$
(VII) (VI)

$$C_6H_5OCH(CH_3)\overset{+}{P}(C_6H_5)_3Br^- \quad (7)$$
(VIII)

$$VIII + C_2H_5OH \xrightarrow{//} IVb$$

$$VIII + VI \xrightarrow{//} III$$

The following mechanism is, therefore, proposed for the phosphonioethylations observed.

$$C_6H_5OCH_2CH_2Br + (C_6H_5)_3P \longrightarrow$$
(II) (I)

$$C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^- \quad (8)$$
(IVf)

$$C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^- + B: \longrightarrow$$

$$C_6H_5OCH_2\bar{C}H{-}\overset{+}{P}(C_6H_5)_3Br^- + B{:}\overset{+}{H} \quad (9)$$

(6) D. Seyferth, J. S. Fogel, and J. K. Heeren, *J. Am. Chem. Soc.*, **86**, 307 (1964).

TABLE II

$$C_6H_5OCH_2CH_2Br + (C_6H_5)_3P + ROH \longrightarrow ROCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$$

ROH	Solvent[a]	Product, m.p., °C.	Products (yield, %)	Analysis, %—Calcd.—C	Calcd.—H	Found—C	Found—H
	Phenol	138–141	$C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (100)	67.39	5.22	66.43	4.93
	Thiocresol	161–163	$C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (95)	67.39	5.22	67.02	5.18
	Thiophenol		$C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (74)				
	Glacial acetic acid		$C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (100)				
CH_3OH	Methanol	207–209[d]	$CH_3OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (47)[b]	62.6	5.5	62.81	5.69
CH_3CH_2OH	Ethanol	179–181	$CH_3CH_2OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (72)	63.6	5.83	63.76	6.16
$CH_3(CH_2)_3OH$	1-Butanol		$CH_3CH_2CH_2CH_2OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (45)[c]				
			$\bar{B}r(C_6H_5)_3\overset{+}{P}CH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (6)				
$C_6H_5CH_2OH$	Benzyl alcohol	176–177.5	$C_6H_5CH_2OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (52)	67.93	5.49	67.98	5.67
$CH_3CHOHCH_3$	2-Propanol		$(CH_3)_2CHOCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (88)[c]				
			$\bar{B}r(C_6H_5)_3\overset{+}{P}CH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (5)				
$CH_3CHOHCH_3$	2-Propanol + 0.5 mole of acetic acid per mole of β-Bromophenetole		$(CH_3)_2CHOCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (50)[c]				
			$\bar{B}r(C_6H_5)_3\overset{+}{P}CH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (42)				

[a] Reaction time ranged from 2 to 5 days at reflux temperature or 100° whichever was lower. [b] Yield is 72% if based on recovered triphenylphosphorous. [c] Yield based on starting materials not consumed by the disalt III found. [d] O. Isler, M. Montavon, R. Ruegg, and P. Zeller [German Patent 1017163; *Chem. Abstr.*, **53**, 18,982c (1959); **53**, 13,412g (1958)] report m.p. 195–197°.

$$C_6H_5OCH_2\bar{C}H{-}\overset{+}{P}(C_6H_5)_3Br^- \longrightarrow C_6H_5O^- + CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3\bar{B}r \quad (10)$$
V

$$C_6H_5O^- + B{:}\overset{+}{H} \longrightarrow C_6H_5OH + B{:} \quad (11)$$

$$B{:} + C_2H_5OH \longrightarrow C_2H_5O^- + B{:}\overset{+}{H} \quad (12)$$

$$C_2H_5O^- + CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3\bar{B}r \longrightarrow C_2H_5OCH_2{-}\bar{C}H{-}\overset{+}{P}(C_6H_5)_3\bar{B}r \quad (13)$$

$$C_2H_5OCH_2{-}\bar{C}H\overset{+}{P}(C_6H_5)_3\bar{B}r + B{:}H \longrightarrow C_2H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r + B{:} \quad (14)$$
IVb

$$CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3\bar{B}r + (C_6H_5)_3P \longrightarrow [(C_6H_5)_3\overset{+}{P}{-}CH_2{-}\bar{C}H{-}\overset{+}{P}(C_6H_5)_3]\bar{B}r \quad (15)$$
V

$$[(C_6H_5)_3\overset{+}{P}{-}CH_2{-}\bar{C}H_2{-}\overset{+}{P}(C_6H_5)_3]\bar{B}r + C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r \longrightarrow$$
IVf

$$\bar{B}r(C_6H_5)_3\overset{+}{P}{-}CH_2{-}CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r + C_6H_5O[CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3] \quad (16)$$
III

The mechanism proposed above, 8 through 16, suggests that high yields of the diphosphonium salt may be obtained by allowing equimolar quantities of triphenylphosphorus (I), β-bromophenetole (II), and triphenylphosphorus hydrobromide (VI) to react together. These expectations were fulfilled by carrying out this reaction in ethyl acetate; the disalt III, was obtained in 81% yield.

The disalt III, was prepared in 87% yield from 1,2-dibromoethane and triphenylphosphorus in ethanol, thus showing that the alkoxyethylphosphonium salts (IV) did not arise by the decomposition of disalt. The latter salts (IV) may be prepared readily from the disalt III, under the influence of a strong base (Table III).

$$\bar{B}r(C_6H_5)_3\overset{+}{P}{-}CH_2CH_2{-}\overset{+}{P}(C_6H_5)_3\bar{B}r + ROH \xrightarrow{R\bar{O}M^+} ROCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r + (C_6H_5)_3P \quad (17)$$
IVa,c

The ready elimination of phenol from 2-phenoxyethyltriphenylphosphonium bromide (IVf), even under the conditions of recrystallization, made it impossible to prepare this salt in analytical purity from phenol solvent. However, when the phenol solvent was replaced by protonic solvents of greater acidity, such as thiophenols or acetic acid, high yields (74–100%) of the phenoxyethyl salt (IVf) could be obtained. Evidently traces of these solvents inhibited the decomposition of salt IVf prepared in this manner because analytically pure samples heated in ethyl acetate or ethanol did not give the expected vinyltriphenylphosphonium bromide (V) or the 2-ethoxyethyltriphenylphosphonium bromide (IVb). However, after repeated precipitations (five–seven times) from chloroform–ether, a lowering in melting point of salt IVf was noted and on refluxing in ethanol at this point a high yield

TABLE III

$$\bar{B}r(C_6H_5)_3\overset{+}{P}CH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r + ROH + ROM \longrightarrow ROCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$$

Salt III, mole	Alcohol (ml.)	Base (mole)	Reaction time, hr.	Product (yield, %)
0.02	Methanol (170)	Sodium methoxide (0.022)	12	$CH_3OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (42)
0.025	1-Butanol (100)	Potassium *t*-butylate (0.0025)	40	$CH_3(CH_2)_3OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (50)[a]

[a] 63% based on recovered disalt.

(67%) of the desired ethoxyethylphosphonium salt (V) was obtained. The conversion of the analytically pure phenoxy salt IVf to the desired ethoxy salt IVb was also accomplished by adding a catalytic amount of triphenylphosphorus (I).

All the alcohols used as solvents gave respectable yields of the alkoxyphosphonium salts (IV) as shown in Table II. However, when *t*-butyl alcohol was used as solvent (Table I) only the diphosphonium salt (III) could be isolated. Furthermore, when *t*-butyl alcohol was allowed to reflux with the vinyltriphenylphosphonium bromide (V), it did not react and, in fact, *t*-butyl alcohol was found to be an ideal solvent for carrying out recrystallizations of salt V. This lack of reactivity may possibly be attributed to steric inhibition or low acidity.

Thiophenol (IX) and diethylamine (XI) both gave the respective adducts X and XII with the vinyltriphenylphosphonium bromide (V) in quantitative yields (Table II), indicating that the ability of the salt V is certainly equivalent to or better than that of the vinyl-

$$\underset{\text{IX}}{C_6H_5SH} + \underset{\text{V}}{CH_2{=}C{-}\overset{+}{P}(C_6H_5)_3\bar{B}r} \longrightarrow \underset{\text{X}}{C_6H_5SCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r}$$

$$\underset{\text{XI}}{(C_2H_5)_2NH} + \underset{\text{V}}{CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3\bar{B}r} \longrightarrow \underset{\text{XII}}{(C_2H_5)_2NCH_2CH_2P(C_6H_5)_3\bar{B}r}$$

tributylphosphonium bromide in phosphonioethylation reactions as described by Grayson and Keough,[3] since present reactions did not require the use of added basic catalysts.[7]

Recently Rauhut, *et al.*,[8] have shown that the reaction of triphenylphosphorus (I) with 2-chloroethylacetate, in the absence of a solvent, yields 2-ethylenebis(triphenylphosphonium chloride), suggesting a reaction path similar to that described herein. It is interesting to note that when equimolar quantities of triphenylphosphorus (I) and β-bromophenetole (II) were allowed to react in isopropyl alcohol contaminated with a 0.5-*M* quantity of acetic acid (Table II), a 42% yield of the disalt was obtained with only a 50% yield of the 2-isopropoxyethyltriphenylphosphonium bromide (IVe) based on the remaining starting material.

The effect of steric hindrance, acidity, and nucleophilicity on the ability of protonic substrates to undergo Michael-like additions are under investigation.

(7) It is recognized that, as the referee pointed out, diethylamine, triphenylphosphorus, and the thiophenoxide ion (the latter from dissociation of thiophenol) are all good bases.

(8) M. M. Rauhut, G. B. Borowitz, and H. C. Gilham, *J. Org. Chem.*, **28**, 2565 (1963).

Experimental

The experiments given are not necessarily the ones that afford the highest yields of an individual salt, but the ones which illustrate a procedure for separating the products obtained. The names of the compounds produced are followed by a "table" reference when they characterize a general reaction procedure.

All melting points were uncorrected and obtained on a Fischer-Johns melting point apparatus. The gas chromatographic analyses (v.p.c.) were obtained on a 6-ft. Dow 710 silicon-on-firebrick column. The infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer; the n.m.r. spectra were obtained on an A-60 Varian analytical n.m.r. spectrometer.

Reagents.—Triphenylphosphorus, obtained from Metal and Thermit Chemicals, Inc., Rahway, N. J., was purified by recrystallization from anhydrous ether. The β-bromophenetole was obtained from Fisher Scientific Co., Philadelphia, Pa., and was used as purchased. Anhydrous, reagent grade solvents were employed in all cases.

2-Phenoxyethyltriphenylphosphonium Bromide (IVf, Table II).—Forty grams of β-bromophenetole and 52.4 g. of triphenylphosphorus were heated at 90° for 48 hr. in 400 g. of phenol. The solution was stirred into 2500 ml. of anhydrous ether and agitated until white crystals formed. The mixture was filtered, washed throughly with hot anhydrous ether, and after drying (60° under reduced pressure) gave an essentially quantitative yield (92 g.) of the phenoxy salt (IVf), m.p. 138–141°. Attempts at crystallization from cold chloroform–tetrahydrofuran lowered the melting point of the salt with the appearance of phenol in the crystallizing solvent (by v.p.c.) indicating decomposition of the salt (IVf). For analysis see Table II. The infrared and n.m.r. spectra were identical with those of the analytically pure sample prepared in thiocresol solvent (Table II).

The n.m.r. spectra of the analytical sample of salt IVf made from thiocresol in deuteriochloroform follow: centered at τ 2.3, aromatic multiplet, weight 15.3, assigned to the triphenylphosphorus phenyls; at τ 2.9 and 3.5, aromatic multiplet and a split doublet assigned to the phenoxy phenyl, weight 2.9 and 2, respectively; at τ 5.5, aliphatic multiplet, weight 3.9, assigned to the methylene hydrogens.

Vinyltriphenylphosphonium Bromide (V).—Three grams of the recrystallized 2-phenoxytriphenylphosphonium bromide (IVf) obtained in the previous experiment was allowed to stir under reflux for 48 hr. in 25 ml. of ethyl acetate. The mixture was cooled, poured into 50 ml. of anhydrous ether, and filtered. The residue was treated once more exactly as described above. The white crystalline residue was washed with tetrahydrofuran and then ether. Drying under reduced pressure gave 2.2 g. (92%) of vinyltriphenylphosphonium bromide (V), m.p. 189–190°.

A sample obtained from a similar reaction was shown to be analytically pure, m.p. 189–190°, lit.[3] m.p. 185–187°.

Anal. Calcd. for $C_{20}H_{18}BrP$: C, 65.05; H, 4.91. Found: C, 64.99; H, 4.93.

The n.m.r. spectra of the analytically pure sample obtained in deuteriochloroform follow: centered at τ 2.2, an aromatic multiplet which overshadowed the —CH of the vinyl group, weight 16; centered at τ 3.62, a sextet with a span of 10.2 p.p.m., weight 1.96, ascribed to the vinyl $=CH_2$ group.

1,2-Ethylenebis(triphenylphosphonium bromide) (III, Table I). A. From β-Bromophenetol (II) and Triphenylphosphorus (I).—Thirty grams of β-bromophenetole (II) and 39 g. of triphenylphosphorus (I) were refluxed with stirring in 200 ml. of ethyl acetate for 48 hr. Phenol was observed as the only by-product by v.p.c. (gas phase chromatography) from the decanted solvent. The tarry residue was washed and stirred with acetone until white crystals remained. The disalt III, 15.5 g. (29%) recovered, m.p. 275–285°, was recrystallized once from dioxane

with a trace of water. The pure product had m.p. 295–300°. The mixture melting point and infrared spectra were identical with that of the authentic sample prepared from 1,2-dibromoethane (Table I).

B. From Vinyltriphenylphosphonium Bromide (V) and Triphenylphosphorus Hydrobromide.—Triphenylphosphorus hydrobromide (1.3 g.) and 1.2 g. of vinyltriphenylphosphonium bromide (V) were stirred and refluxed for 5 days in 25 ml. of ethyl acetate. The product was filtered, washed with ether, and dried to give 2.2 g. (88%) of the disalt III, m.p. 300–305°. Mixture melting point and infrared spectra were identical with that of the authentic sample.

2-Isopropoxyethyltriphenylphosphonium Bromide (IVc, Table II).—Triphenylphosphorus (I, 13.1 g.) and 10.1 g. of β-bromophenetole (II) were placed in a solvent system prepared from 50 ml. of 2-propanol and 1.5 g. of glacial acetic acid and allowed to reflux for 4 days. The solution was poured into 400 ml. of anhydrous ether. The solvent was decanted from the viscous yellow precipitate and the precipitate was triturated with 400 ml. more of ether yielding, after filtration and drying, 15.3 g. of light yellow crystals, m.p. 200–215°. The solvent showed phenol as the only volatile product (v.p.c.). The crystals were refluxed with agitation in 100 ml. of acetone. The mixture was filtered giving 7.4 g. (42%) of 1,2-ethylenebis(triphenylphosphonium bromide) (III), m.p. 305–308°, mixture melting point and infrared spectra identical with that of an authentic sample.

The acetone filtrate was treated with ether and gave 6.1 g. (50% based on starting material left after disalt formation) of 2-isopropoxyethyltriphenylphosphonium bromide (IVe), m.p. 198–201°; infrared spectra and mixture melting point were identical with the analytical sample (Table IV).

TABLE IV

$$CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3\bar{B}r \;(V) + RXH \longrightarrow RXCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r \;(IVa,e,\ X,\ XII)$$

RXH (ml.)	Reaction time, days	Temp., °C.	Product (yield, %)
Methanol (20)[a]	0.833	Reflux	$CH_3OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (100)
Isopropyl alcohol (25)[a]	2	Reflux	$(CH_3)_2CHOCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (88)[b]
Thiophenol (25)[a]	1	90	$C_6H_5SCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (100)[c]
Diethylamine (20)[a]	3	Reflux	$(CH_3CH_2)_2NCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (100)[d]
t-Butyl alcohol (25)[a]	1	Reflux	No reaction[e]

[a] Reactions run with (0.0027 mole) salt $CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3\bar{B}r$. [b] *Anal.* Calcd. for $C_{23}H_{26}BrOP$: C, 64.34; H, 6.10. Found: C, 64.15; H, 5.98. M.p. 198–202°. [c] *Anal.* Calcd. for $C_{26}H_{24}BrPS$: C, 65.13; H, 5.05; Br, 16.68. Found: C, 65.32; H, 4.99; Br, 16.49. [d] *Anal.* Calcd. for $C_{24}H_{29}BrNP$: C, 65.16; H, 6.61; Br, 18.07. Found: C, 64.95; H, 6.62; Br, 18.27. M.p. 178–182°. [e] No reaction, salt $CH_2{=}CH{-}\overset{+}{P}(C_6H_5)_3\bar{B}r$ recovered quantitatively unchanged.

2-Ethoxyethyltriphenylphosphonium Bromide (IVb, Table V).—2-Phenoxyethyltriphenylphosphonium bromide (IVf) (4.63 g., prepared in phenol) and 0.26 g. of triphenylphosphorus (I) were placed in 25 ml. of absolute ethanol and allowed to reflux 40 hr. The solution was poured into 400 ml. of dry ether with stirring, and white crystals precipitated. Filtration and thorough washing of the residue gave 3.0 g. (72%) of pure 2-ethoxyethyltriphenylphosphonium bromide (IVb), m.p. 179–181°. Phenol was found as the only volatile product of the reaction (v.p.c.). Mixture melting point and infrared spectra were identical with an authentic sample prepared from 2-bromoethyl ethyl ether and triphenylphosphorus in acetonitrile (87% yield), m.p. 179–181°, and with the analytical sample (Table II).

TABLE V

$$C_6H_5OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r \;(IVf) + ROH \longrightarrow ROCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r + C_6H_5OH$$

Salt IVf, mole	Solvent (ml.)	Product (yield, %)[a]
0.0065[b]	Ethanol (25)	$CH_3CH_2OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (52)
0.01[b,c]	Ethanol (25)	$CH_3CH_2OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (72)
0.01[d]	Ethanol (25)	$CH_3CH_2OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (67)
0.01[c,e]	Ethanol (25)	$CH_3CH_2OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (45)
0.0032[b]	1-Butanol (25)	$CH_3(CH_2)_3OCH_2CH_2\overset{+}{P}(C_6H_5)_3\bar{B}r$ (97)[f]

[a] Obtained after refluxing solution 40 hr. [b] Phenoxy salt (IVf) prepared in phenol solvent. [c] With triphenylphosphorus (I), 0.001 mole added as catalyst. [d] Phenoxy salt (IVf) prepared in acetic acid followed by repeated precipitations from chloroform–ether (six times). [e] Phenoxy salt (IVf) prepared in thiocresol. [f] *Anal.* Calcd. for $C_{24}H_{28}BrOP$: C, 65.01; H, 6.37. Found: C, 65.24; H, 6.37. M.p. 170–174°.

2-Thiophenoxyethyltriphenylphosphonium Bromide (X, Table IV).—One gram of vinyltriphenylphosphonium bromide (V) was placed in 25 ml. of thiophenol and allowed to stir for 24 hr. at 90°. The reaction mixture was poured into 300 ml. of anhydrous ether with vigorous stirring to give 1.4 g. of white crystals, m.p. 137–142°. Recrystallization from chloroform–tetrahydrofuran–ether solvent system gave 1.3 g. (100%) of analytically pure 2-thiophenoxyethyltriphenylphosphonim bromide (X), m.p. 148–149° (Table IV).

2-*n*-Butoxyethyltriphenylphosphonium Bromide (IVc, Table III).—Commercial potassium *t*-butoxide (2.8 g.), 17.8 g. of 1,2-ethylenebis(triphenylphosphonium bromide) (III), and 100 ml. of 1-butanol were added to a flask in a drybox. The mixture was heated and stirred under a nitrogen blanket at 90° for 40 hr. The mixture was cooled and filtered; 3 g. of potassium bromide was recovered. The mixture was quenched with ether and the crystalline product was extracted with hot acetone; the residue was washed thoroughly with ether and dried, affording 4.3 g. of the disalt III starting material; melting point, mixture melting point and infrared spectra were identical with that of an authentic sample.

The acetone extracts were combined and treated with ether to give 5.5 g. (50%) of 2-butoxyethyltriphenylphosphonium bromide, m.p. 160–165°. Two recrystallizations from 1-butanol–ether gave the analytically pure sample, m.p. 170–172°; mixture melting point and infrared and n.m.r. spectra showed this sample to be identical with the sample obtained by allowing β-bromophenetole (II) and triphenylphosphorous (I) to react in 1-butanol (Table II).

1-Phenoxyethyltriphenylphosphonium Bromide (VIII).—Six grams of phenyl vinyl ether (VII) was added with stirring to a mixture of triphenylphosphorus hydrobromide (VI) in 100 ml. of dry acetone. The hydrobromide (VI) immediately went into solution with the evolution of heat. The reaction was allowed to stir at room temperature for 4 hr., and the solvent was evaporated on a rotary evaporator. The brown gummy residue was triturated with petroleum ether (b.p. 30–60°). Filtration gave 22.0 g. (94.5% yield) of 1-phenoxyethyltriphenylphosphonium bromide (VIII), m.p. 102–110°. On recrystallization three times from chloroform–ether, analytically pure, very hygroscopic white crystals were obtained, m.p. 132–135°.

Anal. Calcd. for $C_{26}H_{24}BrOP$: C, 67.39; H, 5.22. Found: C, 67.49; H, 5.31.

The n.m.r. spectrum in $CDCl_3$ follow: centered at τ 2.23, 2.67, and 2.96, two aromatic multiplets and a doublet somewhat overlapped, assigned to the phenoxy and triphenylphosphorus phenyls and the tertiary proton, weight 21 ± 2; centered at τ 8.24, a split doublet, weight 3, assigned to the C-methyl protons.

Reaction of 1-Phenoxyethyltriphenylphosphonium Bromide (VIII) with Triphenylphosphorus Hydrobromide.—One gram of triphenylphosphorus hydrobromide and 1.35 g. of the salt VIII were allowed to reflux in 20 ml. of benzene for 24 hr. No phenol was observed, with v.p.c., of the solvent. On quenching with ether and decanting, the sirupy product was washed with cold water. Concentration of the water showed no solubility of the product in water. On heating the sirupy product to reflux in water it became soluble.

Formation of the disalt III would produce phenol. The disalt III is highly soluble in cold water. Thus this material (salt VIII) could not be an intermediate in the reaction.

Reaction of 1-Phenoxyethyltriphenylphosphonium Bromide (VIII) with Ethanol.—One gram of the disalt VIII was refluxed 24 hr. in 20 ml. of ethanol. Ether was added and a trace of gummy sirup precipitated. This material was intractable and could not be crystallized to yield 2-ethoxyethyltriphenylphosphonium bromide (IVb). The solvent showed phenol to phenyl vinyl ether in a 2:1 ratio.

None of the 2-ethoxy salt (IVb) was found and phenyl vinyl ether (VII) was observed, with v.p.c. of the solvent system. The ether VII was not observed in the solvent system from the reactions of the 2-phenoxy salts (IVf); thus, it is felt that the 1-phenoxy salt (VIII) cannot be an intermediate in our reaction.

Nucleophilic Substitution at the Pyridazine Ring Carbons. III. Alkoxide Exchange[1]

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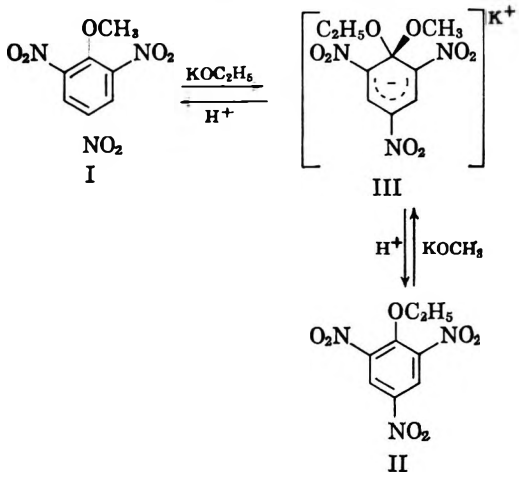
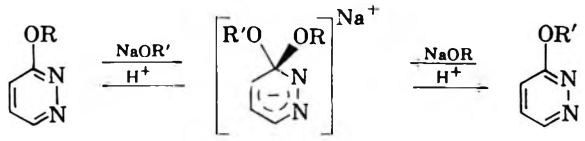
The phenomenon of alkoxide exchange in the mono-, di-, and bisalkoxypyridazines has been experimentally established. It has been utilized in a novel synthesis of monoalkoxypyridazines. A general method for the preparation of nonbisdialkoxypyridazines is described.

Meisenheimer[3] has established that ethers of strongly acidic phenols can be attacked at the benzene ring carbon by alkoxides. Thus, when 2,4,6-trinitroanisole (I) is treated with potassium ethoxide, the corresponding phenetole (II) is produced. Compound II can be

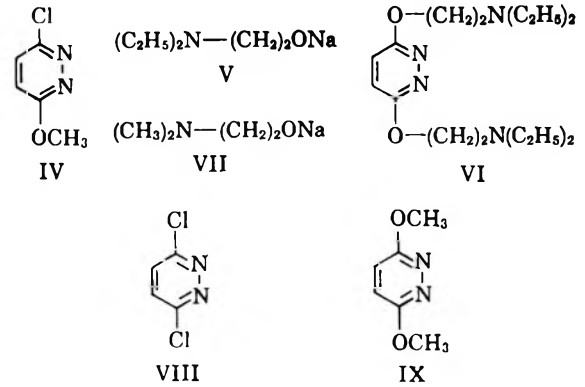


reconverted to I by treatment with excess potassium methoxide. In addition, an isolable adduct (III) is obtained which is identical for both reactions. This gives convincing evidence for the route of the reaction.[4] The success of this exchange is attributed to the positive nature of the benzene ring carbon attached to the ether oxygen and the subsequent attack by the nucleophilic reagent.

In the light of recent work in this laboratory concerning nucleophilic attacks at the pyridazine ring carbons,[5-7] it seemed of interest to attempt to extend alkoxide exchange to the field of pyridazines. A



possibility that such an exchange might occur in the pyridazine ring system is found in the experimental section of a paper by Steck and Brundage.[8] They reported that when 3-chloro-6-methoxypyridazine (IV), the purity of which had not been elucidated, was treated



with an equivalent amount of sodium 2-diethylaminoethoxide (V), a halogen-containing oil was formed. This oil was a mixture which was shown to contain some 3,6-bis(2-diethylaminoethoxy)pyridazine (VI) by formation of the known bismethiodide derivative.

The work of Steck was repeated using sodium 2-dimethylaminoethoxide (VII) in place of V. It became evident in the preparation of 3-chloro-6-methoxypyridazine (IV) using the traditional route that the product contained up to 20% impurities as shown by g.l.c. analysis. The contaminants occurred in equal amounts and were 3,6-dichloropyridazine (VIII) and 3,6-dimethoxypyridazine (IX). Hence, elemental analysis would agree with the desired product IV, and would not reveal the presence of a mixture containing IV along with equal parts of VIII and IX. If Steck

(1) Presented at the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan., 1964.

(2) Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C. 20012.

(3) J. Meisenheimer, *Ann.*, **323**, 205 (1902).

(4) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 367.

(5) P. Coad, R. Coad, S. Clough, J. Hyepock, R. Salisbury, and C. Wilkins, *J. Org. Chem.*, **28**, 218 (1963).

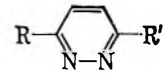
(6) P. Coad and R. Coad, *ibid.*, **28**, 1919 (1963).

(7) P. Coad, R. Coad, and C. Wilkins, *J. Phys. Chem.*, in press.

(8) E. Steck and R. Brundage, *J. Am. Chem. Soc.*, **81**, 6511 (1959).

TABLE I

ALKOXY PYRIDAZINES



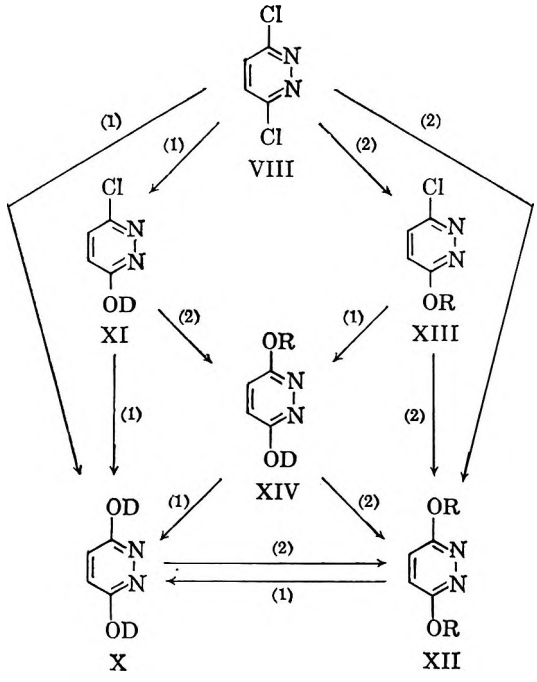
R	R′	M.p., °C.	B.p. (mm.), °C.[a]	λ_{max}^{EtOH}, μ (ε)[b]
-Cl	$-OCH_3$	90–91	174–175 (3)	
	$-OCH(CH_3)_2$	82–84 (83–84)[c]	129–131 (24)	
	-O-*n*-C_4H_9	47–48 (48)[c]	148–150 (17)	
	-O-cyclohexyl	108–110	153–154 (4)	283 (1910)
	$-O(CH_2)_2N(CH_3)_2$	46–47	130–131 (2)	280 (1970)
$-O(CH_2)_2N(CH_3)_2$	$-OCH_3$		120–123 (4)	286 (2020)
	$-OCH(CH_3)_2$		131–132 (4)	289 (2080)
	-O-*n*-C_4H_9		135–137 (3)	287 (2200)
	-O-cyclohexyl	39–41	178–185 (7)	289 (2100)
	$-O(CH_2)_2N(CH_3)_2$	30–31	162–165 (4) [130–132 (0.4)][d]	
$-OCH_3$	$-OCH_3$	106–107[c]	104–105 (8)	
$-OCH(CH_3)_2$	$-OCH(CH_3)_2$	26–28 (25–28)[c]	112–113 (4) [120–122 (11)][c]	
-O-*n*-C_4H_9	-O-*n*-C_4H_9	11–12	155–156 (8) [163–166 (11)][c]	
-O-cyclohexyl	-O-cyclohexyl	133–134	143.5–144.5 (3)	291 (2070)
-H	$-OCH_3$		88–89 (13) [86–87 (13)][e]	
-H	-O-*n*-C_4H_9		112–113 (10)	

[a] Boiling points of products isolated as solids were determined by microboiling point technique. [b] See ref. 10. [c] See ref. 8. [d] See ref. 11. [e] See ref. 12.

had used impure starting material, then alkoxide exchange might not have occurred at all, since compound VIII reacts with V to give VI in excellent yields. Evidence that true alkoxide exchange could have occurred under Steck's experimental conditions will be revealed.

The results of studies in this laboratory are summarized in Scheme I and in Table I. Anhydrous reagents were used throughout to avoid the formation of the nucleophile, hydroxide ion. When VIII was treated with excess VII, 3,6-bis(2-dimethylamino)pyridazine (X) was formed. An equivalent amount of VII at 60° produced 3-chloro-6-(2-dimethylaminoethoxy)-pyridazine (XI). Further treatment of XI with excess VII at 120° also produced X. As reported by Steck[8] and by Druey, *et al.*,[9] 3,6-bisalkoxypyridazine (XII) was formed by treatment of VIII with excess sodium alkoxide. If an equivalent amount of the alkoxide is used and the temperature adjusted to an optimum point, the 3-alkoxy-6-chloropyridazine (XIII) is formed, reasonably pure, in all cases except XIIIa as discussed above.

SCHEME I



(1) Treatment with NaOD
(2) Treatment with NaOR

a, R = $-CH_3$
b, R = $-CH(CH_3)_2$
c, R = $-n-C_4H_9$
d, R = -cyclohexyl
D = $-CH_2CH_2N(CH_3)_2$

In order to convert XI and XIII to XIV, conditions had to be found which were severe enough to cause nucleophilic displacement of the halogen by alkoxide and, yet, were sufficiently mild so as not to induce alkoxide exchange. For all cases studied, without exception, conditions were readily found which would satisfy these criteria. This is the first general synthesis for nonbisdialkoxypyridazines. Only one compound of this type had been previously reported.[9]

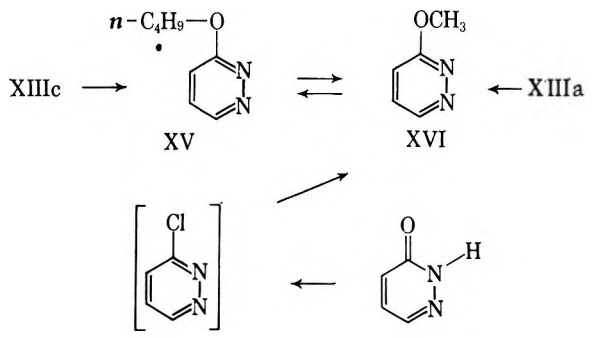
The nonbisdisubstituted pyridazine, XIV, was then converted to either of the two corresponding bis-substituted pyridazines, X or XII, by treatment with excess VII or sodium alkoxide. Conversion of X to XII and XII back to X completed the pattern.

In order to prove that alkoxide exchange at the pyridazine carbons was general, it was necessary to demonstrate experimentally that the above type of exchange was independent of the presence of a dialkylaminoethoxide and not limited to disubstituted pyridazines. This was accomplished by selecting two simple monoalkoxypyridazines with sufficiently different physical properties to be conveniently separated by fractional distillation. 3-Methoxypyridazine and 3-*n*-butoxypyridazine were prepared and

(9) J. Druey, Kd. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

interconverted with excess of the appropriate alkoxide. Work on the detailed mechanism of this reaction is continuing in this laboratory.

The 3-methoxypyridazine prepared by hydrogenolysis of 3-chloro-6-methoxypyridazine contained both pyridazine and dimethoxypyridazine as impurities. It was obtained in high purity, however, from 3-(2H)-pyridazinone. The synthesis was much improved by a work-up which minimized hydrolysis of the reactive 3-chloropyridazine. It was also prepared in good yield by a novel synthesis which was a result of this study, namely from alkoxide exchange of methoxide with 3-*n*-butoxypyridazine. 3-*n*-Butoxypyridazine was prepared from XIIIc by catalytic hydrogenolysis and also from 3-methoxypyridazine by treatment with sodium *n*-butoxide.



Thus, alkoxide exchange occurs in 3-alkoxy, 3,6-bisalkoxy, and 3,6-nonbisdialkoxypyridazines. This exchange gives further experimental evidence of the positive nature of the pyridazine ring carbons to which a group more electronegative than carbon has been attached. Whenever such pyridazines are used as substrates, nucleophilic attacks occur at those ring carbons.

Experimental[10]

3,6-Dichloropyridazine (VIII), m.p. 67–68°, was prepared from maleic hydrazide and phosphorus oxychloride by the method of Coad and Coad.[5,6] Vapor phase chromatography showed this material to be 99.9+% pure.

3-Chloro-6-(2-dimethylaminoethoxy)pyridazine (XI).—In a three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel was placed 70 ml. of anhydrous xylene. The xylene was heated to just below the boiling point, and 4.6 g. (0.20 g.-atom), of sodium metal was added. The mixture was heated and stirred until the sodium was finely dispersed. Over a period of 10 min., 19.6 g. (0.22 mole) of anhydrous 2-dimethylaminoethanol (XVII) was added through the dropping funnel. The mixture was heated and stirred until the last traces of sodium globules disappeared. The reflux condenser was replaced by an internal thermometer and the solution cooled to 60°. A solution of 29.8 g. (0.20 mole) of VIII and 50 ml. of anhydrous xylene was added over a period of 15 min. with sufficient cooling to keep the internal temperature from rising above 60°. The reaction mixture was stirred with the temperature maintained at 60° by heating for a period of 6 hr. The mixture was cooled to room temperature and filtered. The precipitate was triturated with two 60-ml. portions of hot xylene. The combined filtrates were transferred to a separatory funnel and washed with two 25-ml. portions of cold 30% sodium hydroxide solution and dried over anhydrous sodium sulfate. The xylene was removed *in vacuo* and the residue was distilled through a Podbielniak-type column with hot water circulating through the jacket of the side arm. A product was obtained, b.p. 130–131° at 2 mm. It weighed 24.1 g. (60%), m.p. 46–47°.

Anal. Calcd. for $C_8H_{12}ClN_3O$: C, 47.64; H, 6.00; Cl, 17.58; N, 20.84. Found: C, 47.77; H, 5.86; Cl, 17.33; N, 20.52.

3-Alkoxy-6-chloropyridazines (XIII).—A general method was developed for making compounds of this type from VIII. Although it would seem reasonable to add an alkoxide to the dihalo compound in order to obtain monosubstitution, this was not done as a general method owing to the limited solubility of the higher alkoxides. Under the special conditions developed, the reverse addition, dihalo compound to alkoxide, was successful, producing only minor amounts of the bisalkoxypyridazines. In the cases of the lower alkoxides, either order of addition could be used.

The procedure for making XI was modified. The sodium was dispersed in 70 ml. of anhydrous xylene. The alcohol in place of XVII was added over a period of 20 min. The mixture was heated 10 hr. at 60°. The washes with 30% sodium hydroxide solution were omitted. Unchanged VIII came over as the first fraction, followed by the product. The bisalkoxypyridazine remained in the pot as a residue.

Pure XIII was obtained in 70–85% yield, depending on the alkoxide.

3-Chloro-6-methoxypyridazine (XIIIa).—This compound has been made in several ways by several investigators.[11,12] The Steck method gives a product which by g.l.c. analysis contains 5–10% of VIII and 5–10% of XIIa. The general method above gives a product in 90% yield (m.p. 78–86°, b.p. 174–175° at 3 mm.) which is contaminated by <1% of VIII and <1% of XIIa. When recrystallized repeatedly from petroleum ether (b.p. 30–60°) a product is obtained, m.p. 90–91°. The product was shown to be free of VIII and XIIa by g.l.c. analysis.

3-Chloro-6-isopropoxypyridazine (XIIIb) had a yield of 70%, m.p. 82–84° (lit.[9] m.p. 83–84°), b.p. 129–131° at 24 mm.

3-*n*-Butoxy-6-chloropyridazine (XIIIc) had a yield of 85%, m.p. 47–48° (lit.[9] m.p. 48°), b.p. 148–150° at 17 mm.

3-Chloro-6-cyclohexyloxypyridazine (XIIId).—The temperature was raised to 95° and the heating was continued for 6 hr, to yield 77% of XIIId, m.p. 108–110°, b.p. 153–154° at 4 mm.

Anal. Calcd. for $C_{10}H_{13}ClN_2O$: C, 56.46; H, 6.13; Cl, 16.67; N, 13.17. Found: C, 56.73; H, 6.20; Cl 16.55; N, 13.42.

3-Alkoxy-6-(2-dimethylaminoethoxy)pyridazines (XIV) from XI.—By means of the apparatus and procedure described previously, 2.3 g. (0.10 g.-atom) of sodium metal was dispersed in 100 ml. of hot, anhydrous xylene. To this was added 0.11 mole of the appropriate anhydrous alcohol and the mixture was stirred until the sodium disappeared. This mixture was heated to boiling and to it was added dropwise a solution consisting of 20 g. (0.10 mole) of XI and 50 ml. of anhydrous xylene over a period of 5 min. for lower alkoxides and 15 min. for higher alkoxides. The mixture was heated under reflux and mechanically stirred for 3 hr. The mixture was filtered after cooling. The precipitate was triturated with two 25-ml. portions of hot xylene. The combined filtrates were washed with 10 ml. of cold 30% sodium hydroxide solution and dried over anhydrous sodium sulfate. The xylene and excess alcohol were removed *in vacuo*.

Individual procedures for the isolation of each alkoxide had to be used. The product (XIV) had to be separated from varying amounts of X and XII which were formed by alkoxide exchange. Yields ranged from 50 to 65%.

From XIII.—It was found that, whenever more than an equivalent amount of VII was used, the yield of XIV was decreased and more X was formed. In addition, the amount of XVII used was limited to 10% excess of the stoichiometric amount to form VII. Yields varied from 50 to 75%.

3-(2-Dimethylaminoethoxy)-6-methoxypyridazine (XIVa).—Better yields could be obtained by using XI as a starting material. The crude product obtained was distilled through a Podbielniak-type column. The product obtained was a yellow oil, b.p. 120–123° at 4 mm.

Anal. Calcd. for $C_9H_{15}N_3O_2$: C, 54.80; H, 7.65; N, 21.31. Found: C, 54.35; H, 7.41; N, 21.02.

3-(2-Dimethylaminoethoxy)-6-isopropoxypyridazine (XIVb).—Better yields could be obtained by using XI as the starting material. The crude product was dissolved in Shellacol, and subjected to hydrogenolysis of any residual chlorine atoms using a Parr hydrogenation apparatus with 5 ml. of concentrated ammonium hydroxide and 2.0 g. of activated 10% palladium on carbon. The Shellacol was removed *in vacuo*. The residue was washed with cold 10% sodium hydroxide solution and extracted

(10) The studies using gas chromatography were done by Cal-Colonial Chemical Co. on a Beckman G. C. 2A gas chromatograph equipped with a hydrogen flame detector using a 6-ft. column packed with polyester.

(11) T. Itai and H. Igeta, *J. Pharm. Soc. Japan*, **74**, 1195 (1954).

(12) E. Steck, U. S. Patent 2,858,311 (1959).

with four 100-ml. portions of ether. The combined extracts were dried over anhydrous sodium sulfate. The ether solution was filtered through fresh sodium sulfate and flashed distilled. The residue was distilled through an efficient column. The product obtained was a pale yellow oil, b.p. 131–132° at 4 mm.

Anal. Calcd. for $C_{11}H_{19}N_3O_2$: C, 58.63; H, 8.50; N, 18.65. Found: C, 58.57; H, 8.14; N, 18.88.

3-*n*-Butoxy-6-(2-dimethylaminoethoxy)pyridazine (XIVc).—The crude product obtained from treatment of XIIIc with VII was distilled through a column. The desired compound was obtained as a pale yellow oil, b.p. 135–137° at 3 mm.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.21; H, 8.84; N, 17.56. Found: C, 60.50; H, 8.49; N, 17.32.

3-Cyclohexyloxy-6-(2-dimethylaminoethoxy)pyridazine (XIVd).—The crude product obtained by treating XIIId with VII was distilled through a column with steam used in the jacket of the side arm. The product obtained was a pale yellow solid, m.p. 39–41°, b.p. 178–185° at 7 mm.

Anal. Calcd. for $C_{14}H_{23}N_3O_2$: C, 63.40; H, 8.74; N, 15.84. Found: C, 63.10; H, 9.0; N, 15.90.

3,6-Bis(2-dimethylaminoethoxy)pyridazine (X) from XI or XIV.—Compound VII was prepared as described in the preparation of XI. Twice the stoichiometric amount of XVII was employed. The reaction was boiled and stirred for 6 hr. The work-up was similar to that used in making XI. From XI the yield was 85%. From XIV the yields varied from 50 to 60%, depending on the alkoxy group involved.

From VIII.—Caution: 3,6-dichloropyridazine reacts explosively with warm 2-dimethylaminoethanol. Thus, care must be taken to form first XI as described and then proceed as above.

From XII.—A twofold excess of VII and XVII was employed. The reaction mixture was boiled for 8 hr. Yields varied from 40 to 65%. A yellow solid, m.p. 30–31°, b.p. 162–165° at 4 mm. (lit.[12] b.p. 130–132 at 0.4 mm.), was obtained.

3,6-Bisalkoxypyridazines (XII) from VIII.—Procedures were used similar to the procedure used in the preparation of XIII. However, twice the amount of sodium and alcohol was employed. The reaction mixture was heated for 2 hr. under reflux with stirring. The mixture was filtered after cooling. The precipitate was washed with two 60-ml. portions of xylene. The combined filtrates were concentrated *in vacuo*, dissolved in Shellacol, and hydrogenated in a Parr hydrogenation apparatus with ammonium hydroxide and 10% palladium-on-carbon catalyst. The mixture was filtered and the solvents removed *in vacuo*. The residue was distilled through an efficient column separating traces of pyridazine and monoalkoxypyridazine from the product. The yield was approximately 80% in each case.

From XIV.—An equivalent amount of the sodium alkoxide was used along with a tenfold excess of the corresponding alcohol. Yields averaged 70%.

From X.—A twofold excess of alkoxide and a tenfold excess of alcohol were used. Yields all were of the order of 50%.

From XIII.—A second mole of alkoxide was added and the temperature raised to the boiling point of xylene for 3 hr. Yields were around 80% in each case.

3-Bismethoxypyridazine (XIIa) was obtained as a white solid, m.p. 106–107° (lit.[9] m.p. 106–107°), b.p. 105° at 8 mm.

3,6-Bisisopropoxypyridazine (XIIb) was obtained as a white solid, m.p. 26–28° (lit.[9] m.p. 25–28°), b.p. 112–113° at 4 mm. (lit.[9] b.p. 120–122° at 11 mm.).

3,6-Bis-*n*-butoxypyridazine (XIIc) was obtained as a white solid, m.p. 11–12°, b.p. 155–156° at 11 mm.

3,6-Biscyclohexyloxypyridazine (XIId) was obtained as a white solid, m.p. 133–134°, b.p. 143.5–144.5° at 3 mm. The product could be readily recrystallized from Shellacol making distillation unnecessary.

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.50; H, 8.75; N, 10.14. Found: C, 69.88; H, 8.75; N, 10.31.

3-*n*-Butoxypyridazine (XV) from XIIIc.—The Parr hydrogenation apparatus was used in the hydrogenolysis of 74.2 g. (0.4 mole) of XIIIc using 200 ml. of Shellacol, 40 ml. of concentrated ammonium hydroxide, and 5.0 g. of activated 10% palladium on charcoal. The mixture was filtered after hydrogenation and the filtrate slowly distilled. Shellacol was added from time to time and a total of 800 ml. was distilled from the solution. The volume was reduced to 80 ml., cooled, and filtered. The residue was distilled through an efficient column to remove pyridazine from the product. The product was a colorless liquid, b.p. 112–113° at 10 mm. The product weighed 41.9 g. (69%).

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.14; H, 7.95; N, 18.41. Found: C, 62.91; H, 8.08; N, 18.46.

From XVI.—To 125 ml. of anhydrous butanol was added 8.3 g. (0.36-atom) of sodium metal. The mixture was heated until the sodium completely reacted. To the hot solution was added 6.5 g. (0.059 mole) of 3-methoxypyridazine. The flask was attached to a distilling column and heated until a few drops of methanol, b.p. 65°, was collected. The excess solvents were removed *in vacuo* and the residue was extracted with four 50-ml. portions of ether. The extracts were washed with 50 ml. of water, dried over anhydrous potassium carbonate, filtered, and distilled *in vacuo*. The product was distilled from the residue giving 5.6 g. (70%) of XV, b.p. 109–110° at 8 mm. The spectra were identical with the product formed from XIIIc.

3-Methoxypyridazine (XVI) from 3(2H)-Pyridazinone.—This route has been followed by several earlier workers. The procedure herein described was designed to minimize hydrolysis since this is frequently a major undesirable side reaction in the preparation of 3,6-dichloropyridazine from 3,6-pyridazinedione.

In a flask equipped with a magnetic stirrer and a reflux condenser with a drying tube attached was placed 28.8 g. (0.30 mole) of anhydrous 3(2H)-pyridazinone. To this was added 90 ml. of freshly distilled phosphorus oxychloride. The mixture was stirred overnight. Excess phosphorus oxychloride was removed *in vacuo* and the residue was poured onto 300 g. of cracked ice. Solid potassium carbonate was added until the mixture had pH 6. The mixture was extracted with five 100-ml. portions of ether. The extracts were combined, dried over anhydrous potassium carbonate, and concentrated to 150 ml.

Into a flask equipped with a dropping funnel and a reflux condenser was placed 6.9 g. (0.30 g.-atom) of sodium metal. Slowly 150 ml. of anhydrous methanol was added at such a rate as to keep the reaction proceeding rapidly. The solution was cooled to room temperature. The ethereal solution of chloropyridazine prepared above was added dropwise over a period of 1 hr. A precipitate formed immediately and the mixture was allowed to stand overnight. Upon filtration sodium chloride (85%) was collected. The filtrate was distilled yielding 22 g. (65%) of XVI, b.p. 72–73° at 6 mm. (lit.[13] b.p. 86–87° at 13 mm.).

From XIIIa.—The Parr hydrogenation apparatus was used as in the preparation of XV from XIIIc. The product could not be prepared free from pyridazine and 3,6-dimethoxypyridazine formed from VIII and XIVa present in XIIIa.

A New Route from XV.—In a three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser was placed 23.0 g. (1.0-g.-atom) of sodium metal. Slowly 150 ml. of anhydrous methanol was added so that the reaction continued vigorously. When the sodium was dissolved, 15.2 g. (0.10 mole) of XV was added over a period of 5 min. from the dropping funnel. The mixture was stirred and boiled for 3 hr. Excess methanol and butanol were removed *in vacuo*. The solid was cooled and 100 g. of cracked ice was added with mechanical stirring followed by 50 ml. of a cold 10% sodium hydroxide solution. The mixture was extracted with four 100-ml. portions of ether. The combined extracts were dried over potassium carbonate. After removal of the ether, the residue was distilled giving 5.5 g., 50% of XVI. b.p. 88–89° at 13 mm.

Acknowledgment.—The authors wish to express appreciation to the Research Corporation for support of portions of this work; to Mr. Hal Ramsey; to Dr. John E. Campion, head of the laboratories, and the Analytical Staff of Riker Laboratories for analysis and spectra; and to Dr. Charles Braithwaite, Cal-Colonial Chemical Company for the g.l.c. determinations.

(13) K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta*, **39**, 1755 (1956).

New Heteroaromatic Boron Compounds. XIX.[1,2] Water-Soluble Derivatives of 10,9-Borazarophenanthrene and 2,1-Borazaronaphthalene as Potential Agents for Neutron Capture Therapy

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Received January 17, 1964

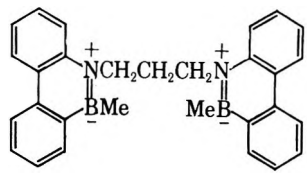
A number of aminoalkyl derivatives of 10-methyl-10,9-borazarophenanthrene and of 2-methyl-2,1-borazaronaphthalene have been prepared by N-alkylation of the parent compounds *via* the N-lithio derivatives for test as possible agents for the neutron capture therapy of cancer. Several other derivatives of these rings systems also are described.

The use of boron compounds for the neutron irradiation therapy of cancer has been hampered by the lack of stable, nontoxic compounds of boron.

Earlier papers[4] of this series have described the preparation of a new class of organoboron compounds containing boron atoms in six-membered heteroaromatic rings; compounds of this type show remarkable resistance to hydrolysis or oxidation. Here we describe the preparation of water-soluble derivatives of two of these ring systems, 10,9-borazarophenanthrene and 2,1-borazaronaphthalene, for test as potential agents for neutron capture therapy.

Dewar and Maitlis[5] found that 10-methyl-10,9-borazarophenanthrene (Ia) could be N-methylated to Ib by treating the N-lithio derivative (Ic) with dimethyl sulfate. We decided to use this reaction to introduce alkyl groups containing a solubilizing substituent.

Ia, R = H
b, R = Me
c, R = Li
d, R = —$CH_2CH_2CH_2Cl$
e, R = —$CH_2CH{=}CH_2$
f, R = —COOEt

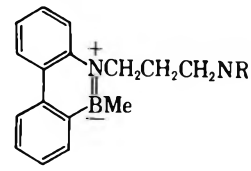


II

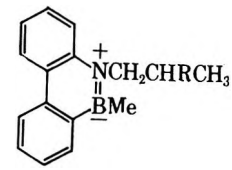
Preliminary experiments in this direction encountered difficulties since the N-alkylation of borazarophenanthrene *via* the N-lithio derivative proved not to be a general reaction. Only unchanged Ia was isolated from the reaction of Ic with ethyl chloroacetate, ethyl β-chloro- or β-bromopropionate, β-chloroethyl- or γ-chloropropyldimethylamine, or acrylonitrile, while 1,3-dibromopropane gave products containing appreciable quantities of the bisborazarophenanthrylpropane (II), even when an excess of dibromide was used.

We finally obtained compounds of the desired type by two different routes. The first of these involved the condensation of Ic with 1-bromo-3-chloropropane to give the 9-(3-chloro-1-propyl) derivatives (Id), followed by reaction with secondary amines to form a series of 9-(3-dialkylamino-1-propyl)-10-methyl-10,9-borazarophenanthrenes.

The intermediate chloropropyl derivative (Id) proved very difficult to purify and the reactions had to be carried out with crude material. However the amines were well characterized.



IIIa, R = Me
b, R = Et
c, R = *n*-Bu
d, NR_2 = piperidino
e, NR_2 = morpholino



IVa, R = Br
b, R = NMe_2
c, R = NEt_2
d, R = NPr_2
e, R = NBu_2
f, R = N-piperidino
g, R = N-morpholino
h, R = CN

The second route involved addition of hydrogen bromide to the double bond of 9-allyl-10-methyl-10,9-borazarophenanthrene (Ie), followed again by reaction with secondary amines. The allyl derivative (Ie) was obtained in good yield from Ic and allyl bromide, but it showed unexpected reluctance to react with hydrogen bromide. We finally brought about addition by passing dry hydrogen bromide through fused Ie at 150°. Since the same product was obtained with or without the addition of benzoyl peroxide as catalyst, and since the amines derived from the bromide were different from the 3-dialkylamino-1-propyl isomers (III), the bromide was formulated as 9-(2-bromo-1-propyl)-10-methyl-10,9-borazarophenanthrene (IVa).

It is true that analogous 2-haloalkyl amines commonly undergo interchange of the halogen and amine functions *via* intermediate ethyleneimine derivatives; however, such a rearrangement is most unlikely to have taken place here since the nitrogen atom in 10,9-borazarophenanthrene shows almost no basic or nucleophilic properties and since formation of a spiroethyleneimine intermediate would involve destruction of the aromaticity of the central ring.

The bromide (IVa) reacted with a series of secondary amines to give the aminopropylborazarophenanthrenes (IVb–g). These were different from the corresponding 3-dialkylamino-1-propyl derivatives (III), as was shown by a comparison of their infrared spectra and by mixture melting point depression. We also prepared the nitrile (IVh) from IVa and potassium

(1) Part XVIII: M. J. S. Dewar and W. M. Poesche, *J. Am. Chem. Soc.*, **85**, 2253 (1963).

(2) This work was supported by the Atomic Energy Commission under Contract No. AEC 889.

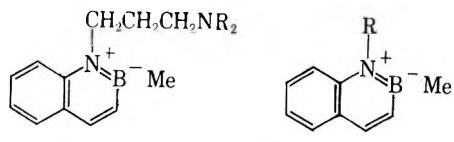
(3) To whom correspondence should be addressed at the Department of Chemistry, The University of Texas, Austin 12, Texas.

(4) For recent paper and references, see M. J. S. Dewar and R. Dietz, *J. Org. Chem.*, **26**, 3253 (1961).

(5) M. J. S. Dewar and P. M. Maitlis, *J. Am. Chem. Soc.*, **83**, 187 (1961).

cyanide in aqueous ethanol in the hope of obtaining the corresponding acid; however, the nitrile proved very resistant to hydrolysis. This resistance to hydrolysis incidentally supports the proposed structure of the bromide (IVa); if this had been the isomeric 1-bromo-2-propylborazarophenanthrene, the derived cyanide would have been a primary nitrile and should have hydrolyzed easily under the conditions we used.

We also prepared a series of 1-(3-dialkylamino-1-propyl)-2-methyl-2,1-borazaronaphthalene derivatives (V) in a similar manner from 2-methyl-2,1-borazaronaphthalene (VIa). Methyllithium with VIa gave the N-lithio derivative (VIb), which reacted smoothly with dimethyl sulfate, allyl bromide, or 1-bromo-3-chloropropane to give the N-methyl, N-allyl, and N-(3-chloro-1-propyl) derivatives (VIc, VId, and VIe), respectively. The chloropropyl derivative (VIe) in turn reacted normally with secondary amines to give the 9-(3-dialkylamino-1-propyl) derivatives (V). In this case, attempts to prepare the isomeric N-(2-dialkylamino-1-propyl) derivatives failed since we were unable to add hydrogen bromide to the double bond of VId, even under drastic conditions.



Va, R = Me
b, R = Et
c, NR_2 = piperidino
d, NR_2 = morpholino
e, R = CN

VIa, R = H
b, R = Li
c, R = Me
d, R = $-CH_2CH{=}CH_2$
e, R = $-CH_2CH_2CH_2Cl$
f, R = —COOEt

In the course of this work we also prepared the cyanopropyl derivative (Ve) from VIe and potassium cyanide, and the urethane (VIf) from VIb and ethyl chloroformate. The urethane seemed quite stable to aerial oxidation, unlike the corresponding derivative (If) of 10,9-borazarophenanthrene which undergoes rapid oxidative demethylation in air.[6] The stability of VIf to oxidation indicates that 2,1-borazaronaphthalene is a more aromatic system than 10,9-borazarophenanthrene, as would be expected from analogy with naphthalene and phenanthrene.

Samples of IIIb, IIId, and IIIe, and of Vc and Vd, were tested for antibacterial activity.[7] They showed little or no growth inhibitory effect against *Escherichia coli*, *Lactobacillus arabinosus* 17-5, or *Leuconostoc dextranieum*, even in saturated solution.

Preliminary tests of the same compounds as possible agents for neutron capture therapy[8] also proved disappointing. The compounds were very toxic; mice receiving intravenous injections of 9 μg. B/g., or intraperitoneal injections of 17.5 μg. B/g., died immediately. The compounds were selectively concentrated in the brains of cancerous mice rather than in brain tumors. However the toxic symptoms indicated that the compounds were stable *in vivo*, suggesting that similar compounds of a more "biological" type may prove effective.

(6) M. J. S. Dewar and P. M. Maitlis, *Tetrahedron*, **15**, 3545 (1961).
(7) By Professor William Shive, University of Texas.
(8) By Dr. Albert M. Sloway at the Massachusetts General Hospital.

Experimental

9-(3-Chloro-1-propyl)-10-methyl-10,9-borazarophenanthrene (Id).—A solution of 10-methyl-10,9-borazarophenanthrene (7 g.) in benzene (40 ml.) was titrated under nitrogen with ethereal methyllithium, the end point being marked by a persistent yellow color.[4] The resulting solution of Ic was added dropwise over 40 min. to a solution of 1-bromo-3-chloropropane (22.8 g.) in boiling benzene (75 ml.) under nitrogen and the solution boiled under reflux overnight. Hydrolysis and evaporation of the solvent in a vacuum gave a brown semisolid mass (7.6 g.) of crude Id which could not be distilled or purified by chromatography. It seemed likely that Id is itself a liquid at ordinary temperatures and that the product was contaminated with the bisborazarophenanthrylpropane (II).

9-(3-Dimethylamino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—A solution of dimethylamine (12.5 g. of 40% aqueous solution) and crude Id (3 g.) in ethanol (100 ml.) was boiled under reflux for 6 hr. and the solvent was distilled. The residue was treated with dilute hydrochloric acid and neutral material was removed with ether. Basification of the aqueous layer and ether extraction gave the **amine IIIa** which crystallized from petroleum ether (b.p. 30–35°) in pale needles (1.8 g., 58%), m.p. 69–71°.

Anal. Calcd. for $C_{18}H_{23}BN_2$: C, 77.7; H, 8.3; N, 10.1; B, 4.0. Found: C, 78.0; H, 8.1; N, 10.0; B, 3.9.

9-(3-Diethylamino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—Prepared similarly from crude Id (4 g.), the **amine IIIb** was isolated as an oil (2.47 g., 55%), b.p. 140–142° (0.04 mm.), $n^{28}D$ 1.6013.

Anal. Calcd. for $C_{20}H_{27}BN_2$: C, 78.4; H, 8.8; N, 9.1; B, 3.6. Found: C, 78.2; H, 8.7; N, 8.9; B, 3.6.

9-(3-Dibutylamino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—Prepared similarly from crude Id (3 g.), the **amine IIIc** was isolated as an oil (2.64 g., 66%), b.p. 154–156° (0.04 mm.), $n^{26}D$ 1.5610.

Anal. Calcd. for $C_{24}H_{35}BN_2$: C, 79.6; H, 9.7; N, 7.7; B, 3.0. Found: C, 79.8; H, 9.7; N, 7.6; B, 2.8.

9-(3-N-Piperidino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—Prepared similarly from crude Id (3 g.), the **amine IIId** crystallized from ethanol in white needles (2.4 g., 68%), m.p. 99–100°.

Anal. Calcd. for $C_{21}H_{27}BN_2$: C, 79.2; H, 8.5; N, 8.8; B, 3.4. Found: C, 79.4; H, 8.8; N, 8.5; B, 3.4.

9-(3-N-Morpholino-1-propyl)-10-methyl-10,9-borazaro-9-phenanthrene.—Prepared similarly from crude Id (4 g.), the **amine IIIe** crystallized from ethanol in small needles (3.0 g., 64%), m.p. 129–130°.

Anal. Calcd. for $C_{20}H_{25}BN_2O$: C, 75.0; H, 7.8; N, 8.7; B, 3.4. Found: C, 75.4; H, 7.9; N, 8.5; B, 3.5.

9-Allyl-10-methyl-10,9-borazarophenanthrene.—Allyl bromide (12.5 g.) in dry benzene (40 ml.) was added to a solution of Ic prepared as above from Ib (8 g.) and the mixture was boiled under reflux. The next day the solution was cooled and hydrolyzed, and the benzene layer was evaporated giving the **allyl derivative (Ie)** which crystallized from methanol in white needles (7.2 g., 75%), m.p. 73–74°.

Anal. Calcd. for $C_{16}H_{16}BN$: C, 82.4; H, 6.9; N, 6.0. Found: C, 82.3; H, 7.2; N, 6.2.

9-(2-Bromo-1-propyl)-10-methyl-10,9-borazarophenanthrene.—A mixture of Ie (3.7 g.) and benzoyl peroxide (0.2 g.) was heated to 90° in a small flask and a current of dry hydrogen bromide passed through the melt. The temperature was raised gradually to 150° and held there for 3 hr. The resulting **bromopropyl derivative (IVa)** crystallized from ethanol in white needles (2.8 g., 56%), m.p. 124–125°.

Anal. Calcd. for $C_{16}H_{17}BBrN$: C, 61.1; H, 5.4; N, 4.5; Br, 25.5. Found: C, 61.6; H, 5.6; N, 4.5; Br, 25.8.

9-(2-Dimethylamino-1-propyl)-10,9-borazarophenanthrene.—Prepared from IVa (2.5 g.) in the same way as the isomer IIIa, the **amine IVb** was isolated as an oil (1.28 g., 58%), b.p. 160–162° (0.4 mm.).

Anal. Calcd. for $C_{18}H_{23}BN_2$: C, 77.7; H, 8.3; N, 10.1. Found: C, 77.3; H, 8.1; N, 8.8.

9-(2-Diethylamino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (1.5 g.), the **amine IVc** crystallized from ethanol in white needles (1.19 g., 82%), m.p. 104–105°.

Anal. Calcd. for $C_{20}H_{27}BN$: C, 78.4; H, 8.8; N, 9.1. Found: C, 78.7; H, 9.1; N, 9.1.

9-(2-Dipropylamino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (3.1 g.), the amine IVd was isolated as an oil (2.14 g., 65%), b.p. 156–158° (0.03 mm.).

Anal. Calcd. for $C_{24}H_{25}BN_2$: N, 7.7; B, 3.0. Found: N, 7.3; B, 3.0.

9-(2-Dibutylamino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (4.0 g.), the amine IVe was isolated as an oil (2.86 g., 62%), b.p. 168–170° (0.04 mm.).

Anal. Calcd. for $C_{26}H_{25}BN_2$: N, 7.7; B, 3.0. Found: N, 7.3; B, 3.0.

9-(2-N-Piperidino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (1.5 g.), the amine IVf crystallized from ethanol in small plates (1.1 g., 72%), m.p. 116–117°, depressed on admixture with IIId.

Anal. Calcd. for $C_{21}H_{27}BN$: C, 79.2; H, 8.5; N, 8.8. Found: C, 79.0; H, 8.4; N, 8.6.

9-(2-N-Morpholino-1-propyl)-10-methyl-10,9-borazarophenanthrene.—Prepared similarly from IVa (2.0 g.), the amine IVg crystallized from ethanol in small plates (1.55 g. 76%), m.p. 129–130°, depressed on admixture with IIIe.

Anal. Calcd. for $C_{20}H_{25}BN_2O$: C, 75.0; H, 7.8; N, 8.7. Found: C, 75.2; H, 7.7; N, 8.8.

9-(2-Cyano-1-propyl)-10-methyl-10,9-borazarophenanthrene.—A solution of potassium cyanide (0.93 g.) in water (20 ml.) was added to one of IVa (1.5 g.) in ethanol (80 ml.) and the mixture was boiled overnight and then evaporated under vacuum. Ether extraction of the residue gave the nitrile IVh which crystallized from ethanol in small prisms (1.00 g., 80%), m.p. 177–178°.

Anal. Calcd. for $C_{17}H_{17}BN_2$: C, 78.5; H, 6.5; N, 10.8. Found: C, 78.7; H, 6.2; N, 10.9.

1,2-Dimethyl-2,1-borazaronaphthalene.—An ethereal solution of methyllithium, prepared from lithium (1.0 g.) and methyl iodide (6.5 g.), was added dropwise to a vigorously stirred benzene solution of VIa (5.0 g.) under nitrogen at room temperature. A benzene solution of dimethyl sulfate (11 g.) was then added and the mixture was boiled 3 hr. under reflux. Hydrolysis and ether extraction gave **1,2-dimethyl-2,1-borazaronaphthalene (VIc)** as an oil (4.4 g., 80%), b.p. 76–78° (0.5 mm.).

Anal. Calcd. for $C_{10}H_{12}BN$: C, 76.4; H, 7.6; N, 8.9; B, 7.0. Found: C, 76.2; H, 7.8; N, 8.9; B, 6.7.

1-Allyl-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from allyl bromide (10.8 g.), the allylmethylborazaronaphthalene (VId) was isolated as an oil (4.99 g., 78%), b.p. 74° (0.04 mm.).

Anal. Calcd. for $C_{12}H_{14}BN$: C, 78.7; H, 7.6; N, 7.6. Found: C, 78.3; H, 7.2; N, 7.8.

Ethyl 2-Methyl-2,1-borazaronaphthalene-1-carboxylate.—Prepared similarly from ethyl chloroformate (9.5 g.), the urethane (VIf) was isolated as an oil (5.7 g., 76%), b.p. 96–98° (0.4 mm.).

Anal. Calcd. for $C_{12}H_{14}BNO_2$: C, 67.0; H, 6.5; N, 6.5. Found: C, 66.7; H, 6.8; N, 6.5.

1-(3-Chloro-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from 1-bromo-3-chloropropane (22.0 g.), the chloropropyl derivative (VIe) distilled at 100–102° (2 mm.) as an oil which crystallized, m.p. 70.0°.

Anal. Calcd. for $C_{12}H_{15}BClN$: C, 65.6; H, 6.8; N, 6.4; Cl, 16.2; B, 5.0. Found: C, 66.1; H, 7.3; N, 6.4; Cl, 16.0; B, 5.2.

1-(3-Dimethylamino-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared in the same way as III from VIe (3.0 g.) and dimethylamine (15.5 g. of 40% aqueous solution), the amine Va was isolated as an oil (2.23 g., 72%), b.p. 110° (1.0 mm.), $n^{28}D$ 1.5608.

Anal. Calcd. for $C_{14}H_{21}BN_2$: C, 73.7; H, 9.2; B, 4.8. Found: C, 73.5; H, 9.3; B, 4.8.

1-(3-Dimethylamino-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from VIe (3.0 g.), the amine Vb formed an oil (2.27 g., 65%), b.p. 119–121° (1.0 mm.), $n^{29}D$ 1.5970.

Anal. Calcd. for $C_{16}H_{26}BN_2$: N, 10.9; B, 4.3. Found: N, 10.8; B, 4.3.

1-(3-N-Piperidino-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from VIe (4.0 g.), the amine Vc formed an oil (3.38 g., 70%), b.p. 122–124° (0.2 mm.), $n^{29}D$ 1.5670.

Anal. Calcd. for $C_{17}H_{25}BN_2$: C, 76.1; H, 9.3; N, 10.4. Found: C, 76.6; H, 9.5; N, 10.1.

1-(3-N-Morpholino-1-propyl)-2-methyl-2,1-borazaronaphthalene.—Prepared similarly from VIe (4.0 g.), the amine Vd (3.73 g., 76%) had b.p. 130–132° (0.2 mm.), $n^{29}D$ 1.5755.

Anal. Calcd. for $C_{16}H_{23}BN_2O$: C, 71.1; H, 8.5; N, 10.4. Found: C, 70.9; H, 8.4; N, 10.2.

1-(3-Cyano-1-propyl)-2-methyl-2,1-borazaronaphthalene.—A solution of potassium cyanide (3.6 g.) in water (20 ml.) was added to one of VIe (4.0 g.) in ethanol (125 ml.), and the mixture was boiled under reflux for 6 hr. and then evaporated. Ether extraction of the residue gave the nitrile Ve as an oil (2.55 g., 67%), b.p. 140–142° (0.4 mm.).

Anal. Calcd. for $C_{13}H_{15}BN_2$: C, 74.3; H, 7.1; B, 5.2. Found: C, 74.9; H, 7.6; B, 5.4.

New Heteroaromatic Compounds. XXI.[1] Some Tetracyclic Systems[2]

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Received August 22, 1963

Several derivatives of 5,4-borazaropyrene, of 9,10-dihydro-5,4-borazaropyrene, and of 6,5-borazarochrysene have been prepared by the general procedures previously described. In the course of this work we have developed an improved synthesis of 4-aminophenanthrene. Attempts to synthesize derivatives of 5,6- and 6,5-borazarobenz[*c*]phenanthrene failed. Limitations on the generality of a recently described[4] new cinnoline synthesis are pointed out.

Previous papers in this series have described a large number of novel heteroaromatic compounds containing boron. These compounds are remarkably stable and show a marked similarity to the related "normal" aromatics in their physical properties; it, therefore, seemed to us that corresponding analogs of carcinogenic hydrocarbons might be of biological interest. The work described here represents a step towards the synthesis of such materials, in particular, analogs of benz[*a*]pyrene.

The obvious route to 5,4-borazaropyrene (I) was by a Friedel–Crafts cyclization of the adduct from 4-aminophenanthrene (II) and boron trichloride.[5] Langenbeck and Weissenborn[6] had reported the preparation of 4-aminophenanthrene by Semmler reaction of the oxime of 4-keto-1,2,3,4-tetrahydrophenanthrene (III); however, one of us (M. J. S. D.) previously had found this reaction capricious and unsatisfactory,[7] and we can confirm that the yields are low and erratic. The

(1) Part XX: M. J. S. Dewar and R. C. Dougherty, *J. Am. Chem. Soc.*, **86**, 433 (1964).

(2) This work was supported by the National Institutes of Health through Grant No. CY-5218.

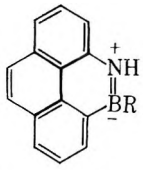
(3) Department of Chemistry, The University of Texas, Austin, Texas 78712.

(4) M. J. S. Dewar and W. H. Poesche, *J. Chem. Soc.*, 2201 (1963).

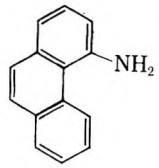
(5) *Cf.* M. J. S. Dewar, V. P. Kubba, and R. Pettit, *ibid.*, 3073 (1958).

(6) W. Langenbeck and K. Weissenborn, *Ber.*, **72**, 726 (1939).

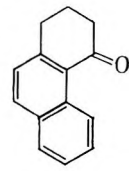
(7) *Cf.* P. M. G. Bavin, Ph.D. thesis, London, 1954.



Ia, R = H
b, R = Cl
c, R = OCH_3
d, R = CH_3
e, R = 0.5O



II



III

method is quite unsuitable for large-scale preparations and we therefore looked for an alternative route from III to II.

Horning and his collaborators[8,9] have converted cyclohexanone and tetralone azines into aniline and naphthylamine derivatives in one step by refluxing with palladized charcoal in triethylbenzene. When we applied this procedure to the azine of III, II was formed reproducibly in 37% yield. The reaction moreover can be run on a large scale, and the product seemed to be free from 4-amino-1,2,3,4-tetrahydrophenanthrene, judging by the n.m.r. spectrum.

With boron trichloride and aluminum chloride, II was converted[4] to 5-chloro-5,4-borazaropyrene (Ib); this was not isolated but was converted by the methods developed previously[10] into the 5-methoxy (Ic) and 5-methyl (Id) derivatives, and also to 5,4-borazaropyrene (Ia) itself.

These borazaro derivatives are of considerable theoretical interest since they are isoelectronic with normal aromatic hydrocarbons; comparisons of such pairs of closely related compounds provide a useful check of quantum mechanical theories of molecular structure. We therefore measured the ultraviolet spectra (see Table I) of Ia in methylcyclohexane and of

TABLE I

ULTRAVIOLET SPECTRA[a] OF 5,4-BORAZAROPYRENE DERIVATIVES

Ia (in methylcyclohexane)	Ib (in chloroform)	Id (in chloroform)
365 (4.14)	365 (3.92)	366 (4.02)
358 (3.54)	359 s (3.43)	359 s (3.48)
351 s (3.38)	348 (3.76)	348 (3.83)
347 (3.92)	340 s (3.38)	341 s (3.38)
340 (3.40)	331 s (3.54)	332 s (3.60)
331 (3.54)	307 (4.05)	308 (4.10)
320 (4.18)	295 (3.91)	296 (3.90)
317 (4.09)	278 (4.39)	279 s (4.28)
307 (4.09)	270 (4.41)	270 (4.42)
295 (3.88)	252 (4.60)	252 (4.61)
267 (4.36)		
250 (4.57)		
238 (4.53)		

[a] λ_{max}, mμ (log ε).

Ic and Id in chloroform, and also the charge-transfer bands (see Table II) of the complexes formed by Ia, Ic, and Id with tetracyanoethylene in chloroform.[11] In the case of Ia, alcohol-free chloroform must be used, for in presence of alcohol Ia, like other analogous boron compounds, is oxidized to the 5-ethoxy derivative.[10]

(8) E. C. Horning and M. G. Horning, *J. Am. Chem. Soc.*, **69**, 1907 (1947).
(9) E. C. Horning and E. F. Platt, *ibid.*, **70**, 288 (1948).
(10) M. J. S. Dewar and W. H. Poesche, *ibid.*, **84**, 2253 (1963).
(11) *Cf.* M. J. S. Dewar and H. Rogers, *ibid.*, **84**, 395 (1962).

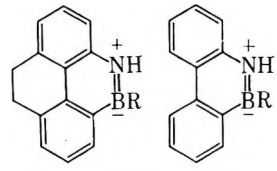
TABLE II

CHARGE-TRANSFER SPECTRA OF COMPLEXES FROM DERIVATIVES OF 5,4-BORAZAROPYRENE AND TETRACYANOETHYLENE IN CHLOROFORM

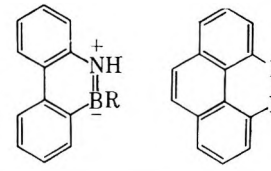
Compound	λ_{max}, mμ
Ia[a]	688, 431
Ic	695, 565, 408
Id	706, 542, 404

[a] In chloroform free from alcohol.

The difficulties we met initially in preparing II led us to explore an alternative route to I *via* its 9,10-dihydro derivative. The necessary amine could be prepared from 4-nitro-9,10-dihydrophenanthrene, which Krueger and Mosettig[12] obtained in low yield (3–4%) by nitration of 9,10-dihydrophenanthrene and separation from the 2-isomer (obtained in 65% yield). We found it more convenient to reduce the crude mixture of nitro derivatives and to react the resulting amines with boron trichloride and aluminum chloride; hydrolysis of the reaction product gave 5-hydroxy-9,10-dihydro-5,4-borazaropyrene (IVa) as its ether, from which we obtained the corresponding methoxy (IVb) and methyl (IVc) derivatives in the usual way.

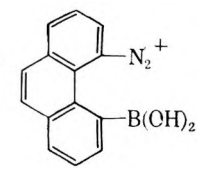


IVa, R = OH
b, R = OCH_3
c, R = CH_3



Va, R = OH
b, R = OCH_3
c, R = CH_3

VI



VII

The ether from IVa could be dehydrogenated with palladized charcoal in benzene, using hexene as hydrogen acceptor, under pressure at 260°. The product, formed in good yield, was shown by its conversion to Ic and Id to be the ether Ie. This provides an alternative route to 5,4-borazaropyrenes.

Table III lists the ultraviolet spectra of IVb and IVc in chloroform, and the charge-transfer bands of their complexes with tetracyanoethylene in chloroform. The spectra resemble those of the corresponding derivatives of 10,9-borazarophenanthrene (V), confirming the structure of IV.

TABLE III

ULTRAVIOLET SPECTRA[a] AND CHARGE-TRANSFER COMPLEXES OF 5-METHOXY- AND 5-METHYL-10,9-DIHYDRO-5,4-BORAZAROPYRENE IN CHLOROFORM

IVb	Vb	IVc	Vc
327 (3.97)	325 (4.03)	330 (4.00)	324 (4.08)
314 (3.87)	312 (3.99)	316 (3.89)	313 (4.00)
300 (3.69)	300 s (3.79)	304 (3.60)	300 (3.81)
284 (3.97)	272 (4.23)	285 s (3.91)	272 (4.08)
275 (3.97)	262 (4.23)	268 s (4.05)	252 (4.48)
		257 s (4.32)	
Complex with tetracyanoethylene			
656	635	629	605
462	515	428	400
	425		

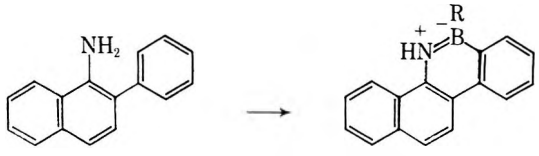
[a] λ_{max}, mμ (log ε).

We had hoped to obtain 4,5-diazapyrene (VI), which Holt and Hughes have unsuccessfully tried to synthe-

(12) F. W. Krueger and E. Mosettig, *J. Org. Chem.*, **3**, 340 (1938).

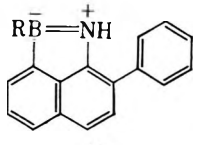
size,[13] by the new cinnoline synthesis which we have lately described.[4] However, while diazotization of 10-hydroxy-10,9-borazarophenanthrene in acetic acid gives benzo[*c*]cinnoline in almost theoretical yield with Ic, only a very small amount of material (*ca.* 2%) was obtained with the properties expected for VI. The main product was a high-melting yellow solid of unknown structure which clung to an alumina column. Attempts to convert IVa into a dihydro derivative of V likewise failed. Presumably the enforced coplanarity of the benzene rings in the intermediate diazonium boronic acid (*e.g.*, VII) hinders cyclization by blocking the approach of the nitrogen moiety to the carbon bearing the boronic acid group. This indicates a limitation on the generality of this cinnoline synthesis.

We also have prepared a series of derivatives of 6,5-borazarochrysene in a similar manner. Condensation[5] of 1-amino-2-phenylnaphthalene (VIII) with boron trichloride in presence of a catalytic amount of aluminum chloride gave 6-chloro-6,5-borazarochrysene (IXa) which was converted without isolation into 6-hydroxy- (IXb) and 6-methyl-6,5-borazarochrysene (IXc), into bis(6,5-borazaro-6-chrysyl) ether (IXd), and into 6,5-borazarochrysene (IXe) itself. The 1-amino-2-phenylnaphthalene was obtained by reduction of 1-nitro-2-phenylnaphthalene, the main nitration product of 2-phenylnaphthalene.[14]

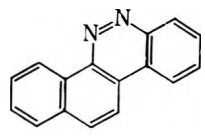


VIII

IXa, R = Cl
b, R = OCH_3
c, R = CH_3
d, R = 0.5O
e, R = H



X



XI

Conceivably, the 3-phenyl-1,2-borazaroacenaphthylene system (X) might have been formed instead of IX. That this was not the case was shown by the fact that 1-naphthylamine failed to cyclize, and that dibenzo[*c*,*h*]cinnoline (XI) was formed in 35% yield by diazotization of the 6-methoxy derivative in the absence of mineral acid.

Table IV lists ultraviolet spectra of IXe, IXb, and IXc, and also the charge-transfer band of their complexes with tetracyanoethylene.

When the diazotization was carried out in presence of mineral acid, a curious high-melting yellow compound was obtained, with the same empirical formula as IV but subliming only above 300° in a vacuum and soluble only in polar solvents such as dimethylformamide or dimethylsulfoxide.

Dr. E. B. Fleischer has very kindly examined the crystal structure and density of the compound. He found that the unit cell contained the equivalent of four dibenzocinnoline units (mol. wt. 230). A tetrameric structure can be ruled out since the material does sublime in a vacuum above 300°; this could not be the case if it had a molecular weight of 920. It is therefore certain that the compound has approximately the composition of a dimer of dibenzocinnoline, and this was confirmed by a molecular weight determination by freezing point depression of camphorquinone.

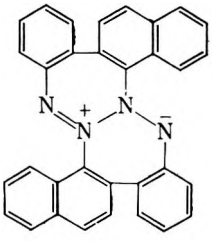
TABLE IV

ULTRAVIOLET MAXIMA AND CHARGE-TRANSFER BANDS OF 6,5-BORAZAROCHRYSENES[a] IN CHLOROFORM

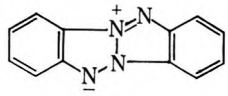
IXe[b]	IXb	IXc
353 (4.04)	356 (4.05)	354 (4.11)
337 (3.98)	339 (4.00)	338 (4.04)
322 (3.95)	324 (3.96)	322 (4.01)
309 (3.98)	311 (3.97)	309 (4.01)
276 (4.67)	278 (4.83)	277 (4.77)
268 (4.64)	268 (4.62)	267 (4.71)
	259 s (4.41)	258 s (4.51)
	251 (4.31)	
700	750	730
495	505	505

[a] λ_{max}, mμ (log ε). [b] In alcohol-free chloroform.

The structure of this material presents an intriguing problem which one of us (W. H. P.) is at present studying. An attractive possibility is the mesoionic heptalene-like structure (XII), analogous to the pentalene analog (XIII) which Carboni and Castle[15] recently reported.



XII

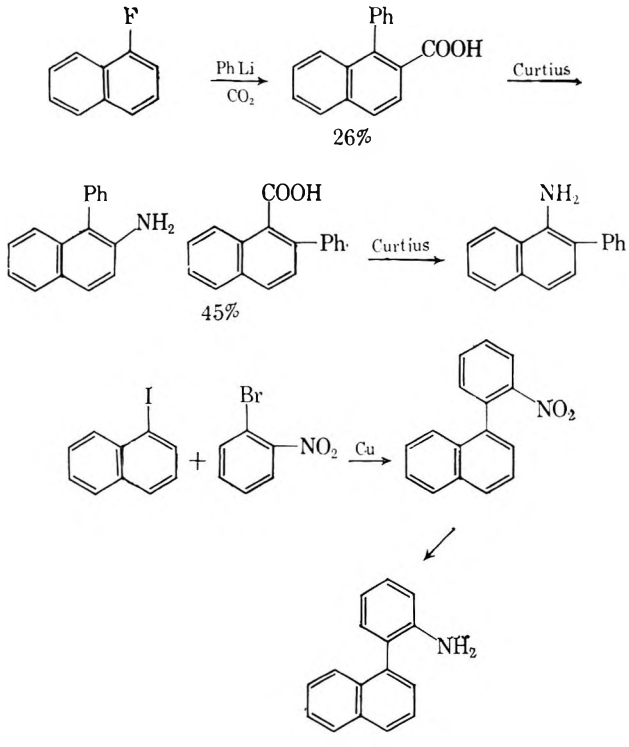


XIII

Our attempts to prepare a borazaro analog of benzo[*c*]phenanthrene met with no success. Apparently cyclization does not take place if the borazarene ring cannot become planar; the phenyl group of 1-phenylnaphthalene is known to be twisted out of the plane of the naphthalene ring[16] (Courtauld models indicate that the angle of twist should be about 40°), and benzo[*c*]phenanthrene is known to be nonplanar.[17]

The routes to the two amines which we tried to cyclize, 1-phenyl-2-naphthylamine and 1-(*o*-aminophenyl)naphthalene, are depicted below. 1-Phenyl-2-naphthylamine had been obtained before by rearrangement of α-phenyl-β-tetralone oxime[18]; it has also been prepared from 2-nitro-1-naphthylamine by a Gomberg reaction[19] and by the action of phenylmagnesium bromide on 1-methoxy-2-benzeneazonaphthalene.[20] 1-(*o*-Aminophenyl)naphthalene is also a known com-

(13) P. F. Holt and A. N. Hughes, *J. Chem. Soc.*, 3218 (1960).
(14) D. H. Hey and S. E. Lawton, *ibid.*, 378 (1940).
(15) R. A. Carboni and J. E. Castle, *J. Am. Chem. Soc.*, **84**, 2453 (1962).
(16) R. A. Friedel, M. Orchin, and L. Reggel, *J. Am. Chem. Soc.*, **70**, 199 (1948); E. Merkel and C. Wiegand, *Naturwissenschaften*, **34**, 122 (1947).
(17) F. H. Herbstein and G. M. J. Schmidt, *J. Chem. Soc.*, 3302 (1954).
(18) H. E. Zaugg, M. Freifelder, and B. W. Horrom, *J. Org. Chem.*, **15**, 1198 (1950); B. Mills and K. Schofield, *J. Chem. Soc.*, 4223 (1956).
(19) D. N. Brown, D. H. Hey, and C. W. Rees, *J. Chem. Soc.*, 3876 (1961).
(20) A. Risaliti, *Ann. Chim.* (Rome), **47**, 1119 (1937); *Chem. Abstr.*, **52**, 6282*f* (1958).



pound.[21] The required nitrophenylnaphthalene was obtained by the method reported recently by Forrest.[22]

Experimental

4-Keto-1,2,3,4-tetrahydrophenanthrene Azine.—A mixture of 4-keto-1,2,3,4-tetrahydrophenanthrene[23] (10 g.), hydrazine hydrate (1.3 ml. of 95%), ethanol (30 ml.), and concentrated hydrochloric acid (3 drops) was refluxed overnight. The red precipitate of the azine (*ca.* 100%) was collected, washed with ethanol, and dried, m.p. 195–200°. A sample crystallized from ethyl acetate in small red needles, m.p. 203.5–204.2°.

Anal. Calcd. for $C_{28}H_{24}N_2$: C, 86.56; H, 6.23; N, 7.21. Found: C, 86.54; H, 6.38; N, 7.51.

4-Phenanthrylamine.—To a solution of 4-keto-1,2,3,4-tetrahydrophenanthrene azine (7.8 g.) in hot triethylbenzene (30 ml.) was added (through the air condenser) palladized charcoal (1.6 g. of 10%); the mixture was refluxed for exactly 30 min. The cold solution was filtered, the residue was extracted with hot benzene (30 ml.) and an equal volume of petroleum ether (b.p. 60–68°) was added to the combined filtrates. The solution was poured on an alumina column (Merck, 60 × 2 cm., deposited in benzene), and the triethylbenzene was washed out with petroleum ether; the column was developed with benzene–petroleum ether, first 1:1 then 3:1, and finally eluted with benzene and benzene–ethyl acetate, fractions being taken. The brown solids obtained on evaporation of the fractions were combined, the red oil in the first fractions being omitted. They were evaporated and the residues were combined and sublimed at 90° (0.1 mm.), giving white 4-aminophenanthrene (2.85 g., 37%), m.p. 60–63° raised by recrystallization from petroleum ether (b.p. 60–68°) to 64.0–64.5° (lit.[7] m.p. 55°). The acetyl derivative after crystallization from petroleum ether (b.p. 90–100°) had m.p. 200–201°, lit.[7] m.p. 203–204°. The compounds were identical (infrared spectrum) with those prepared by the earlier[6,7] procedures.

5-Methoxy-5,4-borazaropyrene.—A solution of 4-phenanthrylamine (3.70 g.) in dry xylene (60 ml.) was added slowly with stirring to an ice-cooled solution of boron trichloride (2.5 g.) in dry xylene (15 ml.). Anhydrous aluminum chloride (0.1 g.) was then added, and the temperature was raised over 4 hr. to 140° and held there overnight in a current of dry nitrogen. The cold solution was taken up in a mixture of ether (150 ml.) and benzene (80 ml.), washed with water, dried ($MgSO_4$), and evaporated on a steam bath. The residue was dissolved in hot absolute methanol (200 ml.); the solution was concentrated to *ca.* 50 ml., and kept in a freezer (−15°). The treatment with methanol was repeated (charcoal) giving 2.56 g. (57%) of **5-methoxy-5,4-borazaropyrene** as yellowish leaflets. After a third crystallization in an efficient dry box, it had m.p. 143–145° (evacuated capillary).

Anal. Calcd. for $C_{15}H_{12}BNO$: C, 77.29; H, 5.19; N, 6.01. Found: C, 77.22; H, 5.49; N, 5.84.

5-Methyl-5,4-borazaropyrene.—Methylmagnesium bromide (15 ml. of 0.6 *M* solution in ether) was added to an ice-cold solution of 5-methoxy-5,4-borazarophenanthrene (1.5 g.) in dry ether (60 ml.). The mixture was stirred for 2 hr., first at 0°, then at room temperature. After the precipitate had settled, the solution was filtered into a sublimator and evaporated. The residue was sublimed at 140° (0.001 mm.), giving **5-methyl-5,4-borazaropyrene** (1.1 g., 79%), m.p. 145°, raised to 155–156.5° by recrystallization (charcoal) from petroleum ether (b.p. 90–100°) as small white plates.

Anal. Calcd. for $C_{15}H_{12}BN$: C, 82.99; H, 5.57. Found: C, 82.98; H, 5.73.

5,4-Borazaropyrene.—A solution of lithium aluminum hydride (1 mmole) in ether was added to one of 5-methoxy-5,4-borazaropyrene (0.90 g., 3.86 mmoles) in ether (30 ml.) at 0°. Aluminum chloride (0.04 g.) then was added, and the mixture was refluxed for 2 hr. The solution was allowed to stand until the precipitate had settled and then was filtered under nitrogen, evaporated, and the residue sublimed at 120° (0.005 mm.), giving **5,4-borazaropyrene** (0.50 g., 64%) which after resublimation had m.p. 129–130° (sintered at 122°).

Anal. Calcd. for $C_{14}H_{10}BN$: C, 82.81; H, 4.96. Found: C, 82.42; H, 4.50.

Bis(9,10-dihydro-5,4-borazaro-5-pyrenyl) Ether. A. Nitration of 9,10-Dihydrophenanthrene.—A mixture of fuming nitric acid (110 ml., *d* 1.5) and acetic anhydride (325 ml.) was added dropwise to a stirred solution of 9,10-dihydrophenanthrene (450 g.) in acetic anhydride (2.2 l.) at 25°. After 20 hr., the solution was concentrated *in vacuo* (distillate, 1.5 l.) and added slowly to boiling water (6 l.). The crude product (307 g.) was isolated with benzene and freed from starting material and tar by chromatography from petroleum ether–benzene (1:1) on alumina.

B. Reduction of the Crude Product.—Hydrazine hydrate (300 ml.) was added gradually to a boiling solution of the crude product (307 g.) in ethanol (5.3 l.) containing palladized charcoal (3 g. of 10%). After 5 hr., the solution was filtered and distilled giving a mixture of aminodihydrophenanthrenes (176 g.), b.p. 152–65° (0.04 mm.).

C. Cyclization.—A solution of the mixed amines (40 g.) in dry xylene (600 ml.) was added slowly to a stirred solution of boron trichloride (28.8 g.) in dry xylene (200 ml.) at 0°. Aluminum chloride (0.1 g.) then was added and dry nitrogen was passed through the mixture while the temperature was raised over 4 hr. to 140° and held there overnight. The cold mixture then was stirred for 24 hr. with dilute hydrochloric acid and the organic layer was washed, dried, and evaporated. The residue was boiled with ethanol and ethyl orthoformate and then distilled in a vacuum. The fraction, b.p. 155° (0.06 mm.), was dissolved in boiling acetic acid and water was added until cloudy; the mixture was allowed to cool to 50°, decanted from the oil, and left to crystallize. The process was repeated with oil and filtrate until no more solid could be isolated. The combined solids were crystallized from petroleum ether (300 ml., b.p. 60–68°) in a Soxhlet, giving **bis(9,10-dihydro-5,4-borazaro-5-pyrenyl) ether** (5.16 g., 11.4% on mixed amines), m.p. 223° after recrystallization from petroleum ether (charcoal, b.p. 90–100°).

Anal. Calcd. for $C_{28}H_{22}B_2N_2O$: C, 79.29; H, 5.23; N, 6.61. Found: C, 78.92; H, 5.24; N, 6.67.

5-Methoxy-9,10-dihydro-5,4-borazaropyrene.—A solution of bis(9,10-dihydro-5,4-borazaro-5-pyrenyl) ether (3.5 g.) in absolute methanol (200 ml.) was boiled under reflux for 4 hr., then concentrated to *ca.* 100 ml. and kept in a freezer (−20°) overnight. The precipitate was collected and recrystallized from methanol (charcoal), giving **5-methoxy-5,4-borazaropyrene** as leaflets, m.p. 135–136° (evacuated capillary).

Anal. Calcd. for $C_{15}H_{14}BNO$: C, 76.63; H, 6.00; N, 5.96. Found: C, 76.39; H, 6.12; N, 6.08.

The combined filtrates were concentrated giving another crop of the compound; the over-all yield was 2.5 g., 65%.

5-Methyl-9,10-dihydro-5,4-borazaropyrene.—Methylmagnesium bromide (13 ml. of 0.7 *M* solution in ether) was added to a solution of 5-methoxy-9,10-dihydro-5,4-borazaropyrene (1.45 g.)

(21) J. Forrest and S. H. Tucker, *J. Chem. Soc.*, 1139 (1948).
(22) J. Forrest, *ibid.*, 589 (1960).
(23) R. D. Haworth, *ibid.*, 1129 (1932); E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1441 (1936).

in dry ether (60 ml.) at 0°. After stirring 2 hr., first at 0° and then at room temperature, and then allowing the precipitate to settle, the solution was filtered and evaporated; the residue sublimed at 110° (0.005 mm.), giving **5-methyl-9,10-dihydro-5,4-borazaropyrene** (0.86 g., 60%), m.p. 99.5–101.3° (after resublimation).

Anal. Calcd. for $C_{15}H_{14}BN$: C, 82.23; H, 6.44; N, 6.39. Found: C, 82.55; H, 6.52; N, 6.70.

Bis(5,4-borazaro-5-pyrenyl) Ether.—A mixture of bis(9,10-dihydro-5,4-borazaro-5-pyrenyl) ether (2.66 g.), palladized charcoal (0.25 g. of 10%), benzene (12.5 ml.), and hexene (25 ml.) was heated in a sealed tube at 265° for 20 hr., giving crude bis(5,4-borazaro-5-pyrenyl) ether (2.34 g., 89%), m.p. *ca.* 240°. Recrystallization from toluene gave colorless leaflets, m.p. 246–247°.

Anal. Calcd. for $C_{28}H_{18}B_2N_2O$: C, 80.05; H, 4.32; N, 6.67. Found: C, 79.87; H, 4.50; N, 7.10.

The compound was converted to 5-methoxy-5,4-borazaropyrene, identical (mixture melting point and infrared spectrum) with the material obtained previously by recrystallization from absolute methanol. This in turn was converted as before to 5-methyl-5,4-borazaropyrene, identical (mixture melting point and infrared spectrum) with an authentic sample.

Action of Nitrous Acid on 5-Hydroxy-5,4-borazaropyrene. A.—Concentrated hydrochloric acid (2.5 ml.) was added to a hot solution of 5-methoxy-5,4-borazaropyrene (0.47 g.) in acetic acid (10 ml.), and the mixture was cooled to 4°. A solution of sodium nitrite (0.15 g.) in a little water was added below 6° and after 3 hr. a solution of sodium acetate (7.0 g. of $C_2H_3O_2Na \cdot 3H_2O$) in water (15 ml.) was added below 8°. Chromatography of the boron-free precipitate from benzene on alumina gave no 4,5-diazapyrene.

B.—The experiment was repeated with the difference that the compound was dissolved in a mixture (1:1, 20 ml.) of acetic and propionic acids, the sodium nitrite was added as a solid, and the sodium acetate was omitted. Chromatography of the product as before gave a small amount (9 mg., 2% calcd. as diazapyrene) of material with an ultraviolet spectrum consistent with 4,5-diazapyrene (λ_{max} in chloroform: 385, 367, 305, 289, and 280 s mμ; λ_{max} in methylcyclohexane: 379, 372, 355, 350 s, 342 s, 303, 285, 281 s, 276, and 235 mμ). The main product formed a yellow band on the alumina column; this could not be eluted, even with ethyl acetate.

Action of Nitrous Acid on 5-Hydroxy-9,10-dihydro-5,4-borazaropyrene.—The reaction, carried out as under B above, failed to give any identifiable product.

1-Amino-2-phenylnaphthalene.—Palladized charcoal (2 g. of 10% was added to a solution of 1-nitro-2-phenylnaphthalene[14] (19 g.), m.p. 128.5–130°, lit. m.p. 127°, in boiling ethanol (570 ml.). Hydrazine hydrate (19 ml.) was added slowly and the mixture was boiled 1 hr. After filtering the catalyst and concentrating the solution, the amine (15.7 g., 94%) which separated was collected, washed with water, and dried, m.p. 103.5–105°, lit.[14] m.p. 104°.

6-Methoxy-6,5-borazarochrysene.—A solution of 1-amino-2-phenylnaphthalene (15.7 g.) in dry xylene (150 ml.) was added slowly with stirring to an ice-cold solution of boron trichloride (10 g.) in dry xylene (650 ml.). Anhydrous aluminum chloride (0.1 g.) then was added; the temperature was raised during 4 hr. to 140° and held there overnight while the hydrogen chloride that formed was swept away with dry nitrogen. The cold solution was taken up in a mixture of ether (600 ml.) and benzene (250 ml.), washed with water, dried ($MgSO_4$), and evaporated on a steam bath in a hood. The residue was refluxed with absolute methanol (750 ml.) and the solution was concentrated and kept in a freezer (−20°). The treatment with methanol (charcoal) was repeated with the residue, giving **6-methoxy-6,5-borazarochrysene** (9.2 g., 50%), m.p. 106–108°.

A sample was recrystallized from absolute methanol (charcoal), m.p. 108–110°. It was necessary to filter and handle the crystals in a dry box.

Anal. Calcd. for $C_{17}H_{14}BNO$: C, 78.80; H, 5.45; N, 5.41. Found: C, 78.84; H, 5.60; N, 5.35.

Bis(6,5-borazaro-6-chrysyl) Ether.—The product of another cyclization, instead of being refluxed with methanol, was recrystallized from toluene (charcoal) until the filtrate was colorless, giving the **ether** as a white powder, m.p. 288–290.5°.

Anal. Calcd. for $C_{32}H_{22}B_2N_2O$: C, 81.40; H, 4.70; N, 5.93. Found: C, 81.56; H, 5.00; N, 5.89.

6-Methyl-6,5-borazarochrysene.—To a stirred solution of 6-methoxy-6,5-borazarochrysene (2.6 g.) in dry ether (100 ml.) was added dropwise at room temperature a solution of methylmagnesium bromide (15 ml. of 1 *M*) in ether. A white precipitate of methoxymagnesium bromide formed immediately. Stirring was continued for 2 hr., and the precipitate then was left to settle, filtered, and washed with dry ether. The filtrate was diluted with ether, shaken with water, and dried ($MgSO_4$); the solvent was removed on a steam bath. The raw product was sublimed at 145° (0.0005 mm.), giving white microcrystals (1.08 g., 45%) of **6-methyl-6,5-borazarochrysene**, decomposing above 150°, depending on the rate of heating.

Anal. Calcd. for $C_{17}H_{14}BN$: C, 83.98; H, 5.80. Found: C, 84.08; H, 5.62.

6,5-Borazarochrysene.—To a stirred suspension of 6-methoxy-6,5-borazarochrysene (1.00 g., 3.86 mmoles) in dry ether (40 ml.) was added at 0° a solution of lithium aluminum hydride in ether (1.38 mmoles) followed by anhydrous aluminum chloride (0.045 g., 0.45 mmole). The mixture was refluxed for 2 hr., the precipitate was left to settle, and the solution was filtered under dry nitrogen into a sublimator. The ether was distilled and the residue sublimed at 120° (0.005 mm.), giving **6,5-borazarochrysene** (0.54 g., 61%) which after sublimation formed a white powder, m.p. 193–195° dec. (sintered at 170°) with moderately rapid heating.

Anal. Calcd. for $C_{16}H_{12}BN$: C, 83.88; H, 5.28. Found: C, 83.87; H, 5.22.

The residue from the second sublimation proved to be bis(6,5-borazaro-6-chrysyl) ether.

Attempted Synthesis of 1-Chloro-1,2-borazaroacenaphthylene.—A solution of 1-naphthylamine (15.5 g.) in dry xylene (350 ml.) was added slowly with stirring to an ice-cold solution of boron trichloride (14.4 g.) in dry xylene (100 ml.). Anhydrous aluminum chloride (0.1 g.) then was added and the temperaure was raised over 4 hr. to 140° and held there overnight while the hydrogen chloride formed was swept away with dry nitrogen. The cold reaction mixture was poured into ether–benzene (1500 ml., 2:1) and washed twice with water (3000 ml.) when the precipitate of 1-naphthylamine hydrochloride (identified by infrared spectroscopy) dissolved. The organic layer was dried ($MgSO_4$) and evaporated to dryness on a steam bath in a hood. The residue (4.4 g.) was refluxed with absolute methanol (250 ml.) and the solvent was evaporated. The residue contained no boron and consisted of 1-naphthylamine (identified by infrared spectroscopy).

Action of Nitrous Acid on 6-Methoxy-6,5-borazarochrysene. A.—Concentrated hydrochloric acid (5 ml.) was added to a solution of 6-methoxy-6,5-borazarochrysene (1 g.) in hot acetic acid (20 ml.) and the mixture was cooled to 4° with vigorous stirring to produce a fine precipitate. Sodium nitrite (0.30 g.) in a little water was added with stirring below 6°, and the dark green solution was kept at 0° overnight, when the color disappeared. Sodium acetate (14 g. of trihydrate) in water (30 ml.) was added below 8°, stirring was continued for 1 hr., and the precipitate then was filtered. Extraction with carbon tetrachloride gave a yellow-brown residue (0.52 g. 56% calcd. as dimer) which after crystallization from dimethylformamide had m.p. >300°; ultraviolet–visible spectrum, λ_{max} (log ε) in EtOH: 380 (3.75), 361 s (3.90), 343 (4.05), 306 (3.85), 276 s (4.52), 264 (4.69), and 257 mμ (4.65); in H_2SO_4: 449 (4.42), 354 (3.85), and 268 mμ (4.98); infrared spectrum, ν (cm.$^{-1}$): 695 w, 708 w, 766 s, 770 s, 782 s, 790 m, 277 m, 925 w, 1015 w, 1082 m, 1093 w, 1120 w, 1140 m, 1275 m, 1322 m, 1358 m, 1380 m, 1407 m, 1440 w, 1460 w, 1550 s, 1508 m, 1575 m, and 3070 m.

Anal. Calcd. for $C_{32}H_{20}N_4$: C, 83.45; H, 4.38; N, 12.17. Found: C, 83.43; H, 4.27; N, 12.42; mol. wt., *ca.* 400 (in camphorquinone).

The compound could be recrystallized from dimethylformamide, dimethyl sulfoxide, or ethylene glycol; in the last solvent it was very sparingly soluble, but separated in tiny yellow plates, monoclinic, $a = 22.02$, $b = 6.36$, $c = 7.40$, $\beta = 98°45'$, density (measured) = 1.49 g./cm.^{3}, mol. wt. (calculated)/unit cell 919.

B. A solution of 6-methoxy-6,5-borazarochrysene (1 g.) in a hot mixture of acetic acid (10 ml.) and propionic acid (10 ml.) was cooled to 4° with stirring and solid sodium nitrite (0.30 g.) was added. Next day water was added and the solid (0.895 g.) was collected, dried, and extracted with benzene. The extract was chromatographed on alumina, the bands being eluted with benzene–ethyl acetate, first 9:1, then 7:1, and finally 5:1. The second (greenish yellow) band consisted of dibenzo[*c,h*]cinnoline (0.31 g., 34%), identified by melting point, mixture melting

point, and comparison of the infrared spectrum with that of an authentic sample prepared by electrolytic reduction[4] of *o*-(nitrophenyl)-1-nitronaphthalene. The residue from the extraction was identical with the main product obtained under A.

1-Phenyl-2-naphthoylhydrazide.—Methyl 1-phenyl-2-naphthoate (24.64 g.)[21] was refluxed with hydrazine hydrate (36 ml.) for 24 hr. with stirring. The resulting **hydrazide** crystallized from ethanol as a white powder (19.4 g., 79%) which after recrystallization had m.p. 189–190.5°.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.69. Found: C, 77.99; H, 5.50; N, 10.90.

Ethyl 2-(1-Phenylnaphthyl)carbamate.—1-Phenyl-2-naphthoylhydrazide (19.6 g.) was added portionwise over 2 hr. at 5° to a stirred solution of nitrosyl chloride (4.9 g.) in dry ethanol (330 ml.). The solution was stirred at 5° for another hour, then refluxed overnight. Water (35 ml.) was added and the hot solution was left to cool in a freezer (−15°) when crystals of the **carbamate** (17.8 g., 81%) separated. After two recrystallizations from 90% ethanol it had m.p. 112–6–112.8°.

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88. Found: C, 78.20; H, 6.05.

1-Phenyl-2-naphthylamine.—Ethyl 2-(1-phenylnaphthyl)-carbamate (17.8 g.) was refluxed for 10 hr. with alcoholic potassium hydroxide (260 ml. of ethanol, 8.4 g. of potassium hydroxide). The amine was precipitated by addition to water (1 l.) affording 13.4 g. (100%) of a product with m.p. 94–102°. Recrystallization (charcoal) from petroleum ether (b.p. 60–68°) gave the pure amine, m.p. 95–96°, lit.[10-12] m.p. 94 and 96°.

Attempted Preparation of 5-Chloro-5,6-borazarobenzo[*c*]-phenanthrene.—The cyclization of 1-phenyl-2-aminonaphthalene was attempted in the same way and with the same lack of success as that of 1-naphthylamine.

Attempted Preparation of 6-Chloro-6,5-borazarobenzo[*c*]phenanthrene.—1-(*o*-Nitrophenyl)naphthalene was prepared from 1-iodonaphthalene and *o*-bromonitrobenzene,[22] m.p. 94–96°, lit.[21] m.p. 90–92° and 93–94°. 1-(*o*-Aminophenyl)naphthalene was obtained from the nitro compound (21.5 g.) by catalytic (palladium-charcoal 10%) reduction in absolute ethanol (475 ml.) under 50 lb./sq. in. initial pressure, m.p. *ca.* 62°, lit.[21] m.p. 65°. The cyclization of 1-(*o*-aminophenyl)naphthalene was attempted in the same way, and with the same lack of success, as that of 1-naphthylamine.

(24) R. Huisgen and H. Rist, *Ann.*, **594**, 151 (1955).

Pyrimidines. III. A Novel Rearrangement in the Syntheses of Imidazo- or Pyrimido[1,2-*c*]pyrimidines[1]

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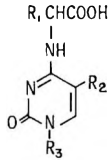
Pyrimidinylamino acids [*e.g.*, N-(1H-2-oxo-4-pyrimidinyl)-β-alanine (**1**)], when treated with acetic anhydride, cyclize with rearrangement to 2-oxopyrimido- or 2-oxoimidazo[1,2-*c*]pyrimidines (*e.g.*, **2**, **15**, **23**, and **30**). This novel rearrangement occurs with pyrimidinyl-α or -β simple amino acid derivatives. A mechanism is given which involves the cleavage of the C^2–N^3 linkage of the pyrimidine ring of **1** with the formation of an amide linkage between the carboxyl group of the amino acid moiety and N^3 to form **B**. Recyclization occurs between C^2 and N^4 of intermediate **B** to furnish **2**. The presence of a hydrogen on N^1 of the pyrimidinyl amino acids is essential for the rearrangement. N^1-Alkylated pyrimidinyl amino acids do not undergo the rearrangement; instead other reactions predominate. γ-Amino acid derivatives yield N-4-pyrimidinylbutyrolactams (**35**).

In a previous paper in another series,[2] the preparation of a number of pyrimidinylamino acids and their nucleosides of the general structure shown in Chart I

CHART I



was reported as part of our program in the synthesis of compounds of potential biochemical interest. During this investigation, the reactions of the β-alanyl derivative **1** with several reagents, particularly with acetic anhydride, were studied. The present paper deals with an interesting rearrangement which led to a general investigation into the reactions of pyrimidinylamino acids with acetic anhydride.

Treatment of N-(1H-2-oxo-4-pyrimidinyl)-β-alanine (**1**) with acetic anhydride could yield several possible products, among them the N^4-acetyl derivative of the mixed anhydride of **1** (Chart II). Such a compound would be expected to cyclize with the loss of acetic acid to form **3**, 1H-1,2,3,4-tetrahydro-4,6-dioxopyrimido[1,2-*c*]pyrimidine or its N^1-acetyl derivative. When **1** was refluxed with acetic anhydride, a 70% yield was obtained of a product with an elemental analysis in accord with **3**. The ultraviolet spectrum of this product differed from **1**, as expected. If this product is **3**, hydrolysis with acid or alkali should regenerate **1**, since it has been reported that ring acylated purines[3] or pyrimidines[4,5] (*e.g.*, 1,3,4-tribenzoylcytosine)[4] regenerate to their parent compounds under hydrolytic conditions.

Mild acid or alkaline hydrolysis of the product obtained from the reaction of **1** with acetic anhydride did not regenerate **1**. Instead, a new product was obtained which was proved to be 3-(2-carboxyethyl)cytosine (**4**) by ultraviolet absorption studies[6,7] (similarity to 3-methylcytosines) and by further alkaline hydrolysis of **4**

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 03190-07). A preliminary report of this work has appeared in the Abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 39L. For part II of this series, see I. Wempen and J. J. Fox, *J. Med. Chem.*, **7**, 207 (1964).

(2) T. Ueda and J. J. Fox, *ibid.*, **6**, 697 (1963).

(3) L. Birkofer, *Chem. Ber.*, **76**, 769 (1943); J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956); B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957); A. H. Schein, *J. Med. Pharm. Chem.*, **5**, 302 (1962).

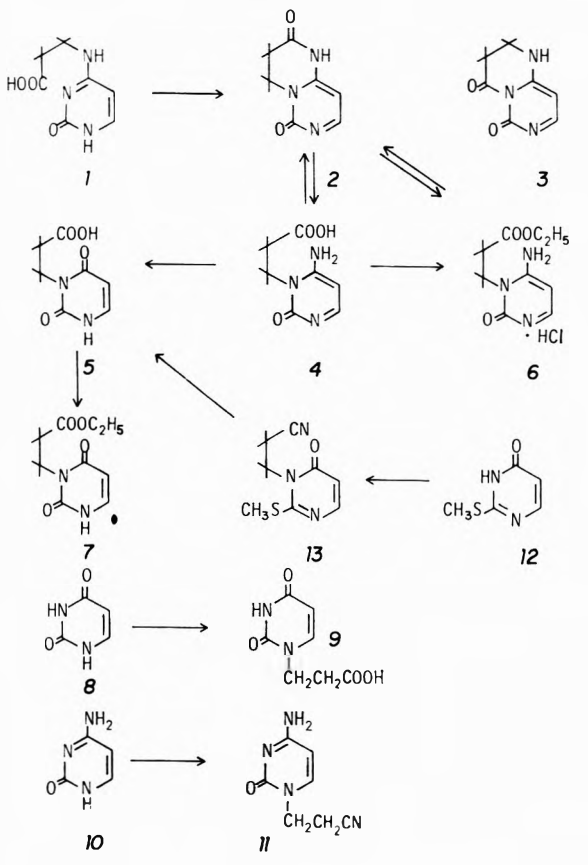
(4) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2384 (1956).

(5) M. Fytelson and T. B. Johnson, *J. Am. Chem. Soc.*, **64**, 306 (1942); L. B. Spencer and E. B. Keller, *J. Biol. Chem.*, **232**, 185 (1958).

(6) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1348 (1962).

(7) T. Ueda and J. J. Fox, *J. Am. Chem. Soc.*, **85**, 4024 (1963).

CHART II



to 3-(2-carboxyethyl)uracil (**5**). The structure of **5** was confirmed by an alternate synthesis which will be described later.

The conversion of **1** → **4** *via* a dehydrated product requires a rearrangement. Structures **2** and **3** are possibilities for the structure of the dehydrated product. If this product is **3**, which could form *via* the expected cyclization of **1** with acetic anhydride, it is necessary to postulate a rearrangement in the conversion of **3** to **4**. If the dehydrated product is **2**, a rearrangement obviously must have occurred during its formation from **1**, and the formation of **4** from **2** would find ready explanation by simple cleavage of the lactam. The following reactions support the conclusion that the dehydrated product is **2** (1H-1,2,3,4-tetrahydro-2,6-dioxopyrimido[1,2-*c*]pyrimidine).

Treatment of **4** with acetic anhydride regenerated **2**. The ethyl ester **6** is formed by treatment of **4** with ethanolic hydrogen chloride. When **6** was dissolved in sodium bicarbonate solution, **2** was obtained. Treatment of **2** with ethanolic hydrogen chloride yielded **6**. These interconversion (pairs **2** ⇌ **4** and **2** ⇌ **6**) establish **2** as the product of the reaction of **1** with acetic anhydride. The ethyl ester of **1** did not cyclize when treated with bicarbonate; instead **1** was regenerated. It is noted that 3-methylcytosine[6] does not undergo rearrangement under these reaction conditions.

The ready cleavage and re-formation of lactams has been observed previously with certain pyrimidines such as with 6-amino-5-carboxymethylthiouracils[8] and with the more closely related 1-(2-carboxyethyl)isocytosine.[9]

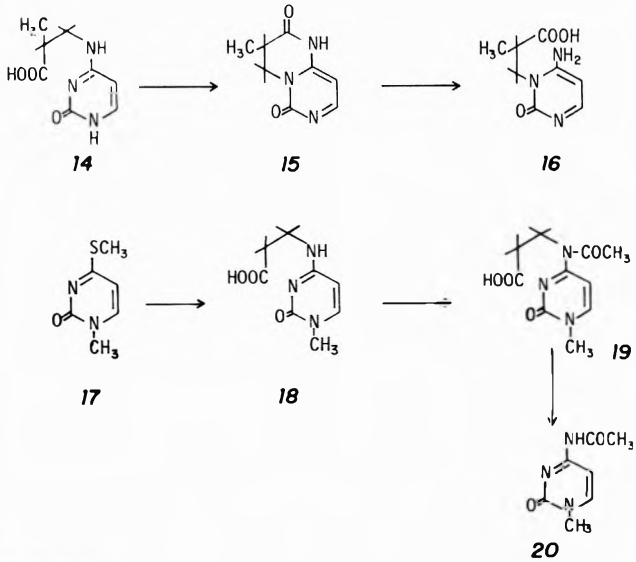
(8) E. F. Schroeder and R. M. Dodson, *J. Am. Chem. Soc.*, **84**, 1904 (1962).
(9) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **26**, 1891 (1961).

The assignment of structure **2** rests in the final analysis on the proof of structure **4** and **5**. The ultraviolet absorption spectrum of **5** is very similar to that for 3-alkyluracils,[10] again indicating that **5** is 3-alkylated. Esterification of **5** with alcoholic hydrogen chloride afforded **7**, which also exhibited spectral properties akin to 3-alkyluracils.

The structures of **5** and **7** were confirmed by synthesis. Angier and Curran[9,11] demonstrated that acrylonitrile is a useful reagent for the introduction of a 2-carboxyethyl group on the ring nitrogen of certain pyrimidines and pteridines. This method was adapted to the synthesis of **7**. Treatment of uracil (**8**) with acrylonitrile in alkali afforded 1-(2-carboxyethyl)uracil (**9**) in high yield. The spectrum of **9** resembled that for 1-substituted uracils,[10] and no evidence for any 3-isomer was observed. Reaction of cytosine (**10**) with acrylonitrile in 50% aqueous pyridine gave only 1-(2-cyanoethyl)cytosine (**11**). Treatment of 2-methylthiouracil (**12**) with acrylonitrile in aqueous pyridine gave 3-cyanoethyl-2-methylthiouracil (**13**) in good yield. The position of alkylation in **13** is established by the close similarity of its ultraviolet spectrum to that of 2-methylthio-3,6-dimethyl-4-pyrimidinone and the dissimilarity to 2-ethylthio-1-methyl-4-pyrimidinone.[12] Hydrolysis of **13** in 5 *N* hydrochloric acid yielded **5**, which was identical by ultraviolet and infrared spectral comparison and migration in paper electrophoresis with **5** obtained from **4**. The ethyl ester **7** was also synthesized from **5** derived from acid hydrolysis of **13**. These syntheses prove structures **5** and **4** and thereby establish structure **2** as the product of the reaction of **1** with acetic anhydride.

A study of the generality of this rearrangement with pyrimidinyl amino acids was undertaken next. Treatment of 4-methylthio-2-pyrimidinone with β-aminoisobutyric acid yielded **14** (Chart III). When refluxed with acetic anhydride, **14** was converted to the dehydrated product **15**, which exhibited ultraviolet spectral properties similar to **2**. The hydrolytic behavior of **15**

CHART III



(10) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).
(11) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, **81**, 5650 (1959); W. V. Curran and R. B. Angier, *J. Org. Chem.*, **26**, 2364 (1961); **27**, 1366 (1962).
(12) D. Shugar and J. J. Fox, *Bull. soc. chim. Belges*, **61**, 293 (1952).

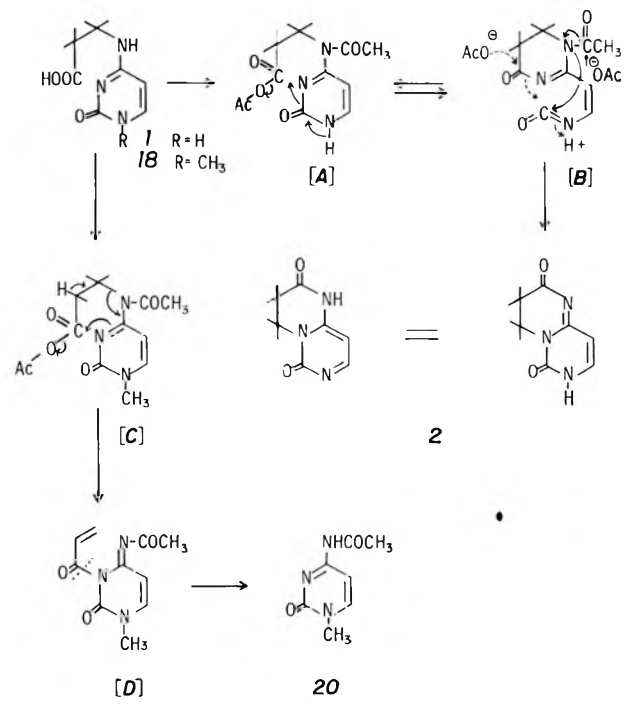
was also similar to 2 since **15** was easily converted to **16**. The spectrum of **16** was akin to **4** and also to other 3-alkylcytosines. It appears that alkyl substituents vicinal to the carboxyl function in **1** do not prevent the transformation to type 2 compounds.

The importance of a proton on N^1 of **1** in this reaction was examined. For the appropriate model compound, 1-methyl-4-methylthio-2-pyrimidinone (**17**) was treated with β-alanine to yield **18**, the 1-methyl analog of **1**. Reaction of **18** with acetic anhydride at reflux temperature for 15 min. gave the N-acetyl derivative **19** as the major product. The absorption spectrum of **19** was fairly similar to that for **20** (see below); however, the elemental analyses and electrophoretic behavior are consistent with **19**. Alkaline hydrolysis of **19** yielded starting material, **18**. With longer reflux of **18** in acetic anhydride, the reaction solution darkened considerably, and a low yield of **20** was obtained and was identified by comparison with authentic material prepared by an alternate route.[13] No other product (not even **19**) could be isolated from the reaction mixture. However, paper electrophoretic examination of the mother liquor showed the presence of three other minor components in addition to **19** and **20**. One of these components showed an ultraviolet absorption maximum at ~312 mμ. The conversion of **19** to **20** was most unexpected. A possible reaction pathway to explain this conversion is discussed below. In general, substitution at N^1 of **1** by alkyl, as in **18**, prevented the type of transformation illustrated by the conversion of **1** to **2**.

The formation of **19** as a major product in the short-term treatment of **18** with acetic anhydride suggested that an N^4-acylated intermediate also formed in the transformation of **1** to **2**. It is to be noted that treatment of cytosine, 1-methylcytosine, or 1,N^4-dimethylcytosine with acetic anhydride gives N^4-acetyl derivatives.[13] Attempts to isolate a crystalline intermediate in the reaction of **1** → **2** were unsuccessful. However, after mild treatment of **1** with acetic anhydride and examination of the reaction solution, spectra were obtained supporting an N^4-acylated intermediate (see Experimental section).

A plausible mechanism for the conversion of **1** to **2** is given in Chart IV. The first intermediate in the reaction of **1** with acetic anhydride is A, in which the carboxyl group is activated as a mixed anhydride. Intermediate B would form from A by cyclization at N^3 accompanied by cleavage of the 2,3 bond. Ring closure on C^2 of the isocyanate would be competitive between N^3 and N^4.[14] If the N^3 attack is on C^2, intermediate A would be re-formed. However, if N^4 is involved in this attack (as depicted in Chart IV), compound **2** is formed with the elimination of acetic anhydride as a result of attack by acetate ion on the acetyl

CHART IV



of N^4. The stability of **2** under these reaction conditions (attempts to acetylate **2** have been unsuccessful and **2** was recovered unchanged) accounts for its formation as the sole reaction product.

This mechanism helps to explain the failure of **18** to form the 1-methyl analog of **2**. Here it is reasonable to postulate the formation of the mixed anhydride C (see Chart IV) as the first intermediate, and the isolation of **19** in Chart III is readily explained by the hydrolysis of anhydride C. The presence of a methyl group on N^1 prevents the electron migration to the 1,2-position necessary for the formation of B from A. Therefore, cleavage of the 2,3 bond did not occur. Under prolonged reflux of **18** with acetic anhydride, attack at N^3 was accompanied by cleavage of the N^4–C bond in C resulting in the acryloyl derivative D. Under the reaction conditions employed, D would be expected to undergo acetolysis to **20**. It is known that N^3-acyl derivatives of 1-methyl-N^4-benzoylcytosine hydrolyze easily to 1-methyl-N^4-benzoylcytosine.[4] The intense darkening of the reaction mixture **18** → **20** may be explained by the polymerization of acrylic acid or its derivatives.

It is interesting to compare the rearrangement of **1** → **2** with the Dimroth rearrangement which has recently been reviewed and elaborated by Brown[15a] and others.[15b] The course of the reaction of **1** → **4** is just the reverse of that which occurs in the Dimroth rearrangement. In the latter rearrangement, the ring alkylated amino- or iminopyrimidine rearranges to an exocyclic alkyl aminopyrimidine. In the conversion of **1** → **4**, however, the exocyclic alkyl aminopyrimidine (**1**) rearranged to a ring alkylated isomer **4**. In both rearrangements, an exchange of ring nitrogen by exocyclic nitrogen occurs.

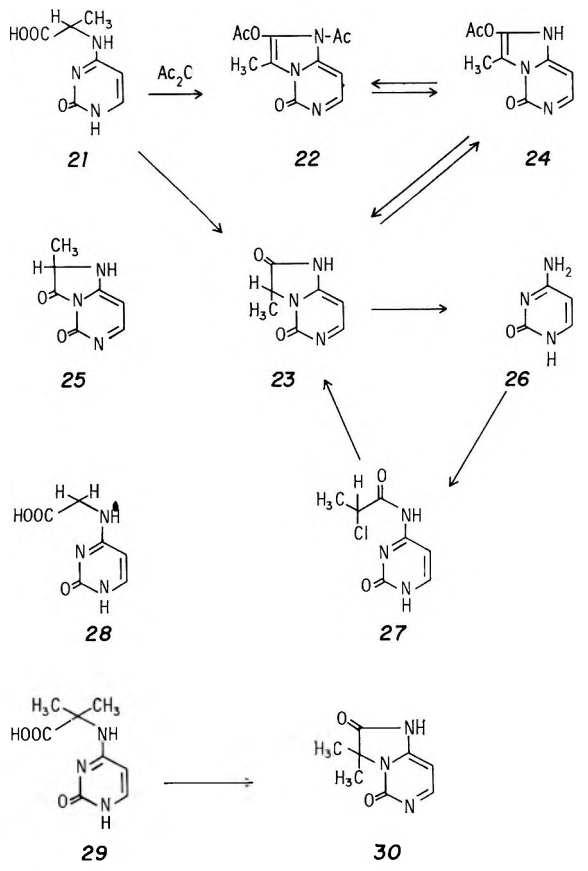
The reaction of pyrimidinyl-α-amino acids with acetic anhydride was also investigated (see Chart V).

(13) G. W. Kenner, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 855 (1955).

(14) N^4 in A, B, and **2** refers to the exocyclic nitrogen atom linked to C^4 as in the original pyrimidine, **1**. In the condensed ring compounds (*e.g.*, **2** of Chart IV or **30** of Chart V) this corresponding nitrogen atom should be referred to as N^4. The carbonyl derived from the amino acid should be designated as "2-oxo" and the carbonyl derived from the original pyrimidine as "6-oxo" (in the case of **2**) and "5-oxo" (in **23** or **30**). To facilitate the discussion, we call the exocyclic nitrogen atom of **1**, **18**, **21**, and **29**, as well as the corresponding nitrogen atom in the condensed ring compounds, as N^4. Similarly, C^2 in B refers to the position corresponding to C^2 of **1**. The *Chemical Abstracts* nomenclature of the condensed ring compounds is given in the Experimental section.

(15) (a) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1276 (1963), and references therein; (b) J. Goerdeler and W. Roth, *Chem. Ber.*, **96**, 534 (1963).

CHART V



N-(1H-2-Oxo-4-pyrimidinyl)-L-alanine (**21**)[2] was refluxed with acetic anhydride to yield **22**, a compound with analysis of a dehydrated **21** with two acetyl groups. The O-acetyl group was indicated by infrared spectra (see Experimental). On hydrolysis in acid or alkali under mild conditions, **22** was converted to **23**. The structure of **23** was confirmed by an alternate synthesis (*vide infra*). Compound **22** was regenerated from **23** by refluxing the latter with acetic anhydride. **22** was a rather unstable compound. In boiling water, **22** was converted to **24**, the structure of which was confirmed on the basis of elemental analyses and the presence of an O-acetyl band (1780 and 1205 cm.$^{-1}$) in the infrared spectrum. Mild alkaline hydrolysis of **24** afforded **23**.

Direct cyclization (with rearrangement) of **21** to **23** was carried out in high yield in refluxing acetic acid–acetic anhydride (10:1) solution for a relatively short time. The ultraviolet absorption spectrum of **23** was similar to that for **2**. A comparison of the pK_a values of **2** (4.00 and ~8) to **23** (2.11 and 7.80) also showed similarity. It is to be noted that **22**, **23**, and **24** were optically inactive.

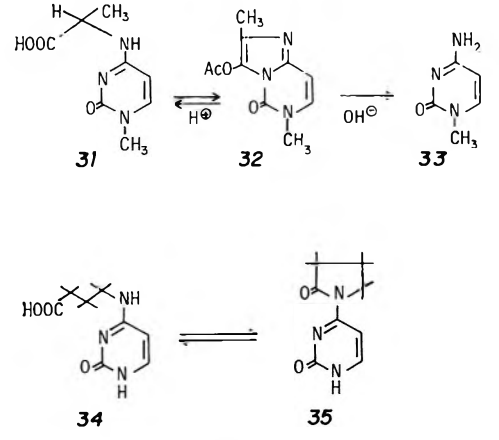
Hydrolysis experiments with **23** failed to establish the structure of **23** as *vs.* **25**. Unlike **2** and **15** (Charts II and III), **23** was rather stable to hydrolysis. After prolonged treatment of **23** with boiling 1 *N* hydrochloric acid or with warm alkali only cytosine (**26**) was found in the hydrolyzate.

Firm proof of structure **23** was established by an alternate synthesis. Prokofév, *et al.*,[16] have synthesized certain imidazo[1,2-*a*]pyrimidines by reaction of 6-methylisocytosine with α-bromopropionic anhydride followed by cyclization in base. During the course of our investigation, Noell and Robins[17] reported the synthesis of imidazo[1,2-*c*]pyrimidines by the use of similar procedures on 4-aminopyrimidines. We used similar procedures for the synthesis of **23**. Treatment of cytosine (**26**) with 2-chloropropionyl chloride yielded crude **27**. The structure of **27** was confirmed by the similarity of its absorption spectrum to N^4-acetylcytosines.[4,13] Cyclization of **27** in methanolic sodium methoxide yielded **23**, identical with that obtained by acetic anhydride treatment of **21**. It is, therefore, concluded that pyrimidinyl-α-amino acids, like the pyrimidinyl-β-amino acids, cyclize *with rearrangement* when treated with acetic anhydride.

Attempts to cyclize the glycine derivative **28** with acetic anhydride resulted in the formation of intractable colored products which were not investigated further. A similar phenomenon has been noted by McKay and Kreling[18] on 3H-3-oxo-1,2,5,6-tetrahydroimidazo-[1,2-*a*]imidazole, and its pyrimidine analog, in which ready oxidation of the active methylene group in the imidazolone ring to indigo-like products was observed. It is highly likely that a similar type of oxidation occurring on the methylene group of the imidazolone moiety when **28** is ring closed with acetic anhydride accounts for intense coloration of the reaction mixture.

When both hydrogen atoms of the 2-methylene group of α-amino acids are substituted by methyl functions, the cyclization–rearrangement reaction occurs. N-(1H-2-Oxo-4-pyrimidinyl)-α-isobutyric acid (**29**) prepared by reaction of 4-methylthio-2-pyrimidinone with α-aminoisobutyric acid was refluxed with acetic acid–acetic anhydride to yield **30**. Intense coloration of the reaction mixture did not occur. The spectrum and the pK_a of **30** were very similar to **23**. When **29** was refluxed in acetic anhydride for 1 hr. (without acetic acid added) the cyclization and rearrangement did not occur. Compounds **1** and **21** rearrange to **2** and **22** within 30 min. under these conditions. Spectral examination of the reaction solution from **29** indicated that only N^4-acetylation of **29** occurred. Upon addition of acetic acid to this reaction solution, **30** was obtained. These experiments also support the view expressed above that the first step in the rearrangement of **1** to **2** (Chart IV) is the formation of A. The requirement of additional

CHART VI



(16) M. A. Prokofév, E. G. Antonovich, and Yu. P. Shvachkin, *Dokl. Akad. Nauk SSSR*, **87**, 783 (1952).

(17) C. W. Noell and R. K. Robins, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 28L.

(18) A. F. McKay and M. E. Kreling, *Can. J. Chem.*, **40**, 205 (1962).

acetic acid may be a reflection of steric effects of the two α-methyl groups which inhibit acetate attack on the carbonyl of the N^4-acetyl in the intermediate corresponding to B (as in Chart IV). Compound **30**, unlike **23**, **15**, or **2**, was resistant to hydrolysis, and no decomposition was observed when **30** was refluxed for prolonged periods in 1 *N* hydrochloric acid or 1 *N* alkali. Like **2**, but unlike **23**, **30** was resistant to acetylation. This aspect will be discussed later.

The effect of N^1-alkylation on the susceptibility of pyrimidinyl-α-amino acids to rearrangement with acetic anhydride was also investigated (see Chart VI). Compound **31**, prepared by reaction of α-DL-alanine with **17** (Chart III) was refluxed with acetic anhydride. A product, **32**, was obtained which showed the presence of an O-acetyl by infrared spectra and the presence of three methyl functions by n.m.r. spectral examination.[19] Compound **32** is strongly basic and forms an acetate salt. Proof that **32** is the cyclized *but not rearranged* product was shown by the fact that acid hydrolysis of **32** regenerated starting material, **31**. Hydrolysis of **32** with alkali gave varying results. With a 10^{-4} *M* concentration of **32** in 1 *N* sodium hydroxide, complete conversion to 1-methylcytosine (**33**) occurred. A higher concentration (~0.03 *M*) of **32** in 1 *N* alkali yielded a mixture of starting material **31**, as well as **33**. These data suggest that the cleavage between N^4 and the amino acid carbon is pH dependent. This matter was not investigated further.

As a final aspect of this study of the generality of the cyclization–rearrangement type reaction of pyrimidinyl amino acids, we examined the behavior of a γ-amino acid homolog of **1** in refluxing acetic anhydride (Chart VI). N-(1H-2-Oxo-4-pyrimidinyl)-γ-aminobutyric acid (**34**) was prepared by reaction of 4-methylthio-2-pyrimidinone with γ-aminobutyric acid and then was refluxed with acetic anhydride with or without acetic acid. A single product was obtained in both cases in high yield, and exhibited ultraviolet spectral properties similar to those for N^4-acetylcytosine[13] and unlike those for **2** (Chart I) or **23** (Chart V). Compound **35** on treatment with alkali regenerated **34**. These data warrant the assignment of the butyrolactam structure to **35** as shown in Chart VI rather than a seven-membered cyclized or rearranged structure.

It is concluded that both α and β simple amino acid derivatives of N-1H-2-oxo-4-pyrimidine in refluxing acetic anhydride will undergo cyclization at N^3 with rearrangement to give 2-oxoimidazo- or -pyrimido-[1,2-*c*]pyrimidines (*Chemical Abstracts* nomenclature) of type **2** or **23**. When the N^1-position of these pyrimidinylamino acids is substituted, this rearrangement does not occur. With γ-amino acid derivatives, butyrolactam formation predominates.

An interesting difference between the pyrimidinyl-α- and -β-amino acid derivatives is to be found in the reactivity of the hydrogen α to the carboxyl group especially after the cyclization–rearrangement reaction occurred. As mentioned previously (Chart V), **23** is easily acetylated to **22**, whereas **30**, **15**, or **2** are resistant to acetylation. This phenomenon may be explained by the presence of an active hydrogen in **23** which is absent in **30**. Since N^1 (ref. 14) of **30** is unacetylatable, it is reasonable to expect that N^4 of **23** is equally resistant. The conversion of **23** to **22** proceeds most likely by O-acetylation to **24**. In this latter compound, N^4 has lost its amide character so that it now undergoes acetylation to **22**. This mechanism (**23** → **24** → **22**) requires tautomerism of **23** to the enolized form. Such tautomerism is not possible with **30**; therefore, the latter fails to acetylate. The failure of **2** and **15** to acetylate (Chart II) under conditions which acetylate **23** is explained by the less active nature of the methylene group alpha to the carbonyl in the former compounds. It is noted that in **23**, the active hydrogen is located on carbon which is adjacent to both a carbonyl and nitrogen.

The mobility of the α-hydrogen in **23** is evidenced by n.m.r. spectroscopy.[19] When the spectrum of **23** was taken in deuterated dimethyl sulfoxide, coupling of the methyl group and hydrogen was observed as a doublet and quartet, respectively (CH_3, τ 8.53; $^{\alpha}H$, τ 5.66; J_{H-CH_3} = 7 c.p.s.). When the spectrum of **23** was taken in D_2O, the methyl group gave a singlet (CH_3, τ 8.77) and no hydrogen peak was observed, indicating that the α-hydrogen was being exchanged.

The lack of optical activity in **22**, **23**, and **24** is consistent with the enolization of the keto group by the α-hydrogen during the cyclization reaction from **21**. It is known[20] that L-amino acids give optically inactive N-acetyl derivatives when treated with acetic anhydride.

Experimental[21]

1H-1,2,3,4-Tetrahydro-2,6-dioxopyrimido[1,2-*c*]pyrimidine (2).—A suspension of N-(1H-2-oxo-4-pyrimidinyl)-β-alanine[2] (**1**, 10 g.) in acetic anhydride (100 ml.) was refluxed for 30 min. and allowed to stand overnight. The precipitate was collected by filtration and washed with ethanol and ether, and recrystallized from 50% ethanol–water, giving 6.0 g. (67%), m.p. >280°; ultraviolet absorption properties: at pH 1, maxima at 304 and 240 mμ (ϵ_{max} 15,000 and 6550), minima at 263 and 227 mμ (ϵ_{min} 2500 and 5050); at pH 6.17, maxima at 312 mμ (ϵ_{max} 17,000), minimum at 253–260 mμ (ϵ_{min} 1800); at pH 9.17, maxima at 325 and 227 mμ (ϵ_{max} 23,600 and 9700), minimum at 273 mμ (ϵ_{min} 1100). In 1 *N* sodium hydroxide, **2** was hydrolyzed quickly and gave a spectrum identical with that for 3-(2-carboxyethyl)cytosine (**4**); pK_{a_1} 4.00, pK_{a_2} ~8; infrared spectrum (potassium bromide): ν_{max} at 1740 (doublet), 1690, 1650, and 1580 cm.$^{-1}$. The same product was obtained when acetic acid–acetic anhydride were used as reagents in the reaction of **1**.

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.78; H, 4.21; N, 25.33.

3-(2-Carboxyethyl)cytosine (4).—Compound **2** (2.5 g.) was dissolved in boiling water and, after cooling, the separated crystals (starting material) were collected by filtration (0.7 g.). The mother liquor was concentrated to dryness and the residue was recrystallized from a small amount of water, 0.97 g., m.p. 277° dec.; ultraviolet absorption properties: at pH 4.72, maximum at 276 mμ (ϵ_{max} 8700), minimum at 242 mμ (ϵ_{min} 2100); at pH 10.58, maximum at 297 mμ (ϵ_{max} 10,700), minimum at 249 mμ (ϵ_{min} 570); in 3 *N* sodium hydroxide, maxima at 294 and 233 mμ (ϵ_{max} 8600 and 7000), minimum at 258 mμ (ϵ_{min} 1700); pK_{a_2} 7.53, pK_{a_1} ~13.5; infrared spectrum (potassium bromide): ν_{max} 1730, 1650, 1615, 1570, 1950, and 2420 (weak and broad) cm.$^{-1}$. The same product was also obtained by treating **2** with 0.1 *N* sodium hydroxide at room temperature for 18 hr. or with concentrated ammonium hydroxide for 3 days at room temperature.

(19) The authors are indebted to Dr. E. Billeter of Hoffmann-LaRoche Inc., Nutley, N. J., for the determination and interpretation of the n.m.r. spectra.

(20) D. M. Greenberg in "Amino Acids and Proteins," Charles C. Thomas Publishers, Springfield, Ill., 1951, p. 33.

(21) All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.84; H, 4.83; N, 22.89.

3-(2-Carbethoxyethyl)cytosine Hydrochloride (6).—Compound **2**, (0.7 g.) was suspended in 20 ml. of ethanol containing dry hydrogen chloride and refluxed for 30 min. After concentration to a small volume, the residue was taken up in ethanol and evaporated to dryness. The residual solid was recrystallized from hot ethanol (0.7 g., m.p. 173–174° dec.); ultraviolet absorption properties showed a maximum in water at 275 mμ. On addition of a few drops of 10% sodium bicarbonate solution the spectrum changed rapidly and gave a new maximum at 325 mμ which is identical with that for **2**. Upon acidification the maximum shifted to 304 mμ.

Anal. Calcd. for $C_9H_{13}N_3O_3 \cdot HCl$: C, 43.64; H, 5.70; Cl, 14.32; N, 16.96 Found: C, 43.58; H, 5.66; Cl, 14.26; N, 16.84.

The same compound was obtained by similar treatment of **4**.

Reaction of 4 with Acetic Anhydride.—Compound **4** was refluxed in acetic anhydride for 15 min. After cooling, the separated crystals were filtered, washed with ethanol, and dried. The ultraviolet and infrared spectra of this compound were identical with those for **2**.

3-(2-Carboxyethyl)uracil (5). Method A from 2.—A solution of **2** (6.0 g.) in 100 ml. of 1 *N* sodium hydroxide was refluxed for 3 hr. Hydrolysis of **2** to **4** was complete within 15 min. The solution was applied to a column (Dowex 50 × 8, H^+ form, 50–100 mesh) and washed with water. The washings containing the product were combined and concentrated to dryness; the residue was taken up in ethanol and precipitated with ethyl acetate. The precipitate (1.0 g., plus 1.7 g. from the mother liquor) gave an absorption maximum at 259 mμ in acid or water and at 285 mμ in alkaline solution, A_{max} in water/A_{max} in OH^- = 0.68, m.p. 169–174°.

Method B from 13.—A solution of 1.08 g. of **13** in 20 ml. of 5 *N* hydrochloric acid was refluxed for 18 hr., and concentrated to dryness; the residue was treated with 30 ml. of acetone. The acetone-insoluble products were separated by filtration and discarded. The filtrate was concentrated to dryness and gave 1.1 g. of crude solid. This solid was recrystallized from acetone, m.p. 168–170°. The infrared absorption spectra of this product and the compound obtained from method A above are almost identical [potassium bromide; ν_{max} 1750, 1670 (sh), 1645, and 1625 cm.$^{-1}$].

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.40; H, 4.29; N, 15.21. Found: C, 45.65; H, 4.38; N, 15.22.

The product from method A and B showed similar paper electrophoretic properties: at pH 9.3 (borate buffer, 800 v., 1 hr.), +5.8 cm. Ultraviolet absorption properties follow: at pH 4–7, maximum 259 mμ (ε 7160), minimum 229 mμ (ε 2580); at pH 14, maximum 284 mμ (ε 10,520), minimum 244 mμ (ε 600); maximum at pH 7/maximum at pH 14 = 0.68; pK_{a_2}, 10.47.

3-(2-Cyanoethyl)-2-methylthiouracil (13).—A solution of 6 g. of 2-methylthiouracil[22] and 30 ml. of acrylonitrile in 180 ml. of 50% pyridine was refluxed for 8 hr. After concentration of the solution, the residue was treated with a small amount of water and the solid (7.4 g.) was collected by filtration. One recrystallization from ethanol gave a pure compound **13**. Ultraviolet absorption properties showed maxima in water at 295 and 225 mμ, and minima at 255 and 215 mμ; maximum in 1 *N* hydrochloric acid at 280 mμ, a minimum at 252 mμ; infrared spectra (potassium bromide): ν_{max} 1710, 1505, and 2280 (weak) cm.$^{-1}$.

Anal. Calcd. for $C_8H_9N_3OS$: C, 49.21; H, 4.65; N, 21.52; S, 16.42. Found: C, 49.22; H, 4.22; N, 21.49; S, 16.72.

Ethyl Ester of 3-(2-carboxyethyl)uracil (7). Method A.—Crude **5** (30 mg.) obtained from the hydrolysis of **4**, was dissolved in ethanolic hydrogen chloride and heated at 50° for 1 hr. After evaporation of the solvent, the residue was dissolved in ethanol and concentrated to a small volume from which white crystals separated. Recrystallization from ethanol–hexane gave needles, 20 mg., m.p. 101–103°; ultraviolet absorption in ethanol: maximum at 259 mμ, minimum at 230 mμ; infrared spectra (potassium bromide): ν_{max} 1760, 1730, 1650, 1620, and 1215 cm.$^{-1}$.

Method B.—Compound **5** (0.5 g.) obtained from **13** was dissolved in 30% saturated ethanolic hydrogen chloride (15 ml.) and refluxed for 30 min. After removal of solvent, the solid residue was recrystallized from ethanol–hexane, yielding 450 mg., m.p. 101–102°. Mixture melting point with **7** gave 102–103°; ultraviolet and infrared spectra were identical.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found (A and B): C, 50.83, 50.76; H, 5.67, 5.56; N, 13.03, 13.03.

1-(2-Carboxyethyl)uracil (9).—A solution of uracil (**8**, 2 g.) and acrylonitrile (3.8 g.) in 100 ml. of 1 *N* sodium hydroxide was refluxed for 2 hr. The solution was treated with excess Dowex 50 (H^+) resin. The filtered solution was concentrated to dryness and the residue recrystallized from water–acetone, yielding 2.5 g., m.p. 183–185°; ultraviolet absorption properties: maximum in water at 266 mμ, in 0.01 *N* sodium hydroxide at 265 mμ.

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.65; H, 4.38; N, 15.22. Found: C, 44.83; H, 4.26; N, 15.76.

1-(2-Cyanoethyl)cytosine (11).—A solution of 2 g. of cytosine (**10**) and 10 ml. of acrylonitrile in 80 ml. of 50% pyridine was refluxed for 7 hr. After removal of solvent by evaporation, the residue was crystallized from a large amount of ethanol–water, yielding 1.6 g., m.p. 249–250° dec.; ultraviolet absorption properties: maximum in water or 1 *N* sodium hydroxide at 272 mμ, minimum at 250 mμ; maximum at pH 1, 280 mμ, minimum at 240 mμ; $A_{272}(H_2O)/A_{280}(H^+)$ = 0.675. Infrared spectrum shows the presence of a nitrile group at 2280 cm.$^{-1}$.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.10; H, 5.58; N, 33.72.

N-(1H-2-Oxo-4-pyrimidinyl)-D,L-β-aminoisobutyric Acid (14).—This compound was synthesized by the general method[2] from 4-methylthio-2-pyrimidinone (4.25 g.) and DL-β-aminoisobutyric acid (3.4 g.). Crude material (5 g.) was recrystallized from water, m.p. 177–178° dec.

Anal. Calcd. for $C_8H_{11}N_3O_3 \cdot 0.5H_2O$: C, 46.59; H, 5.87; N, 20.38. Found: C, 46.62; H, 5.84; N, 20.75.

1,2,3,4-Tetrahydro-3-methyl-2,6-dioxopyrimido[1,2-*c*]pyrimidine (15).—Compound **14** (2.0 g.) in acetic acid (10 ml.) and acetic anhydride (5 ml.) was refluxed for 15 min. After concentrating the solution to dryness, the residue was taken up in ethanol, filtered, and dried to yield 1.65 g. of yellow crystals. One recrystallization from ethanol containing a small amount of water gave pure material, m.p. >290°; ultraviolet properties are almost identical with those for **2**.

Anal. Calcd. for $C_9H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.38; H, 4.84; N, 23.72.

3-(2-Carboxypropyl)cytosine (16).—Compound **15** (0.5 g.) was treated with 10 ml. of 0.5 *N* sodium hydroxide solution under reflux for 20 min. The solution was acidified with acetic acid and concentrated to a small volume. The precipitate was collected by filtration and recrystallized from water, yielding 0.2 g., m.p. >290°; ultraviolet properties were very similar to those for compound **4**.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 49.05; H, 5.91; N, 20.97.

N-(1-Methyl-2-oxo-4-pyrimidinyl)-β-alanine (18).—A solution of 1-methyl-4-methylthio-2-pyrimidinone[23] (**17**, 7 g.), β-alanine (4.8 g.), and sodium carbonate (2.4 g.) in water (40 ml.) was refluxed for 12 hr. and worked up in the usual manner,[2] yielding 5.1 g. of pure **18**, m.p. 231–233°; ultraviolet absorption properties: maximum in water or 1 *N* sodium hydroxide at 276 mμ, minimum at 252 mμ; at pH 1, maximum at 288 mμ, minimum at 245 mμ.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.63; H, 5.45; N, 21.29.

Reaction of 18 with Acetic Anhydride. Method A. Synthesis of 19.—Compound **18** (0.35 g.) in acetic anhydride (5 ml.) was refluxed for 15 min. After concentration of the solution to a small volume, ethanol was added and evaporated again. The residue was recrystallized twice from a small amount of ethanol to give **19** (0.15 g.); ultraviolet properties: in water, maxima at 304 and 252 mμ, minima at 277 and 232 mμ; in 0.1 *N* hydrochloric acid, maxima at 306 and 251 mμ, minima at 275 and 230 mμ. In 0.1 *N* sodium hydroxide, the compound reacted rapidly to give a spectrum identical with that for **18**. Paper electrophoretic mobility at pH 5.16 (0.1 *M* acetate buffer, 800 v., 1 hr.) was +3.8 cm. (due to presence of a carboxyl group). The same compound was obtained as a main product when acetic acid and acetic anhydride (2:1) were used as a reagent for a short time reaction (15 min. refluxing).

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.56. Found: C, 50.26; H, 5.26; N, 17.68.

(22) H. L. Wheeler and H. F. Merrian, *Am. Chem. J.*, **29**, 478 (1903).

(23) H. L. Wheeler and T. B. Johnson, *ibid.*, **42**, 30 (1909).

Method B. Synthesis of 20.—Compound **18** (1.0 g.) in acetic anhydride (15 ml.) and acetic acid (2 ml.) was refluxed for several hours. After several minutes, the ultraviolet absorption spectra showed the formation of **19** as a main product but, after 30 min., the spectrum changed. After 4 hr., the solvent was removed under reduced pressure and the residue was dissolved in ethanol and left overnight in the refrigerator. The precipitated material was separated and recrystallized from ethanol as needles of **20**, 0.1 g., m.p. 271–272°; ultraviolet absorption properties: in water, maxima at 298 and 244 mμ, minima at 267 and 226 mμ; in strong acid, maximum at 310 mμ, minimum at 261 mμ (almost identical with reported values)[13]; mixture melting point with an authentic sample 273–274°, lit.[13] m.p. 268°. The infrared spectrum was identical with an authentic sample.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.10; H, 5.42; N, 24.97.

The mother liquor was subjected to paper electrophoresis (pH 5.36, acetate buffer, 800 v., 3 hr.). Five spots were obtained (+4.5, −0.5, −2.5, −6.4, −8.0 cm.), two of which (+4.5- and −0.5-cm. spots) were identified as **19** and **20**, respectively. The other spots were minor and not identified, but the −2.5-cm. spot, after excision and elution with water, showed an ultraviolet absorption spectrum with a maximum at 312 mμ and two inflections at 290 and 325 mμ.

1-Acetyl-2-acetoxy-3-methyl-5-oxoimidazo[1,2-*c*]pyrimidine (22).—A suspension of compound **21**[2] (L or DL form, 2.0 g.) in 25 ml. of acetic anhydride was refluxed for 1 hr. After removal of the solvent *in vacuo*, the residual solid was treated with ethanol, filtered (2.1 g.), and recrystallized from boiling ethanol to yield white needles, 1.2 g., m.p. 130–132°. The mother liquor was used for the next experiment (see below). The ultraviolet absorption spectrum in ethanol showed a broad maximum at 300–305 and 222 mμ (ϵ_{max} 8600 and 17,000), minimum at 245 mμ (ϵ_{min} 1300); infrared spectrum (potassium bromide): ν_{max} 1785 (sh), 1765, 1670, 1660, 1625, 1230 (sh), and 1210 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.95; H, 4.34; N, 17.02.

The same compound was obtained by treating **23** (0.4 g.) with acetic anhydride (5 ml.) in the same manner. The product (0.3 g.), m.p. 127–128.5°, had the same ultraviolet absorption spectrum as **22**.

1H-2-Acetoxy-3-methyl-5-oxoimidazo[1,2-*c*]pyrimidine (24).—The mother liquor from the above experiment was concentrated to dryness and the residue was heated with dilute acetic acid solution at 80° for 1 hr. The solution was concentrated and the separated crystals were recrystallized from dilute ethanol, yielding 0.4 g., m.p. 204–206°, sintered at 195°; ultraviolet absorption spectrum: maxima at 290 and 282 mμ (ϵ_{max} 9740 and 9800), shoulder at 304 mμ (ϵ_{max} 5500), minimum at 231 mμ (ϵ_{min} 1100); infrared spectra: ν_{max} 1780, 1755, 1650, 1615 and 1205 cm.$^{-1}$.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.81; H, 4.16; N, 20.51.

When this compound was treated with dilute alkali, the ultraviolet spectrum changed rapidly to that of **23**.

1H-3-Methyl-2,3-dihydro-2,5-dioxoimidazo[1,2-*c*]pyrimidine (23) from 21. Method A.—Compound **21** (L-form,[2] 2.0 g.) was suspended in 2 ml. of acetic anhydride and 20 ml. of acetic acid and refluxed for 30 min. The solution was concentrated to dryness, the residue was treated with water and filtered, and the solid was recrystallized from dilute ethanol. Pure crystals (1.5 g. in two crops) were obtained, m.p. 280° dec. Ultraviolet absorption properties follow: in 1 *N* hydrochloric acid, maxima at 299 and 237 mμ (ϵ_{max} 14,500 and 4700), minima at 262 and 224 mμ (ϵ_{min} 1900 and 3700); at pH 4.20, maximum at 303 mμ (ϵ_{max} 18,600), minimum at 238–242 mμ (ϵ_{min} 1800); at pH 9.73, maximum at 318 mμ (ϵ_{max} 19,800), minimum at 266–270 mμ (ϵ_{min} 300); pK_{a_1} 2.11, pK_{a_2} 7.12; infrared spectrum: ν_{max} 1740, 1630, 1565, and 1450 cm.$^{-1}$; n.m.r. spectra in d_6-dimethyl sulfoxide: τ 8.53 (3-CH_3), 5.66 (3-H) ($J_{H^3-CH_3^3}$ = 7 c.p.s.), 3.79 (8-H), and 2.74 (7-H) ($J_{H^7-H^8}$ = 7 c.p.s.), in D_2O and a drop of trifluoroacetic acid, τ 8.77 (3-CH_3) and 3.85 (8-H), 2.30 (7-H) ($J_{H^7-H^8}$ = 7 c.p.s.).

Method B. Synthesis of 23 from 22.—A solution of **22** (0.1 g.) in water (10 ml.) was refluxed for 20 hr. After removal of solvent *in vacuo*, the residue was recrystallized from methanol, 0.05 g., m.p. 278° dec.; ultraviolet spectra are identical with those for the compound prepared by method A. When compound **22** was dissolved in 1 *N* sodium hydroxide, the hydrolysis was very rapid (within 1 hr.) and the solution gave a spectrum identical with that for **23**.

Method C. Synthesis of 23 from Cytosine.—To a suspension of cytosine (**26**, 3 g.) in 30 ml. of dimethylformamide, α-chloropropionyl chloride (5 g.) was added dropwise and the reaction mixture was stirred for 2 hr. at 40–50°. Excess ethyl acetate then was added to the solution, from which the precipitate **27** formed gradually. The solid was collected by filtration, washed with ethyl acetate, and dried (3.6 g.); ultraviolet spectra in water showed maxima at 299 and 244 mμ, minima at 269 and 227 mμ; A_{244}/A_{299} = 2.0.

Crude **27** (1.5 g.) was dissolved in sodium ethoxide in ethanol (1 g. of sodium dissolved in 100 ml. of ethanol), and kept at 40–50° for 30 min. The solution was neutralized to pH 7 with acetic acid, the precipitate was removed by filtration, and the filtrate was concentrated to dryness. The residue was triturated with ethanol to remove colored material, and the insoluble residue then was dissolved in hot ethanol. Upon cooling, crystals separated and were filtered (0.4 g.). One recrystallization from ethanol gave pure material, m.p. 282° dec.; ultraviolet and infrared spectra were identical with those for the product obtained by method A.

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found (by methods A, B, and C, respectively): C, 50.80, 50.91, 50.93; H, 4.40, 4.28, 4.31; N, 25.35, 25.38, 25.09.

Alkaline Hydrolysis of 23 to Cytosine.—A solution of **23** (0.25 g.) in 50 ml. of 1 *N* sodium hydroxide was allowed to stand at 30–40°. After 4 days, about 60% of the starting material was converted to cytosine (as measured spectrally). After 6 days, the solution was neutralized to pH 5 with acetic acid. Paper electrophoresis of an aliquot of this solution at pH 5.16 (0.1 *M* ammonium acetate), 700 v., and 90 min., gave two spots migrating −2.8 and −0.5 cm. (weak spot). Starting material migrates at −0.5 cm. and cytosine migrates at −2.8 cm. The spot migrating at −2.8 cm. was excised and eluted with water; its spectrum[10] was determined: in water, maximum at 267 mμ; at pH 1, maximum at 276 mμ; at pH 14, maximum at 283 mμ; R_f 0.47 [ethanol–concentrated ammonium hydroxide–water (85:5:15); cytosine also gives R_f 0.47]. Picric acid in ethanol was added to the solution and the precipitated yellow needles were filtered, washed with water, then with ethanol, and dried (0.25 g.). One hundred milligrams recrystallized from ethanol gave 60 mg., m.p. 268° dec.; cytosine picrate, prepared from commercially available cytosine, had m.p. 270° dec.

Anal. Calcd. for $C_{10}H_8N_6O_8$: C, 35.39; H, 2.73; N, 25.81. Found: C, 35.31; H, 2.37; N, 24.70.

Acid Hydrolysis of 23 to Cytosine.—A small sample of **23** in 1 *N* hydrochloric acid was refluxed. After 4 hr. very little change in absorption spectra was observed. The solution was kept at room temperature for 2 weeks and subjected to paper electrophoresis (pH 9.4, borate buffer, 700 v., 60 min.). Two spots were obtained, one of which migrated at −1.8 cm. and was identical with that of cytosine under the same conditions. The −1.8-cm. spot was excised and eluted with water. The ultraviolet spectrum was like that for cytosine.[10] The second electrophoretic spot (spread over +0.7 → +5.0 cm.) was shown to be starting material **23** by spectral examination. Measurement of the ultraviolet extinctions of the two spots showed that 70% of **23** had been converted to cytosine.

N-(1H-2-Oxo-4-pyrimidinyl)-α-aminoisobutyric Acid (29).—A mixture of 4-methylthio-2-pyrimidinone[22] (4.26 g.), α-aminoisobutyric acid (3.4 g., 1.1 equiv.), and sodium carbonate (1.75 g., 0.55 equiv.) in 40 ml. of water was refluxed for 60 hr. The solution was acidified to pH 3 by the addition of formic acid and concentrated to half of its volume. The precipitated material (1.7 g.) was filtered and the filtrate was discarded (this filtrate contains 1.4 g. of uracil). The precipitate was dissolved in hot dilute ammonium hydroxide solution and decolorized with charcoal, filtered, and the filtrate was acidified by the addition of formic acid. Crystallization was slow. After filtration, the precipitate was washed with water, with alcohol, and dried, yielding 0.73 g., m.p. 288–289°; ultraviolet spectra: in water, maxima at 266 and 235 mμ; in 1 *N* hydrochloric acid, maximum at 282 mμ; and in 0.1 *N* sodium hydroxide, maximum at 283 mμ.

Anal. Calcd. for $C_7H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.99; H, 5.68; N, 21.49.

1H-2,3-Dihydro-3,3-dimethyl-2,5-dioxoimidazo[1,2-*c*]pyrimidine (30).—A solution of **29** (0.1 g.) in 1 ml. of acetic anhydride and 2 ml. of acetic acid was refluxed for 15 min. After removal of the solvent the residue was taken up in ethanol and concentrated to dryness. This procedure was repeated three times, and the final residue was taken up in ethanol and treated dropwise

with ether. The precipitate of white crystals was collected and dried, yielding 0.08 g., m.p. 292.5–293.5°; ultraviolet absorption properties: in 1 *N* hydrochloric acid, maxima at 300 and 236 mμ (ϵ_{max} 15,000 and 5200), minima at 262 and 223 mμ (ϵ_{min} 1700 and 3900); at pH 4.27, maxima at 303 and 212.5 mμ (ϵ_{max} 19,200 and 8600), minimum at 235–245 mμ (ϵ_{min} 2300); in 0.1 *N* sodium hydroxide, maximum at 318 mμ (ϵ_{max} 20,200), minimum at 265–270 mμ (ϵ_{min} 230); pK_{a_1} 2.47, pK_{a_2} 7.28; n.m.r. spectrum in d_6-dimethyl sulfoxide: τ, 8.54 (3-CH_3), 3.80 (8-H), and 2.30 (7-H) ($J_{H^7-H^8}$ = 7.0 c.p.s.).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.54; H, 5.18; N, 23.64.

When the reaction was carried out in acetic anhydride only, the reaction seemed to stop after acetylation of N^4. On addition of acetic acid to the reaction, rapid cyclization (rearrangement) occurred which could be followed by the change in the ultraviolet spectrum of the reaction solution.

The Reaction of N-(1H-2-Oxo-4-pyrimidinyl)glycine (28) with Acetic Anhydride.—Compound **28**[2] (1 g.) was suspended in 10 ml. of acetic anhydride and refluxed for 1 hr. With heat, an orange color formed that turned to dark red within 20 min. Aside from some starting material, no other product was characterizable. Similar results were obtained when acetic anhydride–acetic acid was used as the reagent.

N-(1-Methyl-2-oxo-4-pyrimidinyl)-DL-alanine (31).—A mixture of 1-methyl-4-methylthio-2-pyrimidinone[23] (3.1 g.), DL-alanine (2.14 g.), and sodium carbonate (1.27 g.) in 50 ml. of water was refluxed for 20 hr. The solution was acidified with formic acid to pH 3, an equal volume of ethanol was added, and the solution was chilled overnight. The separated crystals were collected by filtration, washed with ethanol, and dried (3.0 g., m.p. 248–249° dec.). One recrystallization from ethanol–water gave a pure material, m.p. 250–251° dec.; ultraviolet absorption properties: at pH 9.72, maxima at 275 and 233 mμ (ϵ_{max} 9900 and 7000), minima at 250 and 228 mμ (ϵ_{min} 5300 and 6800); in 0.1 *N* hydrochloric acid, maxima at 288 and 217 mμ (ϵ_{max} 13,500 and 8500), minimum at 246 mμ (ϵ_{min} 1400); pK_a 4.25.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.35; H, 5.47; N, 21.74.

3-Acetoxy-2,6-dimethyl-5-oxoimidazo[1,2-*c*]pyrimidine (32).—A solution of **31** (0.5 g.) in acetic acid (5 ml.) and acetic anhydride (2 ml.) was refluxed for 30 min. After removal of the solvent *in vacuo*, the residue was taken up in chloroform and the chloroform solution was washed with cold saturated sodium bicarbonate solution until the water layer became neutral. The chloroform layer was dried over sodium sulfate and filtered, and the filtrate was evaporated to a sirup which, on trituration with ether, crystallized as prisms, 0.4 g., m.p. 133–135° after recrystallization from chloroform–ether; ultraviolet absorption properties: in ethanol, broad maximum at 283–290 mμ, minimum at 236 mμ; on addition of 1 drop of 5 *N* hydrochloric acid to the 3-ml. cuvette, the maximum shifted to 305 mμ, with a second maximum at 255 mμ; in 1 *N* alkali the compound was converted rapidly to 1-methylcytosine[24] and gave the final curve (2 hr.) with a maximum at 273 mμ, which, when acidified, shifted to 283 mμ; infrared spectrum (potassium bromide): ν_{max} 1810, 1730, 1653, and 1195 cm.$^{-1}$; n.m.r. spectra in d_6-dimethyl sulfoxide τ 7.90, 7.65 (2-methyl and 3-acetyl), 6.56 (6-CH_3), 3.54 (8-H), 2.64 (7-H) ($J_{H^7-H^8}$ = 7.0 c.p.s.).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 18.99. Found: C, 54.17; H, 5.01; N, 19.27.

The acetate salt of **32** was obtained when the reaction solution was concentrated to a sirup and ethyl acetate was added. The acetate crystallized from the solution, m.p. 88–92°; ultraviolet absorption properties were the same as those of **32**; infrared spectra showed additional weak broad peaks at 1920 and 2560 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.42; H, 5.43; N, 15.23.

Hydrolysis of 32 in Water.—Crude **32** (0.4 g.) was dissolved in water and refluxed for 10 min. The spectrum of the solution changed completely and, after cooling, white crystals were collected, 0.15 g., m.p. 245–247°, which were identical with **31** (ultraviolet spectra and paper electrophoretic behavior). Acid hydrolysis or weak alkaline hydrolysis (1 *N* sodium carbonate) gave similar results.

Alkaline Hydrolysis of 32.—Crude **32** (0.4 g.) was dissolved in 60 ml. of 1 *N* sodium hydroxide and allowed to stand overnight. Spectral examination of the reaction solution indicated the formation of a large amount of **31**, along with **33**. The solution was acidified with acetic acid to pH 4, and picric acid in ethanol was added. The crude picrate precipitated and was collected by filtration and recrystallized from water, 250 mg., m.p. 294° dec. The melting point of 1-methylcytosine picrate prepared from authentic 1-methylcytosine (**33**) was 293–295° dec.

Anal. Calcd. for $C_5H_7N_3O \cdot C_6H_3N_3O_7$: C, 37.29; H, 2.84; N, 23.73. Found: C, 37.52; H, 3.00; N, 22.81.

N-(1H-2-Oxo-4-pyrimidinyl)-γ-aminobutric Acid (34).—This compound was synthesized by essentially the same method previously described.[2] Crude material was obtained in nearly quantitative yield; ultraviolet absorption properties: in water, maximum at 266 mμ; in acid, at 280 mμ; and in 1 *N* alkali, at 283 mμ.

Anal. Calcd. for $C_8H_{11}N_3O_3 \cdot H_2O$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.65; H, 5.97; N, 19.67.

N-(1H-2-Oxo-4-pyrimidinyl)butyrolactam (35).—A suspension of **34** (2 g. of hydrate) in acetic acid (5 ml.) and acetic anhydride (10 ml.) was refluxed for 30 min. and allowed to stand overnight. The precipitate was collected and, after washing with hot ethanol, gave 1.2 g. The mother liquor yielded an additional 0.3 g., m.p. >290°; ultraviolet absorption spectrum: in water, maxima at 294 and 251 mμ, minima at 275 and 228 mμ; on addition of 2 drops of concentrated hydrochloric acid to the 3-ml. cuvette, maxima at 310 and 245 mμ, minima at 270 and 227 mμ; in alkali, the compound reacted and gave a spectrum identical with that for **34**; infrared spectra: ν_{max} 1765 (γ-lactam), 1668, 1480, and 1450 cm.$^{-1}$.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.36; H, 5.23; N, 23.09.

Spectral Measurements.—Ultraviolet absorption data were determined with a Cary recording spectrophotometer, Model 15, and apparent pK_a values were determined spectrophotometrically by methods previously employed,[10,12,25] and are accurate to ±0.05 pH units. Infrared spectra (potassium bromide disk) were measured with a Perkin-Elmer Infracord spectrophotometer, and only major and key bands were listed. N.m.r. spectra[19] were taken on a Varian Associates Model A-60 spectrometer. Tetramethylsilane was used as the internal standard.

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(24) J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952).

(25) J. J. Fox and D. Shugar, *Bull. soc. chim. Belges*, **61**, 44 (1952).

Pyrimidines. IV.[1] The Interconversion of N^4-Methylcytosine and 3-Methylcytosine

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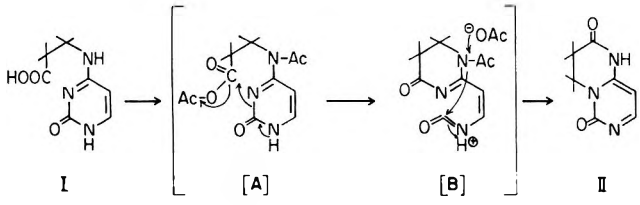
N^4-Methylcytosine (IIIb), when refluxed with acetic anhydride–acetic acid for prolonged periods, rearranges to 3-methylcytosine (IXb). The reversibility of this reaction is shown, and a mechanism for the rearrangement is given.

In a previous paper in this series,[2] we reported that N-(1H-2-oxo-4-pyrimidinyl)-β-alanine (I), when refluxed with acetic anhydride, underwent cyclization with rearrangement to form II (Chart I). The scope and limitations of this cyclization–rearrangement reaction with other pyrimidinyl amino acids was studied, and a plausible mechanism was presented.

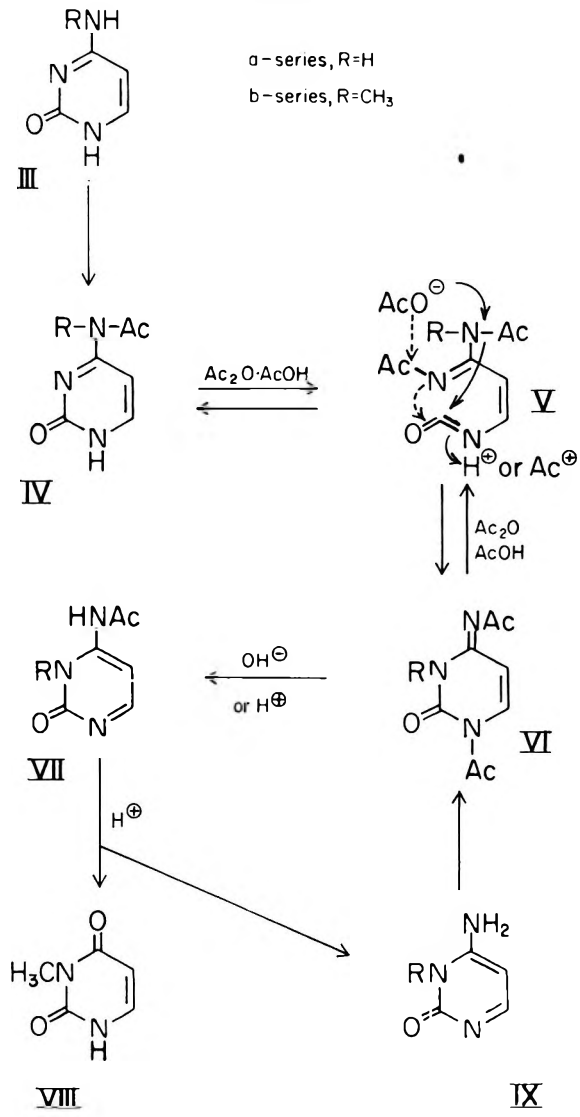
CHART I



This mechanism[2] is based essentially on the intramolecular attack by N^3 on the mixed anhydride group in A. If true, the rearrangement reaction should also occur when N^4-acetylcytosine (IVa, see Chart II) is treated with acetic anhydride. It would be expected that an intermolecular attack by N^3 of IVa on acetic anhydride would give intermediate Va which might cyclize as shown by the solid arrow to VIa and, after alkaline hydrolysis, regenerate cytosine (IXa). In the over-all reaction of IIIa to IXa, N^3 and N^4 should have been exchanged.[3]

To test this hypothesis, we employed N^4-methylcytosine[4] (IIIb) since, according to the above argument, the product of the reaction of IVb → IXb should be the easily identifiable isomer 3-methylcytosine (IXb). Compound IIIb was prepared easily by reaction of the readily available 4-thio-2-pyrimidinone[5] with methylamine. Treatment of IIIb with acetic anhydride or a mixture of acetic anhydride–acetic acid for 3 hr. under reflux gave IVb in good yield. When the reaction was carried out in acetic anhydride–acetic acid for 24 hr., the formation of a new compound was observed by paper chromatography although IVb (acetylated starting material) was still the predominant component. This new compound (sirup) was not isolated in pure form; however, it is most probably the diacetate VIb.[6] (This assignment is based on studies on the acetylation of 3-methylcytosine which will be described later.)

CHART II



The sirup was treated with 1 *N* hydrochloric acid at room temperature overnight and the hydrolysate separated on a Dowex 50 (H^+) ion-exchange column. Elution of the column with water yielded 3-methyluracil (VIII), which was obtained in crystalline form, and whose identity was established by comparison of its melting point[7] and detailed ultraviolet absorption

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 03190-07).

(2) T. Ueda and J. J. Fox, *J. Org. Chem.*, **29**, 1762 (1964).

(3) It is understood, of course, that in intermediate Va, N^3 and N^4 are essentially equivalent; hence this conversion with cytosine isotopically labeled with N^{15} at N^4 should give a 50% loss of the label at N^4. Such an experiment is planned in our laboratory.

(4) (a) D. J. Brown, *J. Appl. Chem.*, **5**, 358 (1955). (b) C. O. Johns, *J. Biol. Chem.*, **9**, 161 (1911); F. H. Case and A. J. Hill, *J. Am. Chem. Soc.*, **52**, 1536 (1930); Y. Chi and S. Chen, *Sci. Sinica* (Peking), **6**, 111 (1957).

(5) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **42**, 30 (1909); Y. Mizuno, M. Ikehara, and K. A. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **10**, 647 (1962).

(6) The position of the acetyl group which attaches on N^1 in VI is tentative. Other positions such as O^2 or N^4 are also possible.

(7) T. B. Johnson and F. W. Heyl, *Am. Chem. J.*, **37**, 628 (1907); C. W. Whitehead, *J. Am. Chem. Soc.*, **74**, 4267 (1952).

spectrum[8] with an authentic specimen. Further elution of the column with 1 *N* hydrochloric acid yielded the basic fraction which contained compound IIIb as the major component. Later eluates when examined spectrally, showed the presence of 3-methylcytosine (IXb).[9]

Similar products (IXb and VIII) were obtained when IVb was refluxed with acetic anhydride–acetic acid solution. With acetic anhydride *or* acetic acid used as the reactant, IVb was recovered unchanged and no formation of VIb was detected either spectrally or by paper chromatography. This data showed that both reagents were required for the rearrangement reaction, as observed previously in some cases with certain pyrimidinylamino acids.[2]

The formation of 3-methyluracil and 3-methylcytosine from IVb shows that the rearrangement reaction must have occurred. This rearrangement could have occurred either in the step involving the acetic anhydride–acetic acid treatment of IVb, or in the hydrochloric acid treatment of the reaction mixture. Treatment of IVb directly with 1 *N* hydrochloric acid or with alkali afforded IIIb. It is almost certain that the rearrangement of IVb to VIII and IXb proceeded *via* such intermediates as Vb, VIb, and VIIb. Data supporting the presence of the rearranged intermediates VIIb or VIb in the reaction mixture was shown by an alternate approach.

When 3-methylcytosine[9a] was treated at room temperature with acetic anhydride, a sirupy product was obtained which showed the same ultraviolet absorption and chromatographic behavior as the minor component obtained previously by refluxing IVb (or IIIb) with acetic anhydride–acetic acid. Treatment of this sirup briefly in solution with 1 *N* sodium hydroxide or with boiling water produced a marked change in the ultraviolet spectrum which now resembled that for II (Chart I), a 3-alkyl-N^4-acylcytosine, and was dissimilar to that for IVb or IXb (Chart II). These data strongly indicate that a compound of structure VIIb had formed in the latter reaction. The spectral change also suggests the presence of a diacetate (VIb) containing one labile acetyl group in the sirupy product obtained either by acetylation of IXb or by acetic anhydride–acetic acid treatment of IVb. The lability of an acetyl group substituted on a ring nitrogen of pyrimidines has been observed previously.[10]

When the sirupy product containing intermediate VIb obtained by acetylation of IXb at room temperature was treated with 1 *N* hydrochloric acid for several hours, crystalline 3-methyluracil (VIII) was obtained as the major product along with 3-methylcytosine as a minor component. Since IXb is known to be stable to acid,[9a] VIII must have been derived *via* VIIb by cleavage of the N^4–C^4 linkage. This hydrolysis (VIIb → VIII) is rather unusual, since most N^4-acetylcytosines or acylaminopyrimidines are cleaved under acidic conditions at the acyl–amide linkage to generate the parent aminopyrimidines.[11] However, there are some examples describing the cleavage at N^4–C^4, such as the conversion of N^4-acetylcytosine in boiling 80% acetic acid to uracil[10a] or of N^4-(*p*-toluoyl)-5-fluoro-2′-deoxycytidine in 0.1 *N* hydrochloric acid to 5-fluoro-2′-deoxyuridine.[12]

This rearrangement reaction (IVb → VIIb) differs in some details from that noted previously[2] in the conversion of I → II (Chart I). In the latter case, the reaction proceeded rapidly with acetic anhydride to II in high yields, leaving no detectable amount of starting material (I). In the present study, VIIb was formed from IVb as a minor component along with a considerable amount of starting material (IVb). These facts suggest that the conversion of IVb → VIIb is reversible through intermediate Vb. To test this hypothesis, IXb was *refluxed* with acetic anhydride–acetic acid for 20 hr., and the reaction mixture was hydrolyzed with 1 *N* hydrochloric acid. Paper ionophoretic examination of the hydrolysate showed three spots which were 3-methylcytosine (IXb), 3-methyluracil (VIII), and N^4-methylcytosine (IIIb). The conversion of IXb to IIIb was about 30%, whereas the conversion of IVb or IIIb to IXb and VIII was ~45%. Though these data attest to the reversibility of the rearrangement, they suggest that the conversions of VIb → Vb and/or of IVb → Vb were not complete.

Experimental[13]

N^4-Methylcytosine (IIIb).—Three grams of 4-thio-2-pyrimidinone[5] was dissolved in 100 ml. of methanol previously saturated with methylamine at 0°, and the solution was heated at 105° for 20 hr. in a sealed cylinder. After cooling, the crystals (2.7 g.) were separated by filtration, and recrystallized from water giving prisms, m.p. 277–280°, lit.[4a] 275–278°; ultraviolet absorption: λ_{max} 267 mμ in water (ϵ_{max} 8600), 277 in 1 *N* hydrochloric acid (11,700), 285 in 0.1 *N* sodium hydroxide (9250).

N^4-Acetyl-N^4-methylcytosine (IVb).—A solution of 0.6 g. of IIIb in 3.0 ml. of acetic anhydride and 1.0 ml. of acetic acid was refluxed for 3 hr. After concentration of the solution to dryness under reduced pressure, the resulting solid (0.8 g.) was washed with methanol and recrystallized from ethanol, m.p. 193–194°; ultraviolet absorption properties: in water, maxima at 296, 256, and 212 mμ, (ϵ_{max} 6530, 9300, and 14,500, respectively); in 1 *N* hydrochloric acid, maxima at 309, 245, and 212.5 mμ (ϵ_{max} 12,900, 4670, and 10,500, respectively).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.30; H, 5.32; N, 25.34.

When IVb was allowed to remain overnight in 1 *N* hydrochloric acid at room temperature, the ultraviolet absorption spectrum changed to that of IIIb in acid. In 1 *N* sodium hydroxide the hydrolysis was rapid and complete within 10 hr., giving a spectrum similar to that for IIIb in base. No formation of uracil was observed in either case.

Reaction of IIIb with Acetic Anhydride–Acetic Acid and Formation of 3-Methyluracil (VIII).—A solution of 1.0 g. of IIIb in 10 ml. of acetic anhydride and 2.0 ml. of acetic acid was refluxed for 24 hr. The resulting brown solution was concentrated *in vacuo* to a sirup, treated with ethanol and concentrated again to a sirup. This procedure was repeated twice, and the final amorphous solid was triturated with ethanol and filtered. The solid, 0.5 g., showed an absorption spectrum identical with that for IVb and, after one crystallization from ethanol, gave 0.4 g. of IVb (identified by absorption spectrum and mixture melting point with authentic material described above).

The dark brown filtrate was concentrated *in vacuo* to a sirup. Paper chromatography of this sirup showed two spots, R_f

(8) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).

(9) (a) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1348 (1962); (b) T. Ueda and J. J. Fox, *J. Am. Chem. Soc.*, **85**, 4024 (1963).

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(11) D. J. Brown in "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, p. 329.

(12) R. Duschinsky, T. Gabriel, J. J. Fox, and M. Hoffer, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 18O.

(13) All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are corrected. Ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, Model 15. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

= 0.60 and 0.90, in *n*-butyl–alcohol–water (86:14). Compound IVb had R_f 0.60 in this solvent system. The substance (VIb) having R_f 0.90 showed an ultraviolet absorption maximum at 275 mμ in water, which shifted to 318 mμ on addition of alkali. Acidification gave a maximum at 308 mμ. The sirup was taken up in 50 ml. of 1 *N* hydrochloric acid and allowed to stand overnight at room temperature. The solution was concentrated *in vacuo* to dryness, the residue was taken up in 30 ml. of water and applied to a column of Dowex 50 (H^+ 2.2 × 15 cm.) resin, and washed with water. The washings were collected in 70-ml. fractions. Fractions 2 and 3, having an absorption maximum at 260 mμ were combined and concentrated *in vacuo* to dryness. The residual semisolid was taken up in ethanol, the insoluble material was removed by filtration, and the filtrate was concentrated *in vacuo*, whereupon crystals formed, m.p. 163–169°. Recrystallization from ethyl acetate gave 0.1 g. of 3-methyluracil (VIII), m.p. 177–179° (lit.[6] m.p. 174–175°); mixture melting point with authentic material (m.p. 177–178°) was 177–179°. The ultraviolet absorption properties are identical to those reported.[7] The infrared spectrum was also identical with that of an authentic sample.

The column was then eluted with 1 *N* hydrochloric acid and fractions containing IIIb were obtained. The presence of trace amounts of 3-methylcytosine (IXb) was observed in the fractions collected after IIIb was eluted, although the separation was not complete.

The Reaction of IVb in Acetic Anhydride and/or Acetic Acid.—Compound IVb (*ca.* 30 mg. each) was dissolved in 5 ml. of acetic anhydride, or acetic acid, or acetic anhydride–acetic acid (2:1) and refluxed for 20 hr. An aliquot of each reaction solution was applied to paper chromatography (*n*-butyl alcohol–water, 86:14). Only the reaction of IVb in acetic acid–acetic anhydride showed the presence of a spot at R_f 0.9, along with the R_f 0.60 spot of the starting material. This reaction solution was concentrated to dryness and the residue was dissolved in 3 ml. of 1 *N* hydrochloric acid and allowed to stand for 2 hr. at 45°. An aliquot of the solution was examined by paper electrophoresis (pH 5.0, 0.1 *M* ammonium acetate, 800 v. for 2 hr.). Three spots were obtained migrating at −1.0, −5.9, and −13.5 cm. (VIII, IIIb, and IXb, respectively, as identified by spectral determination). From the spectral calculations *ca.* 45% of IVb was shown to be converted to VIII and IXb in the ratio of 3:1.

Acetylation of 3-Methylcytosine (IXb) Followed by Acid Hydrolysis.—3-Methylcytosine hydrochloride[5a] (0.5 g.) and anhydrous sodium acetate (0.2 g.) were suspended in 3.0 ml. of acetic anhydride and shaken for 4 hr. or refluxed for 1 hr. After cooling, the precipitate was removed by filtration, and the filtrate was concentrated *in vacuo* to a sirup (VIb). This sirup showed a single spot at R_f 0.9 in *n*-butyl alcohol–water (86:14) paper chromatography. The ultraviolet absorption maximum in water was at 275 mμ. On addition of 1 drop of 30% sodium hydroxide in the 3-ml. cuvette, the maximum shifted to 318 mμ, and acidification of the solution showed a new maximum at 308 mμ. The sirup was dissolved in 10 ml. of 1 *N* hydrochloric acid and the solution was allowed to stand overnight at room temperature. The solution was concentrated *in vacuo* to dryness, the residue was dissolved in ethanol at room temprature, the insoluble material was separated by filtration, and the filtrate was concentrated *in vacuo* to a solid mass (0.2 g.), which showed the characteristic ultraviolet absorption spectra for VIII.[7] The alcohol-insoluble material was treated with boiling ethanol and separated from a small amount of insoluble material. The ethanol solution was concentrated to dryness to give 0.4 g. of a solid. Paper electrophoretic examination of this solid showed the presence of 3-methylcytosine along with a large amount of 3-methyluracil. The ratio of IXb to VIII was 1:9.

Reaction of 3-Methylcytosine with Acetic Anhydride–Acetic Acid.—The hydrochloride salt of 3-methylcytosine (IXb, 0.1 g.) and anhydrous sodium acetate (0.5 g.) was suspended in acetic anhydride (3.0 ml.) and acetic acid (2.0 ml.), and refluxed for 20 hr. The solution was concentrated *in vacuo* to a small volume, treated with ethanol, and evaporated to a sirup. The sirup was dissolved in 5 ml. of 1 *N* hydrochloric acid and kept for 18 hr. at room temperature. After concentration *in vacuo* to a solid mass, this amorphous solid was dissolved in 25 ml. of water. An aliquot of the solution was examined by paper electrophoresis (pH 5.0, 0.1 *M* ammonium acetate, 800 v., 90 min.). Three spots were obtained migrating −0.2, −4.2, and −12.0 cm. Each spot was excised, eluted with 40 ml. of water, and examined spectrophotometrically. From the comparison of the migration of authentic materials and ultraviolet absorption spectra, the spots were characterized as 3-methyluracil (−0.2), N^4-methylcytosine (−4.2), and 3-methylcytosine (−12.0 cm.).

The ratio of formation of 3-methyluracil, 3-methylcytosine, and N^4-methylcytosine was approximately 1.6:1.0:1.0, respectively. These data show that ~30% of 3-methylcytosine was converted to N^4-methylcytosine (IIIb). The water solution of the acid hydrolysate was further applied to a column of Dowex 50 (H^+ form, 2.5 × 12 cm.), washed with water, and eluted with 0.5 *N* hydrochloric acid. From the water washings, fractions containing 3-methyluracil were obtained. With 0.5 *N* hydrochloric acid, fractions containing N^4-methylcytosine, which was eluted first, and 3-methylcytosine were obtained, although the separation of the latter two was not complete.

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Nucleosides. XXI. Synthesis of Some 3′-Substituted 2′,3′-Dideoxyribonucleosides of Thymine and 5-Methylcytosine[1]

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The disulfide of 3′-deoxy-3′-mercaptothymidine (VI) was synthesized by reaction of anhydronucleoside II with potassium thiobenzoate in dimethylformamide followed by removal of the protecting groups. Potassium phthalimide in dimethylformamide was shown to be a useful reagent for the conversion of a 3′-*O*-mesylthymidine (I, R = trityl) to the 3′-deoxy-3′-phthalimido derivative (VIII). This latter reaction also proceeds *via* anhydronucleoside II. Removal of the protecting groups from VIII yielded 3′-amino-3′-deoxythymidine (X). Detritylation of VIII followed by acetylation yielded XII which was thiated to the 4-thionucleoside and converted to the 3′-amino-3′-deoxy derivative (XV) of 5-methyl-2′-deoxycytidine. Under certain conditions, the 4-amino group of cytosine nucleosides was readily exchanged with *n*-butylamine to produce 4-*n*-butylamino nucleoside derivatives.

It was demonstrated in a previous study[2] that under acid-catalyzed conditions di-*O*-mesylthymidine (I, R = mesyl) is converted directly in refluxing *N*,*N*-dimethylformamide containing sodium benzoate to di-*O*-benzoylthymidine (III, R = benzoyl). This reaction was

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(2) Paper XVI in this series: J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).

shown to proceed *via* the 2,3′-anhydronucleoside[3,4] intermediate (II, R = mesyl). It was further demonstrated that II (R = mesyl) also is converted easily to III with the same reagent and reaction conditions only when benzoic acid was added to the reaction mixture. It was suggested,[2] therefore, that under acid-catalyzed conditions other appropriate nucleophiles might be introduced into the "down" configuration of the sugar moiety of anhydronucleosides (*i.e.*, II) (or their sulfonyloxy precursors, *i.e.*, I) of 1-β-D-aldosylpyrimidines bearing a 2-carbonyl function in the aglycon. The present study deals with the successful application of this rationale to the syntheses of 3′-deoxy-3′-mercaptothymidine and 3′-amino-3′-deoxythymidine as part of our program in the synthesis of nucleosides of potential biochemical interest. Preliminary reports have appeared.[5]

Reaction of II (R = trityl) with potassium thiobenzoate in dimethylformamide at reflux temperature for two hr. gave intractable material from which no definable product could be isolated. When this reaction was repeated with the addition of approximately 1 equiv. of benzoic acid, crude 5′-*O*-trityl-3′-*S*-thiobenzoate (IV) was obtained as an amorphous powder. The ultraviolet absorption spectrum of IV was similar to that for III (R = trityl)[2] as would be expected if thiobenzoate ion attacked the 3′-position of anhydronucleoside II. Detritylation of IV with acid yielded the crystalline thiobenzoate (V). Saponification of V with dilute alkali at room temperature for 1 day afforded the crystalline disulfide of 3′-deoxy-3′-mercaptothymidine (VI). Disulfide VI also was obtained by brief, hot alkaline hydrolysis of V followed by titration of the reaction solution with iodine. After the consumption of iodine ceased (~1 molar equiv. consumed), the disulfide VI crystallized from the acidified reaction solution. A molecular weight determination of VI was consistent with the disulfide structure. Attempts to isolate the thiol of VI by saponification of V were unsuccessful. The disulfide VI also was obtained by alkaline treatment of IV to afford crude VII which was probably a mixture of the 3′-thiol derivative and its disulfide. Detritylation of VII yielded the disulfide VI (see Fig. 1).

The disulfide VI exhibited an ultraviolet absorption spectrum similar to that for thymidine[6] showing that the sulfur atoms in VI were not located in the aglycon.[7] That the thiobenzoate group in IV (and thereby in V) is in the ribo (or "down") configuration is established by virtue of its synthesis from anhydronucleoside II and by analogy with the conversion of II to III under similar reaction conditions with a similar type nucleophile (benzoate).[2] Compound VI, therefore, is the 3′-deoxy-3′-mercapto analog of thymidine.

Reaction of I (R = trityl) with potassium phthalimide in dimethylformamide for 10 hr. at reflux afforded VIII as an amorphous powder. Treatment of this powder with methylamine in methanol at ~105° for

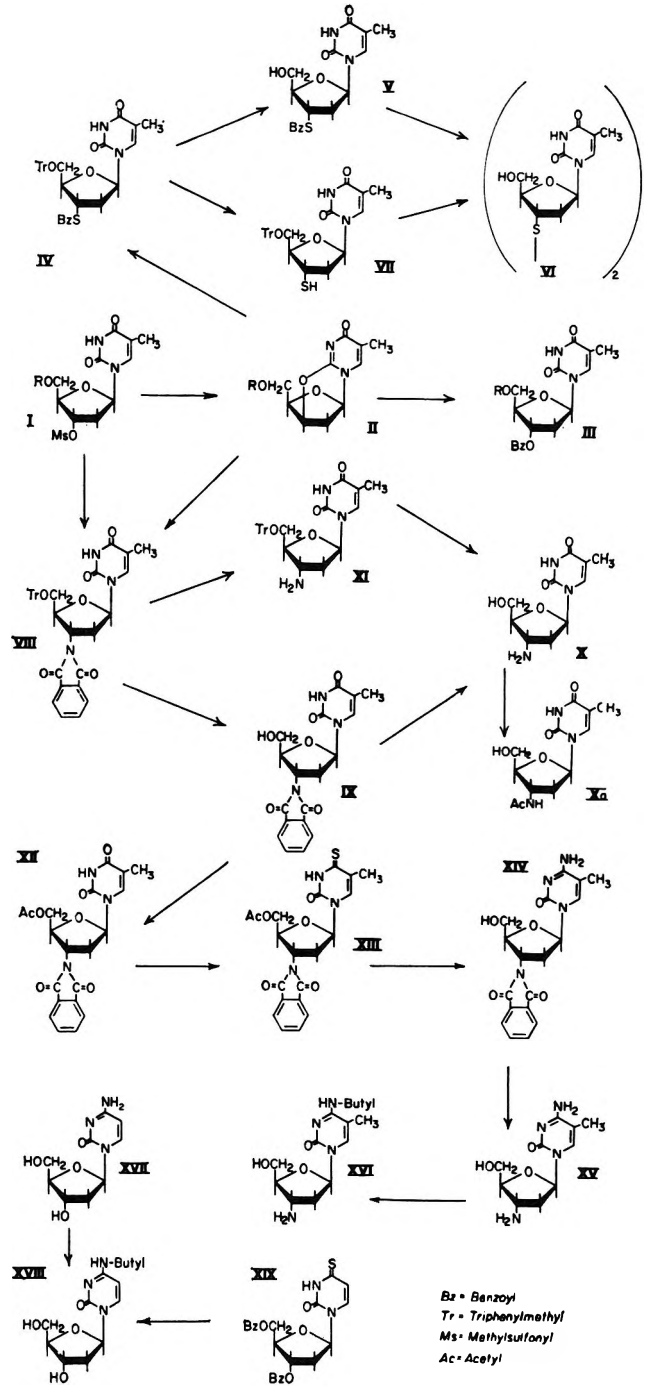

Figure 1.

20 hr. yielded XI as a sirup which was detritylated with acid to yield crystalline X in ~35% over-all yield from I. As expected, the ultraviolet absorption spectrum of X was similar to that for thymidine but differed from that for isocytidine[8] again showing that the nucleophile (phthalimido ion) had entered the sugar moiety (in VIII) and not the aglycon. An alternate synthesis of X was achieved by detritylation of VIII to afford crystalline IX which was deacylated to X. This latter procedure gave poorer yields of X. Treatment of X with acetic anhydride in water yielded the *N*-acetyl derivative (Xa).

(3) Although the term "cyclonucleoside" has been employed for naming this class of compounds, the term "anhydronucleoside"[4] is more in keeping with carbohydrate nomenclature.

(4) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959).

(5) J. J. Fox and N. C. Miller, Abstracts of the 144th National Meeting of American Chemical Society, Los Angeles, Calif., April, 1963, p. 4C; N. Miller and J. J. Fox, Abstracts of 145th National Meeting of American Chemical Society, New York, N. Y., Sept., 1963, p. 21D.

(6) J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952).

(7) Location of the sulfur atom on position 2 or 4 of the aglycon would markedly alter the ultraviolet spectrum from that for thymidine; [see D. Shugar and J. J. Fox, *Bull. soc. chim. Belges*, **61**, 293 (1952), and G. B. Elion, W. S. Ide, and G. H. Hitchings, *J. Am. Chem. Soc.*, **68**, 2137 (1946)].

(8) D. M. Brown, D. B. Parihar, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958).

As in the case of the reaction of I → III,[2] the conversion of I to VIII proceeded *via* the anhydronucleoside II. Short-term treatment of I with potassium phthalimide in dimethylformamide (120° for 10 min.) gave a high yield (~80–90%) of II. Moreover, when II was treated with potassium phthalimide in dimethylformamide with added phthalimide (10 hr., reflux), amorphous VIII was obtained which was also converted to IX. Thus it is established that the phthalimido group entered by attack at C-3′. By analogy with the synthesis of VI from II described above and the synthesis of III from II reported previously,[2] the amino group in X (and the phthalimido group in IX and VIII) must be in the "down" (ribo) configuration and X is, therefore, 3′-amino-3′-deoxythymidine, that is 1-(3′-amino-2′,3′-dideoxy-β-D-ribofuranosyl)thymine. The adenine derivative of this sugar moiety has been synthesized by Lee, *et al.*,[9] by a different route.

Compound IX served as starting material for the synthesis of the 3′-amino-3′-deoxy analog of 5-methyl-2′-deoxycytidine. Acetylation of IX yielded the blocked nucleoside (XII). Thiation of XII with phosphorus pentasulfide in pyridine yielded a yellow glass (XIII) which was heated with alcoholic ammonia to form the cytosine derivative (XIV) as a sirup. Spectral examination of the sirup (absence of absorption at 330 mμ) showed that the 4-thio group had been replaced. This sirup was not purified but was treated directly with *n*-butylamine in methanol at ~105° for 20 hr. XV was obtained in ~40% over-all yield from XII. A chromatographic examination (1-butanol–water, 86:14) of the mother liquor showed that a second major ultraviolet absorbing spot (R_f 0.87) was formed along with some fluorescent material. The ultraviolet absorbing spot (R_f 0.87) like XV (R_f 0.12) also gave a 5-methylcytidine-like spectrum.[10] This chromatographic behavior is generally similar to that shown by 5-fluoro-2′-deoxycytidine (R_f 0.29) and its *N*-*n*-butyl derivative (R_f 0.85).[11] It is highly likely, therefore, that the faster migrating component obtained by treatment of sirup XIV with butylamine in methanol at ~105° for 20 hr. is the *N*-*n*-butyl derivative (XVI) of XV. Attempts to separate and crystallize XVI were unsuccessful. However, support for the structural assignment to XVI was obtained by treatment of the closely related 2′-deoxycytidine (XVII) with *n*-butylamine in methanol in a manner similar to that used in the synthesis of XV and XVI. Only a trace of XVIII was obtained. However, when 1 equiv. of ammonium acetate was added to this reaction (impure XIV should contain this salt) the proportion of XVIII formed increased to about one-third. When the hydrochloride salt of XVII was employed in this reaction, the yield of XVIII isolated as the picrate salt was increased to 90%. For comparative purposes, XVIII was prepared from XIX[11,12] by refluxing the latter in methanolic *n*-butylamine. It is thus evident that cytosine-type nucleosides can undergo amine exchange which may provide a simpler route for the synthesis of *N*-substituted cytosine nucleosides.

This amine-exchange reaction with nucleosides has its counterpart in pyrimidine chemistry. Whitehead and Traverso[13] have shown that certain 4- or 6-aminopyrimidines will exchange with amine hydrochlorides under rigorous conditions (165–170° for several hours) to yield 4- or 6-*N*-substituted aminopyrimidines. Curran and Angier[14] recently have demonstrated that certain 4- and 6-aminopyrimidines will undergo a similar amine-exchange reaction when heated with alkylammonium acetates.

Experimental[15]

Disulfide of 3′-Deoxy-3′-mercaptothymidine (VI).—2,3′-Anhydro-1-(5′-*O*-trityl-2′-deoxy-β-D-lyxosyl)thymine[2] (II, R = trityl; 4.65 g.) was refluxed under nitrogen for 1.5 hr. in 500 ml. of dimethylformamide with 10.5 g. of potassium thiobenzoate and 1.22 g. of benzoic acid. The solvent was removed *in vacuo* and the residue treated with 2 l. of water. After filtration, the amorphous tan solid (crude IV) was washed well with water. The tan solid was dissolved in 100 ml. of 95% ethanol, treated with 3 ml. of 10 *N* sodium hydroxide, refluxed for about 5 min., and allowed to remain at room temperature overnight. Upon neutralization of the reaction solution with acetic acid, precipitation of an amorphous solid occurred. The volume of the reaction mixture was reduced *in vacuo* to about 30 ml. and water was added to complete precipitation. The solids were collected on a filter and washed well with water. The residue was dissolved in chloroform and dried over sodium sulfate. After filtration, the filtrate was concentrated to about 50 ml., to which 150 ml. of ether was added with stirring to prevent the formation of a gum. Detritylation of crude VII was effected by bubbling hydrogen chloride into the cooled ether–chloroform mixture to saturation during which time precipitation occurred. After 40 min. in the ice bath, solvents were removed *in vacuo* and most of the remaining hydrogen chloride removed azeotropically with benzene. Trituration of the sirupy brown residue several times with ether extracted the triphenylcarbinol leaving an acidic brown sirup. This sirup was dissolved in ethanol and neutralized with triethylamine after which crystallization occurred (1.0 g.), m.p. 230–235°. A second crop gave 0.2 g. with a similar melting point. Average yields in this over-all reaction from II were ~45%. Recrystallization from 70% ethanol gave minute crystals, m.p. 239–241.5°. For analytical purposes, further purification was achieved by dissolving the solid in dilute sodium hydroxide followed by careful neutralization with dilute acetic acid to turbidity. After several hours, precipitation of VI was completed, m.p. 245.5–246.5°, $[\alpha]^{23}D$ −7 ± 2° (*c* 0.61, 0.1 *N* sodium hydroxide). Ultraviolet absorption properties follow: at pH 1–7, maximum at 267 mμ (ϵ_{max} 10,900), minimum at 234 mμ (ϵ_{min} 2700); in 0.1 *N* sodium hydroxide, maximum at 261.5 mμ (ϵ_{max} 8100), minimum at 244 mμ (ϵ_{min} 5200).

Anal. Calcd. for $C_{20}H_{26}N_2O_8S_2$: C, 46.68; H, 5.09; N, 10.89; S, 12.46; mol. wt., 515. Found: C, 46.34; H, 5.78; N, 10.77, 10.84; S, 12.32; mol. wt., 510 ± 50.[16]

3′-Deoxy-3′-thio-*S*-benzoylthymidine (V).—The amorphous tan solid (IV), obtained above from 0.005 mole of II (R = trityl), was dissolved in 10 ml. of chloroform and the stirred solution treated with ether (100 ml.). The stirred mixture was saturated with hydrogen chloride with cooling and the mixture was allowed to remain for 1 hr. at ~5°. Solvents were removed *in vacuo* (bath temperature, 35–40°); benzene was added and removed three times leaving a thin brown sirup which still contained traces of hydrogen chloride. Cyclohexane (100 ml.) was added and the resulting solution was separated by filtration from a small amount of insolubles. The yellow filtrate was evaporated

(9) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 1906 (1961).

(10) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *ibid.*, **81**, 178 (1959).

(11) I. Wempen, R. Duschinsky, L. Kaplan, and J. J. Fox, *ibid.*, **83**, 4755 (1961).

(12) The authors are indebted to Miss I. Wempen for a sample of XIX.

(13) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **82**, 3971 (1960).

(14) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **28**, 2672 (1963).

(15) All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(16) The authors are indebted to Dr. A. Motchane of Hoffmann–LaRoche, Inc., Nutley, N. J., for the determination of this molecular weight. The thermoosmotic method used here depends on efficient equilibration of solvent and solution. Since the solvent used (*N*,*N*-dimethylformamide) has a low vapor pressure, equilibration is slow and the variations are, therefore, large.

to a thin sirup which was treated with a *minimal* amount of ethanol to cause solution. The solution was treated with cyclohexane to turbidity. Crystallization occurred as needles, which were collected on a filter and washed with cyclohexane to yield 0.7 g., m.p. 90°, with resolidification at ~120°, and final melting at 170–172°. One recrystallization from ethanol gave pure V, m.p. 179–180°, $[\alpha]^{23}D$ +14° (*c* 0.29, ethanol). Ultraviolet absorption properties in ethanol follow: maxima at 267.5 and 246.5 mμ, minima at 251 and 224 mμ, shoulder at 240 mμ.

Anal. Calcd. for $C_{15}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73; S, 8.85. Found: C, 56.80; H, 4.96; N, 7.61; S, 8.71.

Synthesis of VI from V.—Compound V (100 mg.) was treated with 10 ml. of 0.1 *N* sodium hydroxide and allowed to remain overnight with stirring at room temperature. The reaction solution was treated with dilute acetic acid until precipitation began. After cooling to complete crystallization, the product was collected, 65 mg., m.p. 242–244°. A mixture melting point with VI obtained above did not show any depression.

Compound V also may be converted to VI by saponification followed by titration with iodine. V (100 mg.) was treated with 5 ml. of water and 9 ml. of 0.1 *N* sodium hydroxide. The mixture was warmed (with stirring) until solution occurred. The solution was titrated immediately with an aqueous iodine solution, ~0.5 *N* (sodium iodide–iodine, 2:1 by weight), whereupon approximately 0.75 equiv. of iodine was consumed. (The low consumption of iodine is probably due to the fact that some disulfide formation had occurred in the prior alkaline de-esterification.) The resulting clear solution was treated with dilute acetic acid until turbidity was reached. The product, 54 mg., m.p. 235–240°, was purified in a manner similar to that described above. The recovery was almost quantitative, yielding product with m.p. 244–246°.

3′-Deoxy-3′-phthalimidothymidine (IX).—Compound I (R = trityl, 2.4 g.)[17] was refluxed for 10 hr. in 300 ml. of dimethylformamide with 3.7 g. of potassium phthalimide. Solvents were removed *in vacuo* and the residual brown gum was extracted with chloroform (500 ml.). The insolubles were filtered and discarded and the chloroform filtrate was washed twice with 250-ml. portions 0.1 *N* sodium hydroxide. Sodium chloride was added to the chloroform–water mixture to facilitate separation of the emulsion into distinct layers. The chloroform layer was finally washed with water three times and concentrated to a thick yellow gum (compound VIII). Crude VIII was refluxed for 10 min. with 100 ml. of ethanol and 5 drops of concentrated hydrochloric acid. Upon removal of solvent precipitation of a tan granular solid began. The residue was triturated with ether and the solid collected, 1 g., softening at 180° and melting at 235–240°. Treatment with ethanol removed the color and gave 0.65 g. of a colorless solid, m.p. 265–266°. Recrystallization from ethanol gave m.p. 269–269.5°, $[\alpha]^{22}D$ −45° (*c* 0.40, dimethylformamide). Ultraviolet absorption properties in ethanol follow: maxima at 266 and 242 mμ, minima at 248 and 239 mμ, shoulder at 302 mμ.

Anal. Calcd. for $C_{18}H_{17}N_3O_6$: C, 58.21; H, 4.61; N, 11.31. Found: C, 57.95; H, 4.90; N, 11.31.

Isolation of Intermediate II (R = trityl).—Compound I (R = trityl, 1.12 g.) in 200 ml. of dimethylformamide and 1.85 g. of potassium phthalimide was heated with stirring to 120°. When this temperature was reached, the reaction was cooled to precipitate salts. After filtration, the filtrate was evaporated to dryness, the residue extracted with chloroform, and the chloroform extract evaporated to a thin yellow sirup. The sirup was triturated with ether and stirred. The mixture was cooled and the crystals separated, 0.75 g., m.p. 231–232°. An additional 0.1 g. (same melting point) was obtained from the mother liquor. The ultraviolet spectrum and melting point properties were identical with those for anhydronucleoside II (R = trityl).[2]

3′-Amino-3′-deoxythymidine (X).—5′-*O*-Trityl-3′-*O*-mesylthymidine (I, R = trityl; 5.2 g.) was refluxed for 12 hr. with 10 g. of potassium phthalimide in 500 ml. of dimethylformamide. Crude VIII (5.3 g.), obtained by the same procedure as described above, was treated at 105° with 17 ml. of methylamine[18] in 100 ml. of methanol for 20 hr. The amber reaction mixture was evaporated to a semicrystalline residue and extracted with water. The aqueous extracts were discarded and the oily residue was treated with 100 ml. of ethanol and enough concentrated hydrochloric acid to neutralize the residual methylamine. Four drops of acid were then added; the solution was refluxed for 8 min. The acidic solution was concentrated *in vacuo* after which crystallization began. Benzene was added and removed *in vacuo* a few times to remove water and as much acid as possible. The crystalline residue was triturated with ethanol and ether. The reddish crystals (hydrochloride of X), 1.2 g., m.p. 250° dec. (efferv.), gave a thymidine-like ultraviolet absorption spectrum. The hydrochloride of X was absorbed on Dowex 50 (H^+), washed with water, and eluted with 1 *N* ammonium hydroxide. The eluates were evaporated to dryness, whereupon colorless crystals, 0.7 g., m.p. 180–182°, separated. Pure material was obtained by dissolving a sample in methanol followed by concentration of the solution to a smaller volume, whereupon crystallization began. The mixture was allowed to remain at room temperature until crystallization was complete. The sample was collected and washed with ethanol, m.p. 187–187.5°, $[\alpha]^{23}D$ +20° (*c* 0.64, water). Ultraviolet absorption properties follow: in 0.1 *N* hydrochloric acid, maximum at 265 mμ (ϵ_{max} 9400), minimum at 233 mμ (ϵ_{min} 2300); at pH 7.53, maximum at 266.5 mμ (ϵ_{max} 9300), minimum at 233 mμ (ϵ_{min} 1900); in 0.1 *N* sodium hydroxide, maximum at 266.5 mμ (ϵ_{max} 7400), minimum at 244 mμ (ϵ_{min} 4400).

Anal. Calcd. for $C_{10}H_{15}N_3O_4$: C, 49.78; H, 6.26; N, 17.41. Found: C, 49.85; H, 6.09; N, 17.20.

3′-Acetylamino-3′-deoxythymidine (Xa).—X (500 mg.) was added to 3 ml. of water and treated with 0.4 ml. of acetic anhydride. The stirred solution formed a precipitate. After 10 min., the precipitate (460 mg., m.p. 108–116°) was removed. The mother liquor yielded an additional 90 mg. The combined crops were dissolved in a minimal amount of hot water. Upon cooling, a precipitate formed which was dried at 60° *in vacuo* for 4 days, m.p. 183–184°, with some softening at 115°, $[\alpha]^{23}D$ +23° (*c* 0.77, water). Ultraviolet properties in water follow: maximum at 266 mμ, minimum at 234.5 mμ.

Anal. Calcd. for $C_{12}H_{17}N_3O_5 \cdot H_2O$: C, 47.83; H, 6.35; N, 13.95. Found: C, 47.27; H, 6.33; N, 14.25.

5′-*O*-Acetyl-3′-deoxy-3′-phthalimidothymidine (XII).—Compound IX (2.1 g.) was treated with 40 ml. of anhydrous pyridine and 6 ml. of acetic anhydride and allowed to remain at room temperature overnight. Solvents were evaporated *in vacuo* and the thick sirup was triturated repeatedly with ether. A white granular solid was obtained, 1.9 g., m.p. 230–237°. After two recrystallizations from ethanol (with treatment with charcoal), pure material was obtained, m.p. 238–239°, $[\alpha]^{23}D$ −40° (*c* 0.39, dimethylformamide). Ultraviolet properties in ethanol follow: maxima at 265 and 242 mμ, minima at 248 and 239 mμ.

Anal. Calcd. for $C_{20}H_{19}N_3O_7$: C, 58.11; H, 4.63; N, 10.16. Found: C, 57.78; H, 4.95; N, 9.79.

3′-Amino-2′,3′-dideoxy-5-methylcytidine (XV).—Crystalline XII was heated with 11 ml. of reagent grade pyridine and 0.9 g. of "reactive" phosphorus pentasulfide.[19] When reflux temperature was reached, 0.02 ml. of water was added and the reaction mixture refluxed for 2.5 hr. The brown reaction mixture was cooled and decanted from a thick green oil, and the decantate was evaporated to about 3 ml. and treated with water. The insolubles were filtered and washed well with water. The solids were extracted with chloroform and filtered. The chloroform filtrate was dried with sodium sulfate and evaporated to a thin yellow sirup which contained some residual pyridine. The residual pyridine was removed azeotropically by codistillation *in vacuo* with water. The sirup was taken to dryness (yellow glass, 950 mg., XIII) by codistillation with benzene. Methanolic ammonia, 100 ml., was added to glass XIII and the solution was heated in a bomb at 105° for 22 hr. The amber sirup, after evaporation of solvents, was treated with methanol and filtered from some insoluble material. The solution was evaporated to dryness *in vacuo* and the residual brown sirup was treated with 50 ml. of methanol containing 10 ml. of *n*-butylamine in a bomb for 20 hr. at 105°. After removal of solvents the sirupy residue was triturated with ether, which gave a yellow hygroscopic flocculent solid. This solid was dissolved in water; the solution was extracted three times with chloroform. The aqueous fraction was concentrated to a slightly yellow amorphous solid which was treated with 10 ml. of methanol and allowed to remain at room temperature for a few days. Clusters of needles (XV) were obtained, 260 mg., m.p. 200–208° dec. (efferv.). This solid showed only one spot by paper chromatography (1-

(17) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(18) L. Goldman and J. W. Marsico, *J. Med. Chem.*, **6**, 413 (1963).

(19) Obtained from Monsanto Chemical Co., St. Louis, Mo.

butanol–water, 86:14). The mother liquor from this solid was saved for later examination. Crude XV was then absorbed on Dowex 50 (H^+), washed with water, and then eluted with 1 *N* ammonium hydroxide. The basic eluates were combined and concentrated to dryness. Ethanol was added and removed several times. The colorless sirup was treated with a few milliliters of ethanol and allowed to remain at room temperature overnight. XV was obtained as colorless needle clusters, 200 mg. (40% from XII), m.p. 229–230° with yellowing at 217°, $[\alpha]^{23}D$ +47° (*c* 0.35, water). Ultraviolet properties follow: in 0.1 *N* hydrochloric acid, maximum at 285 mμ (ϵ_{max} 11,900), minimum at 243.5 mμ (ϵ_{min} 1200); at pH 7.53, maximum at 276 mμ (ϵ_{max} 8300), minimum at 254 mμ (ϵ_{min} 5100), shoulder at 240 mμ (ϵ 6700); in 0.1 *N* sodium hydroxide, maximum at 277.5 mμ (ϵ_{max} 8200), minimum at 254 mμ (ϵ_{min} 4600), shoulder at 240 mμ (ϵ_{sh} 6300).

Anal. Calcd. for $C_{10}H_{16}N_4O_3$: C, 49.98; H, 6.71; N, 23.32. Found: C, 50.43; H, 6.86; N, 22.90.

The methanolic mother liquor from crude XV was examined chromatographically in two solvent systems (ascending method, Whatman No. 1 paper, 1-butanol–water, 86:14, and 1-butanol–ammonium hydroxide (1 *N*), 86:14), each of which showed two ultraviolet absorbing spots along with some fluorescence. The lower spot corresponded to XV. The upper spot (assumed to be the 4-*N*-*n*-butyl derivative, XVI) was excised and showed a cytidine-like spectrum. A crystalline sample of XVI could not be isolated.

Picrate of 4-*N*-*n*-Butyl-2′-deoxycytidine (XVIII) from 2′-Deoxycytidine (XVII).—The hydrochloride salt of 2′-deoxycytidine (XVII, 1.0 g.) and 12 ml. of *n*-butylamine in 60 ml. of methanol was heated in a sealed tube at 105° for 20 hr. The tube was cooled and opened, and the contents were evaporated to dryness. The residue was partitioned between water and chloroform, the organic layer was discarded, and the aqueous layer was concentrated to dryness. The residue was examined by paper chromatography (1-butanol–water, 86:14, ascending system, Whatman No. 1 paper). The major spot (R_f 0.83) corresponded to that for *N*-*n*-butyl-2′-deoxycytidine (see below). A trace spot corresponding to 2′-deoxycytidine (R_f 0.25) was also present. The residue was then dried azeotropically with benzene. The residue was dissolved in ethanol and treated with a saturated solution of picric acid in methanol. Concentration of the solution to a small volume and addition of water yielded the crystalline picrate (1.65 g.) which was filtered and washed with water, cold alcohol, and ether. One recrystallization from 95% ethanol gave pure material, m.p. 165–166° dec., which was not depressed when admixed with an authentic sample of picrate of XVIII.

When 2′-deoxycytidine was treated with *n*-butylamine in a manner similar to that described above, only a faint trace spot of the *N*-*n*-butyl derivative (XVIII) was detected chromatographically.

Treatment of 2′-deoxycytidine with *n*-butylamine in methanol plus 1 equiv. of ammonium acetate in a sealed tube at 105° for 20 hr. yielded a mixture of products which by chromatographic examination showed two spots corresponding to starting material XVII and product XVIII in the proportion of 2:1, respectively.

Picrate of 4-*N*-*n*-Butyl-2′-deoxycytidine (XVIII) from XIX.—XIX[11] (0.8 g.) was refluxed in 40 ml. of methanol containing 6 ml. of *n*-butylamine for 1 day. The solution was concentrated to dryness and fractionated between chloroform and water. The almost colorless aqueous layer was concentrated to dryness and the residue azeotroped with benzene. The residue was dissolved in ethanol and treated with alcoholic picric acid. The picrate salt crystallized (0.4 g.), m.p. 157–159°. After recrystallization from ethanol, needle clusters were obtained, m.p. 165–166° dec.

Anal. Calcd. for $C_{19}H_{24}N_8O_{11}$: C, 44.54; H, 4.72; N, 16.39. Found: C, 44.90; H, 4.69; N, 16.38.

Acknowledgment.—The authors are indebted to Dr. George B. Brown for his warm and continued interest.

The Anomeric 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-D-glucopyranoses

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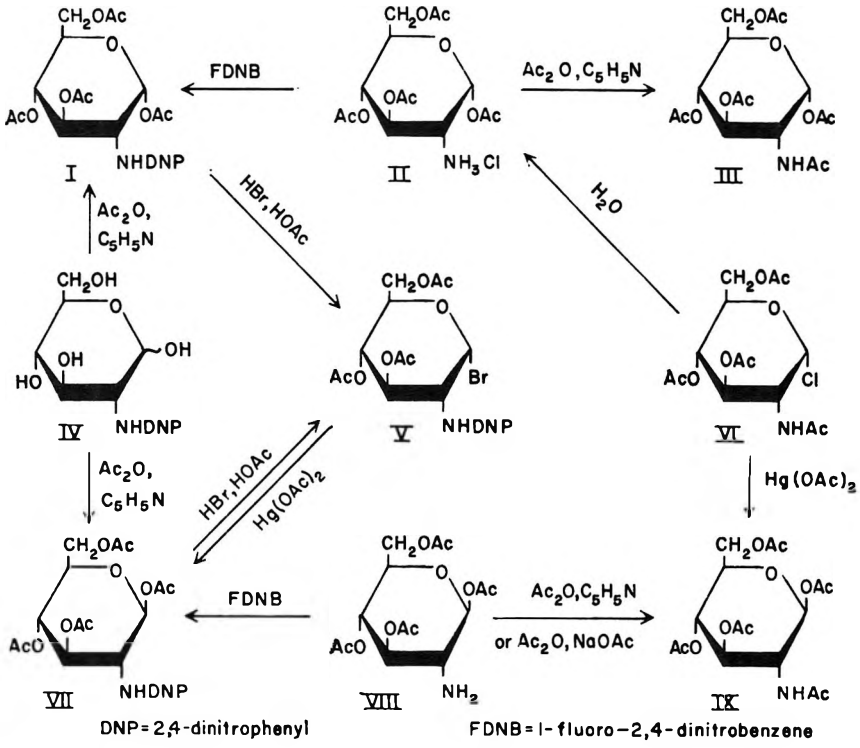
1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α- and -β-D-glucopyranose (I and VII) were prepared by several different procedures. The evidence of nuclear magnetic resonance, as well as route of synthesis, indicate that the isomer having m.p. 218–219° and $[\alpha]D$ +9.1° (chloroform) is the α-D anomer (I), and the isomer having m.p. 167.0–167.5° and $[\alpha]D$ +50° (chloroform) is the β-D anomer (VII), contrary to predictions based on the Hudson rules of rotation. The relative difference between the specific rotations of I and VII increases at shorter wave lengths. The corresponding 2-acetamido analogs (III and IX) of I and VII give plain rotatory dispersion curves in agreement with the Hudson rules at all wave lengths between 300 and 700 mμ.

Conflicting reports exist in the literature for the physical constants of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I) and its β-D anomer (VII). A compound of unspecified anomeric configuration was reported by Kent[1,2] to have m.p. 159–160° and $[\alpha]D$ +73° (chloroform), while Lloyd and associates[3,4] give m.p. 166–167°, $[\alpha]D$ +47.9° (chloroform) for a compound described as I. It has been suggested by Wang and Tai[5] that Lloyd's product[3] is in fact the β-D anomer (VII), and the Chinese workers describe a product, m.p. 214–215°, $[\alpha]D$ +12° (chloroform), which they consider to have the structure I; this assignment would involve a violation of Hudson's empirical rule[6] that the more dextrorotatory isomer of a pair of anomeric D sugar derivatives has the α-D-configuration.

This work describes the preparation of compounds I and VII by various independent routes (Chart I). The homogeneity of the product has been rigorously established with a thin layer chromatographic technique by which the anomers are well differentiated. The structures of the products are defined by the route of synthesis and are supported by nuclear magnetic resonance data. All evidence indicates that 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I) has m.p. 218–219° and $[\alpha]D$ +9.1° (chloroform), and the β-D anomer (VII) has m.p. 167.0–167.5° and $[\alpha]D$ +50° (chloroform). This direct contradiction[5] of Hudson's rule[6] holds true over a range of observed wave lengths.

(1) P. W. Kent, *Research* (London), **3**, 427 (1950).
(2) P. W. Kent, G. Lawson, and A. Senior, *Science*, **113**, 354 (1951).
(3) P. F. Lloyd and M. Stacey, *Tetrahedron*, **9**, 116 (1960).
(4) P. F. Lloyd and G. P. Roberts, *J. Chem. Soc.*, 2962 (1963); *cf.* related work on disaccharide derivatives, P. F. Lloyd and G. P. Roberts, *Proc. Chem. Soc.*, 250 (1960).
(5) Y. Wang and H.-I. Tai, *Acta Chim. Sinica*, **24**, 368 (1958).
(6) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909); *Advan. Carbohydrate Chem.*, **3**, 15 (1948).

CHART I



A definitive synthesis of I was made starting from the very stable 1-halo sugar, 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (VI).[7,8] A synthesis of I by Wang and Tai[5] had utilized the labile bromide analog[9] of VI. Treatment of VI in wet chloroform with a trace of acid[10] gave 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride (II) in high yield; the reaction presumably involves an *ortho*-acetyl amide intermediate[10] and results in stereospecific formation of the α-D anomer. The anomeric configuration of the free base of II has been proved[11] to be α-D by acetylation under nonequilibrating conditions to give the known[12,13] 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (III). The hydrochloride salt II used in this work could likewise be converted into III by acetylation with acetic anhydride in excess pyridine. *N*-Arylation of II with 1-fluoro-2,4-dinitrobenzene in the presence of sodium bicarbonate gave I in approximately 70% yield. This product could be obtained in two dimorphous forms, m.p. 218–219° and m.p. 191°, having different X-ray powder diffraction patterns. The low melting point form spontaneously recrystallized a few degrees above its melting point to give the high melting point form. The two forms had identical specific rotations and chromatographic mobilities, and gave very closely similar infrared spectra. On thin layer chromatography the compound I gave a single, fast-moving yellow zone, which was well resolved from the slower moving β-D anomer (VII), and from minor side products formed in the reaction.

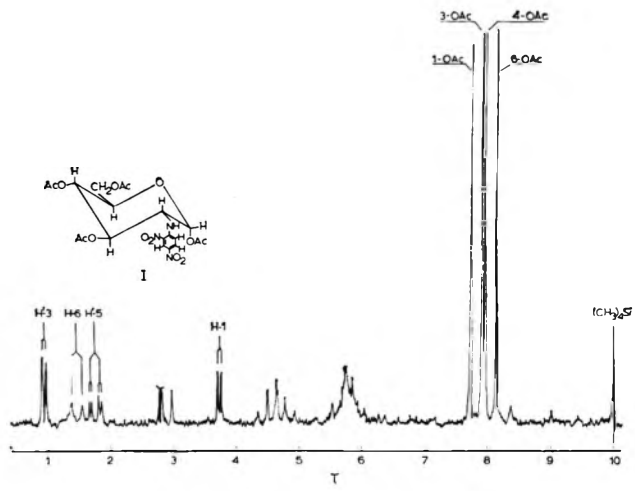


Fig. 1.—Nuclear magnetic resonance spectrum of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I) in $CHCl_3$–$CDCl_3$, Varian HR-60 n.m.r. spectrometer. The solvent peak at τ 2.72 has been omitted.

Direct acetylation of carefully purified 2-deoxy-2-(2,4-dinitroanilino)-D-glucose[14] (IV) with acetic anhydride in excess pyridine gave I in high yield,[5] indicating that IV has the α-D-configuration. Preparation of IV from 2-amino-2-deoxy-D-glucose[3] gives a nearly quantitative yield of crude product, but after purification it was seldom found possible to obtain the product in more than 35% yield, as observed by others.[3] Acetylation of the dried crude product, however, gave I in good yield by direct crystallization; the mother liquors contained three additional yellow substances migrating more slowly than I on thin layer chromatograms. The four components in the crude acetylated product could be readily separated by silicate extrusion chro-

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(8) D. Horton and M. L. Wolfrom, *ibid.*, **27**, 1794 (1962).
(9) F. Micheel and H. Petersen, *Ber.*, **92**, 298 (1959).
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(11) F. Micheel, F.-P. van de Kamp, and H. Wulff, *ibid.*, **88**, 2011 (1955).
(12) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **18**, 77 (1899).
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(14) K. H. Meyer and D. E. Schwartz, *Helv. Chim. Acta*, **33**, 1651 (1950); E. F. Annison, A. T. James, and W. T. J. Morgan, *Biochem. J.*, **48**, 477 (1951).

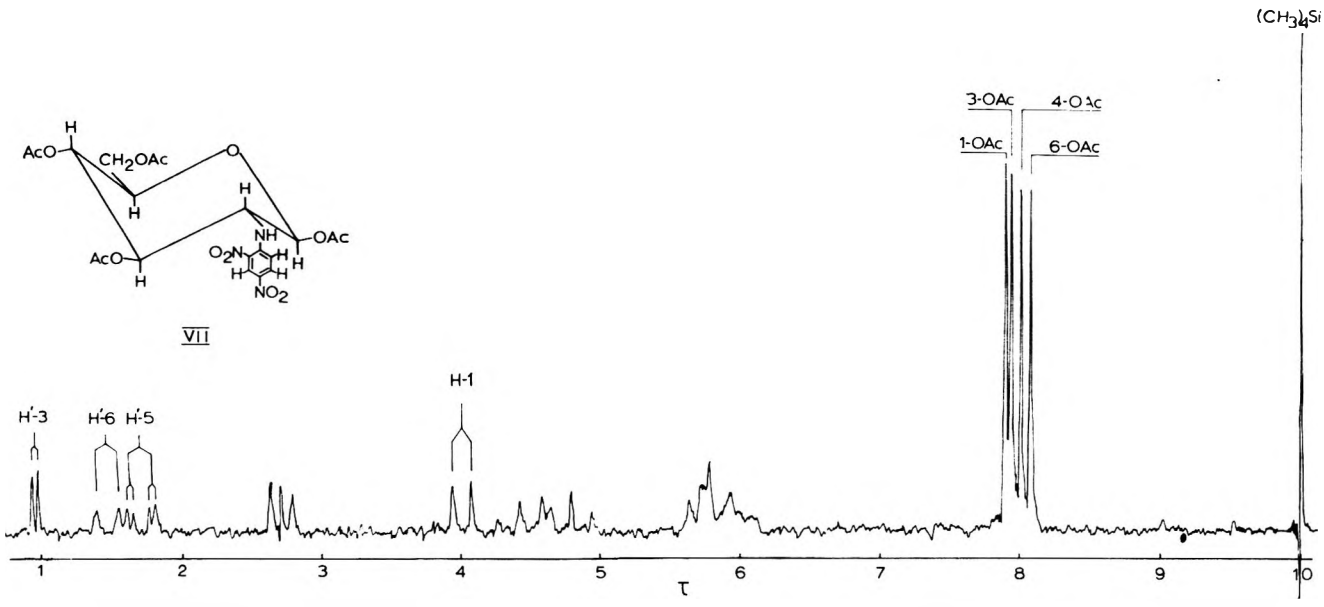

Fig. 2.—Nuclear magnetic resonance spectrum of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranose (VII) in $CDCl_3$, Varian A-60 n.m.r. spectrometer.

matography, and were all obtained crystalline. The fastest migrating component had m.p. 217–219°, and was identical with I prepared by the definitive route. The component which followed I had m.p. 166°, and was shown to be identical with the anomer of I (VII), which had been prepared by a definitive route (see below). The other two slow-moving components, m.p. 200° and 188°, were apparently tri-*O*-acetyl derivatives of IV, and were not further investigated.

The reaction of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose[15] (VIII), or its hydrochloride salt, with 1-fluoro-2,4-dinitrobenzene provided a definitive route to 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranose (VII). Either the free base or the salt underwent *N*-arylation to give VII, having m.p. 167–167.5°, $[\alpha]_D$ +50° (chloroform). A product having similar constants, and prepared similarly from the hydrochloride (VIII-HCl) of the compound of Bergmann and Zervas[15] had been described[3] as the α-D anomer. Acetylation of either of the starting materials (VIII or VIII-HCl) used in the present work, under nonequilibrating conditions (acetic anhydride and excess pyridine in the cold) gave the known[12,13] 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (IX) in high yield; this establishes the anomeric configuration of the tetra-*O*-acetyl derivatives used, and confirms the observation of Bergmann and Zervas[15] on the free base VIII.

The highest yield of VII, essentially quantitative, was obtainable by treatment of 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide[3,8] (V) with mercuric acetate[16] in acetic acid, and no side products were detectable by thin layer chromatography. The glycosyl bromide derivative V[3] could be prepared, in almost quantitative yield from I, VII, or the crude mixture from acetylation of IV, by treatment with hydrogen bromide in acetic acid.

A facile preparative route to 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (IX) was found in the reaction of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[7,8] (VI) with mercuric acetate[16] in acetic acid. This route gives IX in high yield in three stages,[8] and provides a useful alternative to the four-step procedure of Bergmann and Zervas.[15]

The nuclear magnetic resonance (n.m.r.) spectra of I and VII (Fig. 1 and 2) provide independent physical proof of the structures assigned on the basis of synthesis. The anomeric proton of I appeared as a doublet at τ 3.72 with a coupling constant ($J_{1,2}$ = 3.5 c.p.s.) that was indicative[17,18] of an equatorially oriented C-1 proton having a projected valence angle[19] of 60° with the C-2 proton. In contrast, the anomeric proton of VII appeared at higher field, τ 4.01, characteristic[17,18] of the axial orientation, and this structure is supported by the large coupling constant, $J_{1,2}$ = 8.3 c.p.s., which is in agreement with a projected valence angle of 180° between the C-1 and C-2 protons. The corresponding 2-acetamido analogs (III and IX) of I and VII, whose n.m.r. spectra are recorded in Fig. 3, give closely comparable data for the anomeric protons. In the α-D anomer (III) the equatorial anomeric proton appears at τ 3.82 with a coupling constant, $J_{1,2}$ = 3.5 c.p.s., while for the β-D anomer (IX) the corresponding values are τ 4.27 and $J_{1,2}$ = 8.5 c.p.s. The coupling constants recorded are the directly observed doublet spacings, and may be considered to be minimum values of the absolute coupling constant $J_{1,2}$. It is recognized that the observed spacings may be somewhat smaller than the absolute value of $J_{1,2}$ owing to second-order effects[20] which depend on the relative chemical shift of the 2- and 3-protons and the $J_{2,3}$ coupling constant.

Further supporting data may be deduced from the chemical shifts of the C-1 acetoxy groups.[17] In I the acetoxy singlet at lowest field, τ 7.71, may be assigned

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(16) B. Lindberg, *Acta Chem. Scand.*, **3**, 1355 (1949).

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(18) L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, in press.

(19) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLaughlan, *J. Chem. Soc.*, 3699 (1962); R. U. Lemieux, J. D. Stevens, and R. R. Fraser, *Can. J. Chem.*, **40**, 1955 (1962).

(20) R. U. Lemieux and J. W. Lown, *ibid.*, **41**, 889 (1963).

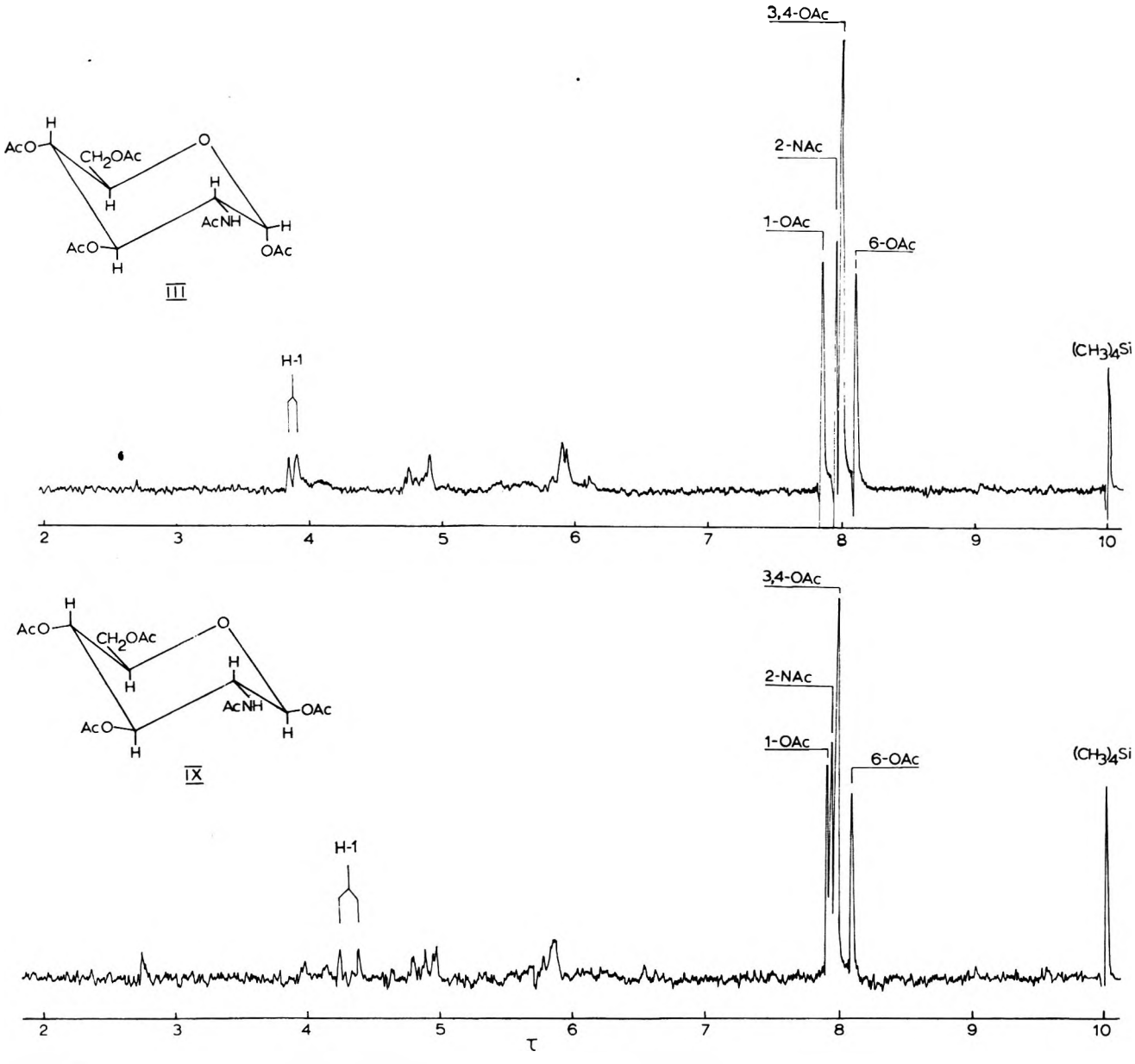

Fig. 3.—Nuclear magnetic resonance spectra of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α- and -β-D-glucopyranose (III and IX) in $CDCl_3$, Varian A-60 n.m.r. spectrometer.

to the axial C-1 acetoxy group, while in VII the group is equatorial and appears at higher field as a singlet, τ 7.89. In like manner, the singlet at τ 7.81 in the spectrum of III may be assigned to the axial C-1 acetoxy group, and the corresponding equatorial C-1 acetoxy group in IX appears as a singlet at higher field, τ 7.89. The integrated peak intensities of the anomeric protons and C-1 acetoxy groups in all four compounds were in the expected ratios. The anomeric proton resonances in I and VII were shifted to lower field in comparison with those of III and IX and other sugars,[18] presumably because of the extra deshielding effect of the 2,4-dinitroanilino sustituent. All of the foregoing n.m.r. data fully support the anomeric configurations assigned to I and VII.

Further empirical analysis of the n.m.r. spectra is possible. All four compounds show at highest field an acetyl singlet in the region τ 8.09–8.12 which may reasonably be assigned[18] to the primary C-6 acetoxy group. Compounds III and IX each show a singlet at τ 7.98 corresponding to two acetyl groups, attributable to the C-3 and C-4 acetoxy groups, and additionally a singlet at τ 7.93 corresponding to one acetyl group, presumably that of the acetamido function. In the 2,4-dinitroanilino derivatives I and VII, the C-3 and C-4 acetoxy groups gave singlets resolved from each other, lying in the region between the singlets for the C-1 acetoxy group (at lowest field) and the C-6 acetoxy group (at higher field). Since the deshielding effect of the C-2 substituent would be expected to influence the adjacent C-3 acetoxy group but probably not the C-4 substituent, the lower of the C-3, C-4 acetoxy resonances is assigned to the C-3 substituent. The low field doublet at τ 2.81 (in I) and 2.72 (in VII), of unit proton intensity, is very probably due to the proton on the nitrogen atom, but the resonance is partially obscured by the peak due to chloroform in the solvent. The three aryl protons in I and VII appeared at different fields; an empirical first-order analysis would indicate the 3-proton at τ 0.97 as a doublet, $J_{3,5}$ = 2.7 c.p.s.,

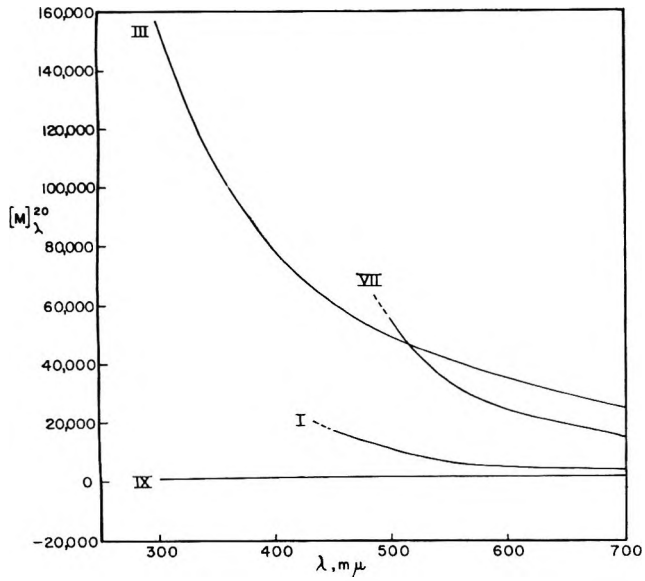

Fig. 4.—Optical rotatory dispersion spectra of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α- and -β-D-glucopyranose (I and VII) and 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α- and -β-D-glucopyranose (III and IX).

the 5-proton at τ 1.71 as a quartet, $J_{5,3}$ = 2.7 and $J_{5,6}$ = 9.5 c.p.s., and the 6-proton at τ 1.47 as a doublet, $J_{6,5}$ = 9.5 c.p.s.

The n.m.r. data for the bromo derivative V (see Experimental) are consistent with the assigned α-D anomeric configuration.

Optical rotatory dispersion curves for the two pairs of anomers I and VII, and III and IX (Fig. 4) show that the specific rotation of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranose (VII) is higher than that of its α-D anomer (I) at all observed wave lengths, and the difference increases at shorter wave lengths. Both derivatives show plain[21] positive curves from 700 to 450–500 mμ; absorption bands prevented observations below this limit. In contrast, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (III) shows a plain positive curve from 700 to 300 mμ, and its specific rotation is at all wave lengths greater than that of its β-D anomer (IX), which shows little change in specific rotation over this range of wave lengths.

Discussion

The foregoing data establish beyond reasonable doubt that the specific rotations of the anomeric pair of compounds I and VII do not accord with the Hudson rule[6] that "in the D series the more dextrorotatory member of an α,β-pair of anomers is to be named α-D, the other being β-D." The Hudson rule for assignment of anomeric configuration is based "on the hypothesis that optical superposition holds for [anomeric pairs of sugar derivatives] in an approximation that is at least sufficient to exclude a complete reversal of relative rotations for an α,β-pair of anomers."[6] This rule holds true for many thousands of anomeric pairs, although exceptions have been noted[22] with the anomeric 1-(2-deoxy-D-*erythro*-pentofuranosyl) derivatives of 5-methyl (and 5-fluoro) uracil and other 2′-deoxynucleosides; in these examples the carbon atom vicinal to the anomeric carbon is not asymmetric.

The present example demonstrates a case of the complete reversal of the normal relative rotations of an α,β-pair of anomers, in a pyranose ring sugar having an asymmetric center at C-2, when the 2,4-dinitroanilino group is introduced at C-2. It would appear probable[5] that the methyl (and ethyl) 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α(and β)-D-glucopyranoses[3,4] also show a similar reversal of the normal relative rotations, although there is lack of agreement[3–5] on the specific rotations of these glycoside derivatives. The present observations indicate that assignment of anomeric configuration[4] should not be based solely on optical rotatory data when the 2,4-dinitroanilino group, and possibly other groups of high polarizability, are present.

The Hudson rules are based on the Van't Hoff principle of optical superposition,[23] and on the assumption that vicinal effects do not greatly influence the magnitude of the rotatory contribution of C-1 in relation to the rotatory contribution of the rest of the molecule. The relatively large magnitude of the C-1 contribution normally outweighs the small-magnitude effect of vicinal action, and ensures the general applicability of the rules. More recent views[24–26] of optical activity regard an optically active center as an asymmetric screw pattern of polarizability arising from (a) the difference in polarizability of groups attached to an asymmetric carbon atom (atom asymmetry), and (b) the spatial arrangement of groups in the molecule (conformational asymmetry); the latter effect usually provides the larger rotatory contribution. Calculations of molecular rotation of cyclic sugars, in good agreement with experimental values, have been made[24] from considerations of conformational asymmetry, by algebraic summation of a series of empirical rotation parameters, along each bond of the ring in its favored conformation. Rotation parameters have been calculated[25] from the polarizabilities of the substituent groups. The conformational rotatory power of the amino group is approximately the same as that of the hydroxyl group[26]; hence, the 2-amino sugars and their derivatives in general obey the isorotation rules well,[27] but *N*-substitution with the 2,4-dinitrophenyl group would appear to produce a large change in the group polarizability and, by the consequent large change in conformational rotatory power, gives rise to a large vicinal effect which overrides the rotatory contribution of the anomeric center in its effect on the net rotation.

Further studies are in progress to determine the effect of temperature changes on the specific rotations of I, VII, and related derivatives.

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Experimental[28]

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I). A. From 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose Hydrochloride (II).—A related procedure from the hydrobromide analog of II has been described,[5] but the yield was very low, and there was no chromatographic verification of product homogeneity. A solution of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride (II,[10] 2.00 g.) in water (10 ml.) and acetone (30 ml.) was stirred overnight at room temperature with sodium bicarbonate (0.44 g.) and 1-fluoro-2,4-dinitrobenzene (1.00 g.). The solution was evaporated, the residue was washed with petroleum ether (b.p. 30–60°), and the washings were discarded; then the product was extracted with chloroform (50 ml.), and inorganic material was removed by filtration. The extract was evaporated to 10 ml., and ethanol (50 ml.) was added, whereupon the product I crystallized rapidly, yielding 1.10 g. (41%), m.p. 218–219°. Recrystallization from chloroform–ethanol was effected with little loss to give pure material as very fine lemon yellow needles, m.p. 218–219°, $[\alpha]^{21}D$ +9.7 ± 0.2° (*c* 1.5, chloroform); λ_{max}^{KBr} 3.00 (NH), 3.17 (aryl CH), 5.66, 5.75 (OAc), 6.18, 6.29, 6.65 (aryl C=C, 6.50 (NH, NO_2), 7.42 (NO_2), 13.48, 13.90 μ (substituted benzene); λ_{max}^{EtOH} 208 mμ (ε 6400), 264 (5000), 333 (7800); n.m.r. data[28]: τ 8.02 (6-OAc), 7.94 (4-OAc), 7.89 (3-OAc), 7.71 (1-OAc), 3.72 (doublet, H-1, $J_{1,2}$ 3.5 c.p.s.); X-ray powder diffraction data[28]: 13.19 w, 11.95 s (3), 7.76 vs (1,1), 6.15 s (2,2), 5.50 w, 5.19 m, 4.87 vs (1,1), 4.46 m, 4.35 w, 4.15 w, 3.97 s, 3.75 s (2,2), 3.53 vs (1,1) 3.38 s (2).

Anal. Calcd. for $C_{20}H_{23}N_3O_{13}$: C, 46.78; H, 4.52; N, 8.19. Found: C, 46.68; H, 4.49; N, 8.29.

The product gave a homogeneous yellow zone, R_f 0.60 (R_x 1.00), on thin layer chromatography. The mother liquors contained approximately 50% of the same component, which could be isolated by column chromatography (see below) to raise the total yield to approximately 70%. Smaller proportions of two other yellow components, R_x 0.5 and 0.3, were present, together with a colorless component, R_x 0.1, which appeared after spraying with sulfuric acid.

One preparation of this material crystallized in a second form having m.p. 191°, which on further heating resolidified at about 195° and finally melted at 218–219°. The mixture melting point of the two forms was 218–219°. The second form had X-ray powder diffraction data[28]: 10.78 m, 9.31 vs (1), 7.25 m, 5.87 w, 5.54 s, 5.31 vw, 4.96 s (2,2), 4.80 m, 4.42 s (3), 4.00 s (2,2), 3.74 s (3), 3.56 s, 3.39 s (2,2), 3.10 w, 2.90 m. The specific rotations and chromatographic mobilities of the two forms were identical. A supersaturated solution of I gave either dimorph by appropriate nucleation.

B. From 2-Deoxy-2-(2,4-dinitroanilino)-D-glucose (IV).—Crude IV was prepared[14] in almost quantitative yield from 2-amino-2-deoxy-D-glucose hydrochloride, and was not recrystallized. Dried IV (27 g.) in pyridine (160 ml.) was treated at 0° with acetic anhydride (65 ml.). After 3 days at 0° the solution was poured on ice (1.5 kg.), stirred for 3 hr., then filtered to give the crude acetylated product in a 35-g. (88%) yield. Thin layer chromatography revealed the presence of four yellow components in this mixture, R_x 1.0, 0.9, 0.5, and 0.3, in the relative intensity ratios 10:2:3:1. Recrystallization of a 5-g. sample of the crude product from ethanol gave yellow needles of I in a 3.5-g. yield (corresponding to 62% in the over-all reaction), m.p. 217–219°. The product was identical by mixture melting point and by thin layer chromatography with the product isolated in A above.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranose (VII). A. From 1,3,4,6,-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose Hydrochloride (VIII-HCl).—A solution of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride (VIII-HCl)[15] (2.00 g.) in water (10 ml.) containing sodium bicarbonate (0.44 g.) was treated with a solution of 1-fluoro-2,4-dinitrobenzene (0.98 g.) in acetone (30 ml.); the mixture was stirred overnight, and then evaporated. The residue was partitioned between chloroform (30 ml.) and water (20 ml.); the chloroform extract was dried over magnesium sulfate and evaporated. Crystallization of the product from ethanol gave canary yellow needles, 1.30-g. yield, m.p. 167°. Concentration of the mother liquors gave a further 0.32 g. of product, m.p. 164–166°, to give a total yield of 61%. Recrystallization from ethanol gave pure product with little loss, m.p. 167.0–167.5°, $[\alpha]^{21}D$ +50.0 ± 0.1° (*c* 1.1, chloroform); λ_{max}^{KBr} 3.02 (NH), 3.22 (aryl CH), 5.75 (OAc), 6.18, 6.24 (aryl C=C), 6.48 6.58, 6.69 (NH, aryl C=C, NO_2), 7.40 (NO_2), 13.50, 13.90 μ (substituted benzene); λ_{max}^{EtOH} 208 mμ (ε 7250), 261 (ε 5250), 336 (ε 8300); n.m.r. data[28]: τ 8.09 (6-OAc), 8.00 (4-OAc), 7.93 (3-OAc), 7.81 (1-OAc), 4.01 (doublet, H-1, $J_{1,2}$ = 8.3 c.p.s.); X-ray powder diffraction data[28]: 10.16 s (2), 8.51 w, 7.56 w, 5.19 vw, 4.75 m (3,3), 4.53 w, 4.37 vw, 4.17 w, 4.00 m (3,3), 3.75 s (1).

Anal. Calcd. for $C_{20}H_{23}N_3O_{13}$: C, 46.78; H, 4.52; N, 8.19. Found: C, 46.69; H, 4.71; N, 8.39.

The product was chromatographically homogeneous, R_x 0.9, on thin layer chromatography. The noncrystalline mother liquor contained an estimated 40% of this component, together with traces of yellow components R_x 1.0 and 0.5, and a moderately intense yellow component R_x 0.3. A colorless zone of weak intensity appeared near the origin after spraying with sulfuric acid.

The reaction was repeated, but with 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose (VIII)[15] as starting material, in place of the hydrochloride salt. The product VII was isolated in 51% yield, and the mother liquors contained a similar distribution of components to those in the preceding preparation.

B. From 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl Bromide (V).—A solution of the bromo sugar (V,[8] 0.25 g.) and mercuric acetate (0.20 g.) in acetic acid (10 ml.) was stirred for 2 hr. at room temperature. Chloroform (50 ml.) was added; the solution was washed with three 30-ml. portions of water, dried over magnesium sulfate, and evaporated; the residue crystallized from ethanol to give canary yellow needles of the product VII in a 0.22-g. (92%) yield, m.p. 166.5–167.0°. The product was identical with that obtained in A above by mixture melting point and thin layer chromatography.

C. From 2-Deoxy-2-(2,4-dinitroanilino)-D-glucose (IV).—A 3-g. amount of the crude product obtained by acetylation of 2-deoxy-2-(2,4-dinitroanilino)-D-glucose (IV), as described for preparation of I by procedure B, was resolved by chromatography on a 27 × 8 cm. Magnesol[29] Celite column,[30] using 200:1 benzene–*t*-butyl alcohol (5 l.) as eluent. Four yellow zones were observed, centered at 15, 11, 5, and 0 cm. from the top of the column. The zones were sectioned from the extruded column and extracted with acetone, and the products crystallized from chloroform–petroleum ether. The fastest moving zone gave a crystalline product in an 0.86-g. yield, m.p. 217–219°, indistinguishable from I, while the zone which had moved 11 cm. gave fine needles in a 0.10-g. yield, m.p. 166–166.5°, indistinguishable from VII by mixture melting point, infrared spectrum, and the X-ray powder diffraction pattern. The 5-cm. zone gave an unidentified product in a 0.13-g. yield, m.p. 200°, and the stationary zone gave a second unidentified product in an 0.08-g. yield, m.p. 188°.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl Bromide (V).—Treatment of either 1,3,4,6-tetra-*O*-acetyl-2-(2,4-dinitroanilino)-α-D-glucopyranose (I) or its β-D anomer (VII), or the crude mixture of both, with hydrogen

(28) Melting points were determined with a Hershberg-type apparatus and are corrected. Specific rotations were determined at the D line in a 4-dm. tube, optical rotatory dispersion measurements were made with a Rudolph Model 260/655/850/810-614 recording photoelectric spectropolarimeter. Microanalyses were performed by W. N. Rond. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord spectrophotometer, with potassium bromide pellets pressed from a finely ground mixture of the sample with dried analytical reagent grade potassium bromide. Ultraviolet absorption spectra were measured by L. D. Sannes with a Cary Model 10 recording spectrophotometer. The proton magnetic resonance spectra were measured at 60 Mc./sec. in deuteriochloroform or deuteriochloroform–chloroform, with tetramethylsilane as internal standard. Thin layer chromatography was performed with Desaga equipment (Brinkmann Instruments, Great Neck, N. Y.) using the ascending technique with a 250-μ layer of silica gel G (E. Merck, Darmstadt, Germany) activated for 2 hr. at 100°. The developing solvent was 3:1 chloroform–ether, and zones were detected visually and after spraying with sulfuric acid. R_x values denote mobility relative to 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I). X-Ray powder diffraction data give interplanar spacings, Å., for Cu Kα radiation. Relative intensity was estimated visually: s, strong; m, moderate; w, weak; v, very. First three strongest lines are numbered (1, strongest), double numbers indicate approximately equal intensities.

(29) A product of the Westvaco Chemical Division of Food Machinery and Chemical Corp., South Charleston, W. Va.

(30) A. Thompson, *Methods Carbohydrate Chem.*, **1**, 36 (1962). This separation was carried out by Mr. L. D. Sannes.

bromide in acetic acid according to the conditions of Lloyd and Stacey[3] for a compound described as I, gave V in almost quantitative yield, with physical constants in agreement with those reported[8]; n.m.r. data[28]: τ 8.15 (6-OAc), 7.93 (4-OAc), 7.89 (3-OAc), 3.40 (doublet, H-1, $J_{1,2}$ = 3.5 c.p.s.).

2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (III).—This compound[12,13] was prepared in 56% yield by direct acetylation of 2-amino-2-deoxy-D-glucose hydrochloride by the acetic anhydride–sodium acetate procedure.[12] It could also be obtained by acetylation of II with acetic anhydride in an excess of pyridine.[11] The pure material had m.p. 139.5–140.5°, $[\alpha]_D$ +93° (c 1.0, chloroform); λ_{max}^{KBr} 2.92 (NH), 5.74 (OAc), 6.00, 6.57 (NHAc), and 11.82 μ (equatorial H at C-1); n.m.r. data[28]: τ 8.09 (6-OAc), 7.98 (3,4-OAc), 7.93 (2-NAc), 7.81 (1-OAc), 3.82 (doublet, H-1, $J_{1,2}$ = 3.5 c.p.s.); X-ray powder diffraction data[28]: 12.28 m, 9.31 vs (1), 7.03 w, 6.28 w, 5.99 vw, 5.44 s, 5.13 m, 4.80 m, 4.58 vw, 4.37 m, 4.17 s (2), 4.00 m, 3.63 s (3), 3.52 m, 3.35 m, 3.13 m.

2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (IX).—The following procedure provided a facile route to this compound. 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (VI)[8] (3.47 g.) was dissolved in acetic acid (30 ml.), mercuric acetate (3.18 g.) was added, and the mixture was stirred for 2 hr. at room temperature. Chloroform (150 ml.) was added to the clear solution followed by water (10 ml.), the mixture was shaken, and the organic layer was separated and dried over magnesium sulfate. After evaporation of the chloroform, the product was crystallized from methanol–ether yielding 3.20 g. (86%), m.p. 186–186.5°. A second recrystallization gave small prisms, m.p. 186.0–186.5°, $[\alpha]_D$ +1.5 ± 0.5° (c 1, chloroform); λ_{max}^{KBr} 3.10 (NH), 5.73 (OAc), 6.02, and 6.50 μ (NHAc); n.m.r. data[28]: τ 8.09 (6-OAc), 7.97 (3,4-OAc), 7.93 (2-NAc), 7.89 (1-OAc), 4.27 (doublet, H-1, $J_{1,2}$ 8.5 c.p.s.); X-ray powder diffraction data[28]: 9.31 m, 7.08 s, (2,2), 6.66 w, 6.24 m, 5.19 w, 4.85 vs (1), 4.60 w, 4.21 m, 3.79 s (2,2), 3.55 s (3), 3.25 w. The product was only moderately soluble in chloroform, almost insoluble in water, and readily soluble in methanol. The above route provides a synthesis of IX from 2-amino-2-deoxy-D-glucose hydrochloride, in 67% over-all yield, by way of 2-acetamido-2-deoxy-D-glucose and VI.[7,8]

A sample of VIII (347 mg.), as used in the conversion to VII, was acetylated with acetic anhydride in excess pyridine solution, and after conventional processing crystalline IX was obtained in 290-mg. (75%) yield, m.p. 185–186°. A repeat preparation with the hydrochloride salt of VIII (383 mg.) also gave IX in 310-mg. (80%) yield. Similar results were obtained when VIII-HCl was acetylated by the acetic anhydride–sodium acetate procedure.[16] In all cases the product was identical with that prepared by the first procedure.

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Aryl Thioglycopyranosides, Aryl Glycopyranosyl Sulfones, and the Novel Oxidation–Acetylation of Aryl 1-Thio-β-D-glucopyranosides to 6-*O*-Acetyl-β-D-glucopyranosyl Aryl Sulfones[1]

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When *p*-tolyl 1-thio-β-D-glucopyranoside in a mixture of glacial acetic acid and 30% hydrogen peroxide is allowed to stand for several days at room temperature, the product, obtained in nearly quantitative yield, is not the expected β-D-glucopyranosyl *p*-tolyl sulfone but the 6-*O*-acetyl derivative of the sulfone. Experiments indicate that this novel acetylation reaction may occur at the intermediate sulfoxide stage. A number of other aryl thioglycosides and aryl glycosyl sulfones are described, and some of their reactions and their infrared and nuclear magnetic resonance spectra are discussed.

In an attempt to find new antimalarials, Montgomery, Richtmyer, and Hudson[3] prepared a series of substituted phenyl 1-thio-β-D-glucopyranosides. In 1947, one of these compounds, the *p*-tolyl 1-thio-β-D-glucopyranoside (IV), was dissolved in glacial acetic acid and oxidized with an excess of 30% hydrogen peroxide for several days at room temperature. The product, obtained in nearly quantitative yield, was expected to be the β-D-glucopyranosyl *p*-tolyl sulfone (III),[4] but carbon and hydrogen analyses corresponded almost exactly to the values required for a 1:1 double compound between the sulfone and the sulfoxide.[5] This seemed quite plausible in view of a paper entitled "Mixed Crystals of Sulfoxides and Sulfones" that had been published shortly before.[6] Ten years later, however, when an infrared spectrum of our compound revealed what appeared to be strong carbonyl absorption at 1695 cm.$^{-1}$, the problem seemed to warrant further study.

A survey of the literature showed that the oxidation products of thioglycosides included both sulfones and sulfoxides. Wrede and Zimmermann[7] prepared the first sulfones; these were mainly of the bis(β-D-glycopyranosyl) sulfone type and were made by oxidation of the acetylated bis(β-D-glycopyranosyl) sulfides with potassium permanganate in acetic acid and then deacetylating the crystalline products. Micheel and Schmitz[8] described the first sulfoxide, ethyl α-D-glucopyranosyl sulfoxide; this was obtained by the oxidation of ethyl 1-thio-α-D-glucopyranoside with dilute aqueous hydrogen peroxide. Bonner and Drisko[9] oxidized five acetylated thioglycosides to their respective sulfones by heating either with aqueous potassium

(1) Presented in part before the Division of Carbohydrate Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) Associate in the Visiting Program of the National Institutes of Health, Oct., 1961, to Sept., 1963.

(3) E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Org. Chem.*, **11**, 301 (1946).

(4) It was thus listed, under Survey No. 15418* and N.I.H. No. 2873 by G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg in "Survey of Antimalarial Agents," Public Health Monograph No. 9, U. S. Government Printing Office, 1953, p. 214.

(5) *Anal.* Calcd. for $C_{26}H_{36}O_{12}S_2$: C, 50.31; H, 5.85. Found: C, 50.30; H, 5.80.

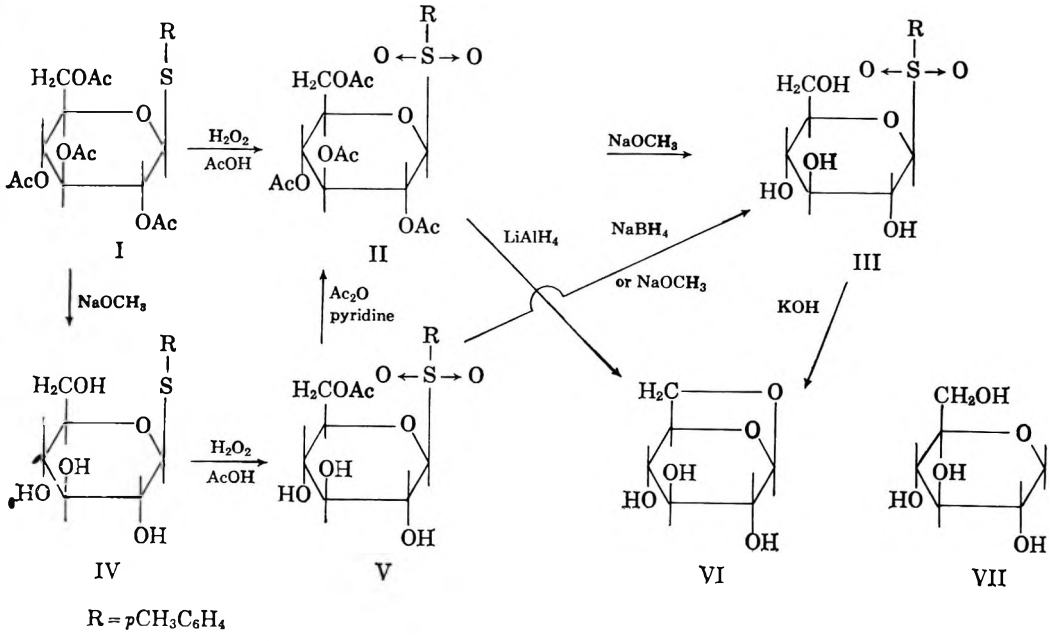
(6) H. Rheinboldt and E. Giesbrecht, *J. Am. Chem. Soc.*, **68**, 973 (1946).

(7) F. Wrede and W. Zimmermann, *Z. physiol. Chem.*, **148**, 65 (1925).

(8) F. Micheel and H. Schmitz, *Ber.*, **72**, 992 (1939).

(9) W. A. Bonner and R. W. Drisko, *J. Am. Chem. Soc.*, **70**, 2435 (1948).

SCHEME I



permanganate in acetic acid or with 30% hydrogen peroxide in acetic acid. They attempted to oxidize phenyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside with one molecular equivalent of permanganate and thus obtain the sulfoxide, but isolated instead only a mixture of sulfone and starting thioglucoside. Wagner and Kühmstedt,[10] however, were able to prepare sulfoxides by the action of one and sulfones by the action of two or more molecular equivalents of 30% hydrogen peroxide in glacial acetic acid upon the completely acetylated derivatives of *p*-hydroxyphenyl 1-thio-β-D-glucopyranoside and *p*-β-D-glucopyranosyloxyphenyl 1-thio-β-D-glucopyranoside.

In this investigation we have prepared three new aryl 1-thio-β-D-gluco- and galactopyranosides (X, XVII, and XX) and their tetraacetates (VIII, XIV, and XVIII) by well-known procedures; five new aryl β-D-gluco- and β-D-galactopyranosyl sulfone tetraacetates (II, IX, XI, XV, and XIX) by the action of 30% hydrogen peroxide in glacial acetic acid upon the corresponding thioglycoside tetraacetates[11]; and, by deacetylation, three new aryl β-D-gluco- and β-D-galactopyranosyl sulfones (III, XII, and XVI). Although sulfoxides have been isolated in the sugar series,[8,10] we, like Bonner and Drisko,[9] were unsuccessful with *p*-tolyl 1-thio-β-D-glucopyranoside tetraacetate (I) and limited amounts of hydrogen peroxide or sodium metaperiodate,[12] and with iodosobenzene.[13] When one molecular equivalent of potassium permanganate in glacial acetic acid was used and the product deacetylated, a paper chromatogram dipped in silver nitrate reagents revealed mainly the thioglucoside with some sulfone; a paper chromatogram sprayed with a new specific reagent sensitive to sulfoxides[14] indicated the probable presence of only a very small amount of sulfoxide. In an example outside the sugar series an interesting possibility of disproportionation reactions between two sulfoxide molecules has been suggested[15] to explain the failure of repeated efforts to isolate the desired sulfoxide.

The degradation of β-D-glucopyranosyl *p*-tolyl sulfone (III) with hot aqueous potassium hydroxide, like that of the unoxidized phenyl and *p*-dimethylaminophenyl 1-thio-β-D-glucopyranosides reported earlier,[16] yielded 1,6-anhydro-β-D-glucopyranose (levoglucosan, VI). The reductive desulfurization with Raney nickel of tetra-*O*-acetyl-β-D-glucopyranosyl sulfone (II), followed by deacetylation, yielded 1,5-anhydro-D-glucitol (polygalitol, VII) just as the desulfurization of the unoxidized *p*-phenyl and *p*-tolyl 1-thio-β-D-glucopyranosides had.[17] These degradation and desulfurization reactions confirm the pyranoside ring structures of the sulfones as determined by periodate oxidation methods. The attempted reduction of the sulfone tetraacetate (II) with lithium aluminum hydride also yielded levoglucosan (VI), and the sulfone thus appears to be sensitive to the basicity of that solution even at room temperature. Acetolysis and bromine in chloroform[18] seemed to cause no reaction with the sulfone tetraacetate (II). (See Scheme I.)

As noted earlier in this paper, the action of 30% hydrogen peroxide in glacial acetic acid upon the free *p*-tolyl 1-thio-β-D-glucopyranoside (IV) led not to the expected sulfone (III) but to a compound that showed carbonyl absorption in its infrared spectrum. Subse-

(10) G. Wagner and H. Kühmstedt, *Naturwissenschaften*, **46**, 425 (1959); *Arch. Pharm.*, **294**, 147 (1961).

(11) Bonner and Drisko (ref. 9) reported that partial deacetylation occurred when their reaction mixture was refluxed for 2 hr.; we have observed no deacetylation when the reaction is carried out at room temperature.

(12) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(13) A. H. Ford-Moore, *J. Chem. Soc.*, 2126 (1949).

(14) J. F. Thompson, W. N. Arnold, and C. J. Morris, *Nature*, **197**, 380 (1963).

(15) H. H. Szmant and L. Alfonso, unpublished work cited by H. H. Szmant, "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, p. 161.

(16) E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Org. Chem.*, **10**, 194 (1945).

(17) H. G. Fletcher, Jr., and N. K. Richtmyer, *Adran. Carbohydrate Chem.*, **5**, 1 (1950); N. K. Richtmyer, *Methods Carbohydrate Chem.*, **2**, 193 (1963).

(18) W. A. Bonner [*J. Am. Chem. Soc.*, **70**, 770 (1948)] found that bromine in glacial acetic acid effects acetolysis with the unoxidized compounds; *e.g.* phenyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside is converted into α-D-glucose pentaacetate in good yield. The corresponding tetra-*O*-acetyl-β-D-glucopyranosyl phenyl sulfone was unaffected by bromine in glacial acetic acid [W. A. Bonner, *ibid.*, **70**, 3491 (1948)].

quent experiments and analyses showed that it contained an acetyl group at C-6 and accordingly must be the 6-*O*-acetyl-β-D-glucopyranosyl *p*-tolyl sulfone (V). Since acetylation of this compound produced the sulfone tetraacetate (II) and deacetylation produced the free sulfone (III), the presence of an *O*-acetyl group was established. When oxidized with periodate, the compound consumed 2 moles of oxidant and liberated 1 mole of formic acid per mole of compound; thus, the hydroxyls at C-2, C-3, and C-4 were free and the acetyl group could be only at C-6. This allocation was verified by the nuclear magnetic resonance spectra (see Experimental) of this compound and of 6-*O*-acetyl-β-D-glucopyranosyl *p*-bromophenyl sulfone, the only other similar compound that could be obtained crystalline following the action of hydrogen peroxide and glacial acetic acid upon nine other thioglycosides. Compound V could be prepared also, but in low yield, by the unimolecular acetylation of III with acetic anhydride and pyridine.

The acetylating action of acetic acid upon carbohydrates has been reported by Duff,[19] who obtained modest yields of the 6-*O*-acetyl derivatives of D-glucose and D-galactose by heating the sugars in 50% aqueous acetic acid for about 24 hr. at 100°. Appreciable amounts of esters were detected even with lower concentrations of acetic acid and at lower temperatures. On the basis of rotational and paper chromatographic evidence only, de Grandchamp-Chaudun[20a] has reported that, when D-glucose, D-fructose, D-galactose, and maltose are dissolved in glacial acetic acid at room temperature and left for several months, each is converted completely into two acetates. The identification of these products has not yet been revealed.

In an effort to learn something of the mechanism of formation of the 6-*O*-acetyl compounds, we dissolved small amounts of the *p*-tolyl 1-thio-β-D-glucopyranoside (IV) and the corresponding β-D-glucopyranosyl *p*-tolyl sulfone (III) each separately in (a) glacial acetic acid, (b) glacial acetic acid plus 30% hydrogen peroxide, and (c) glacial acetic acid plus water equal in volume to that of the hydrogen peroxide solution in (b). The six solutions were kept for 7 days at 25° and then concentrated in a vacuum desiccator. Only the thioglucoside (IV) in solution (b) yielded the 6-*O*-acetylsulfone (V), while the other solutions gave unchanged starting materials.[20b] The practically quantitative unimolecular acetylation that accompanies the oxidation of *p*-tolyl 1-thio-β-D-glucopyranoside to the corresponding sulfone by hydrogen peroxide in glacial acetic acid thus appears to be a novel type of acetylation. Since the thioglucoside (IV) was not attacked by glacial acetic acid and the sulfone (III) was not acetylated by the glacial acetic acid–hydrogen peroxide mixture, we can only postulate that acetylation takes place at the intermediate sulfoxide stage. Since we have been unable to isolate the intermediate sulfoxide, the problem remains a puzzle and warrants still further investigation.

Data on infrared and n.m.r. spectra are reported in the Experimental section.

(19) R. B. Duff, *J. Chem. Soc.*, 4730 (1957).

(20) (a) A. de Grandchamp-Chaudun, *Compt. rend.*, **252**, 1397 (1961). (b) NOTE ADDED FEBRUARY 24, 1964.—Phenyl β-D-glucopyranoside also was unaffected by a mixture of glacial acetic acid and 30% hydrogen peroxide under these conditions.

Experimental

Paper chromatography was carried out on Whatman No. 1 filter paper by the descending method at room temperature in 1-butanol–pyridine–water (6:4:3). The locations of the spots were revealed by dipping the papers in silver nitrate in acetone followed by sodium hydroxide in aqueous ethanol.[21a] The values for R_{gal} and R_{glu} refer to the rate of migration of the compounds on paper chromatograms relative to that of galactose and glucose, respectively. Melting points were determined in capillary tubes.

Tetra-*O*-acetyl-β-D-glucopyranosyl *p*-Tolyl Sulfone (II).[21b]—To a solution containing 3.7 g. of *p*-tolyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (I)[3] in 40 ml. of glacial acetic acid was added 7.4 ml. of 30% hydrogen peroxide. After 9 days at 25° the solution was diluted with water until crystallization appeared to be complete. The product weighed 3.6 g. (91%) and melted at 151–153°. After three recrystallizations from six parts of 95% ethanol the prismatic needles of the sulfone tetraacetate showed m.p. 152–153° and $[\alpha]^{20}D$ −35.1° (c 1, chloroform).

Anal. Calcd. for $C_{21}H_{26}O_{11}S$: C, 51.85; H, 5.39; S, 6.6; OAc, 35.4. Found: C, 51.95; H, 5.17; S, 6.7; OAc, 35.3.

β-D-Glucopyranosyl *p*-Tolyl Sulfone (III).—Deacetylation of 4.0 g. of the sulfone tetraacetate (II) in 150 ml. of methanol was accomplished catalytically by the addition of 2 ml. of 0.4 *N* methanolic barium methoxide. After 36 hr. at 25° the solution was neutralized with carbon dioxide and concentrated *in vacuo* to a sirup that crystallized as needles (2.0 g.) upon the addition of a small amount of water. Recrystallization from ethyl acetate afforded glistening needles of the sulfone, m.p. 153–154° (followed by slow charring), $[\alpha]^{20}D$ −28.4° (c 1, pyridine), λ_{max}^{MeOH} 225 mμ (ε 15,400), R_{gal} 2.55.

Anal. Calcd. for $C_{13}H_{18}O_7S$: C, 49.05; H, 5.70; S, 10.1. Found: C, 49.32; H, 5.81; S, 10.5.

6-*O*-Acetyl-β-D-glucopyranosyl *p*-Tolyl Sulfone (V) from *p*-Tolyl 1-Thio-β-D-glucopyranoside (IV).—Ten grams of anhydrous[22] IV was dissolved in 47 ml. of glacial acetic acid, 18 ml. of 30% hydrogen peroxide was added, and the mixture was left at 25° for 7 days. It was then concentrated to a crystalline residue (11.7 g.) in a vacuum desiccator over potassium hydroxide pellets. The product was recrystallized from 200 ml. of boiling water to give 9.8 g., m.p. 187–188°, and then several times from ethyl acetate. The fine, silky, plate-like needles of the sulfone monoacetate melted sharply at 191° with the evolution of gas and blackening, $[\alpha]^{20}D$ −4.4° (c 3, pyridine), λ_{max}^{MeOH} 225 mμ (ε 15,000), R_{gal} 2.73.

Anal. Calcd. for $C_{15}H_{20}O_8S$: C, 49.99; H, 5.59; S, 8.9; OAc, 11.9; mol. wt., 360. Found: C, 50.05; H, 5.60; S, 8.8; OAc, 12.4; mol. wt. (Mechrolab vapor pressure osmometer), 347.

6-*O*-Acetyl-β-D-glucopyranosyl *p*-Tolyl Sulfone (V) from β-D-Glucopyranosyl *p*-Tolyl Sulfone (III).—The unimolecular acetylation of 1.6 g. of III was attempted by dissolving it in 3 ml. of dry pyridine and 0.47 ml. of acetic anhydride and leaving the mixture overnight at 25°. The mixture was concentrated *in vacuo* to a sirup; paper chromatograms showed this sirup to consist of starting sulfone predominantly, together with the sulfone monoacetate and higher acetates. The sirup, when dissolved in ethanol and left overnight, deposited a small amount of crystalline material whose R_{gal} value corresponded to that of the monoacetate. Recrystallization from ethanol afforded fine needles that were identified by melting point and mixture melting point as the sulfone monoacetate (V).

Some Reactions of Tetra-*O*-acetyl-β-D-glucopyranosyl *p*-Tolyl Sulfone (II). With Lithium Aluminum Hydride.—To 2.3 g. of powdered lithium aluminum hydride suspended in 40 ml. of

(21) (a) W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950). (b) NOTE ADDED FEBRUARY 24, 1964.—Since submitting this paper for publication we found that we had overlooked a remarkable reaction observed by B. Helferich and H. Schirp [*Chem. Ber.*, **86**, 547 (1953)]. They treated the *p*-tolylsulfonylhydrazone derived from 2,3,4,6-tetra-*O*-acetyl-β-D-glucose with dinitrogen trioxide and obtained a 13% yield of the tetra-*O*-acetyl-β-D-glucopyranosyl *p*-tolyl sulfone (II), m.p. 148° and $[\alpha]^{21}D$ −33.8° in chloroform. They suggested that the hydrazone might first have been oxidized to an azo compound that then, by analogy with the Sandmeyer reaction, decomposed into nitrogen and the acetylated sulfone. Deacetylation gave the β-D-glucopyranosyl *p*-tolyl sulfone (III), m.p. 145–148°, and rotation was not reported.

(22) Originally described as the monohydrate with $[\alpha]^{20}D$ −57.0° when recrystallized from water, the compound crystallizes in the anhydrous form as elongated prisms from ethyl acetate, m.p. 146–147°, $[\alpha]^{20}D$ −60.3° (c 2.1, pyridine). *Anal.* Calcd. for $C_{13}H_{18}O_8S$: C, 54.53; H, 6.34; S, 11.2. Found: C, 54.78; H, 6.37; S, 11.3.

tetrahydrofuran was added dropwise, with stirring, a solution of 4.7 g. of the sulfone tetraacetate (II) in 40 ml. of tetrahydrofuran. An additional 0.6 g. of lithium aluminum hydride was added, stirring was continued for another 3 hr., and the reaction mixture was left overnight. The excess reagent then was decomposed by the addition of 50 ml. of water, the precipitate was filtered and washed with hot water, and the solution was deionized by passage through columns of Amberlite IR-120 and Amberlite IR-45 ion-exchange resins. Concentration *in vacuo* left a yellowish sirup that crystallized slowly to yield 1,6-anhydro-β-D-glucopyranose (levoglucosan, VI); the product, after one recrystallization from ethanol, had m.p. 175–176°, undepressed on admixture with authentic material of m.p. 177–178°.

Reductive desulfurization of 1 g. of the sulfone tetraacetate (II) with 10 g. of Raney nickel in boiling ethanol for 5 hr. yielded a sirup that crystallized only very slowly. It was, therefore, deacetylated catalytically with methanolic barium methoxide and the product was identified as 1,5-anhydro-D-glucitol (polygalitol, VII) by paper chromatography and, after one recrystallization from methanol, by melting point and mixture melting point of 141–142°.

When the sulfone tetraacetate (II) was refluxed 8.5 hr. with an **excess of methanolic sodium methoxide**, the product appeared to consist, from paper chromatographic evidence alone, principally of 1,6-anhydro-β-D-glucopyranose with a small proportion of a methyl D-glucopyranoside. Under the same conditions *p*-tolyl 1-thio-β-D-glucopyranoside tetraacetate (I) appeared only to be deacetylated, for paper chromatography showed only a spot with the same R_f value as *p*-tolyl 1-thio-β-D-glucopyranoside (IV).

The attempted **acetolysis** of the sulfone acetate (II) by letting it stand a month at 25° with a 70:30 mixture of acetic anhydride and glacial acetic acid containing 2% of concentrated sulfuric acid resulted in no reaction and the starting material was recovered. Similarly, **bromine** seemed neither to substitute nor cleave the molecule when a mixture of 1.14 g. of the sulfone acetate (II), 0.4 g. of bromine, 1 g. of sodium bicarbonate, and 25 ml. of chloroform was stirred vigorously while being irradiated with an ultraviolet lamp. After the color of the bromine had been discharged (*ca.* 30 min.), the solution was filtered and concentrated, and the crystalline residue recrystallized from benzene–petroleum ether (b.p. 20–40°) to give unchanged sulfone acetate.

Some Reactions of β-D-Glucopyranosyl *p*-Tolyl Sulfone (III). With Periodate.—The sulfone was oxidized overnight with sodium metaperiodate and the excess of reagent was determined by the ion-exchange method described by Smith and Willeford.[23] The reaction consumed 2.2 moles of oxidant and liberated 0.9 mole of formic acid per mole of sulfone. Formaldehyde was not detectable with the dimedon reagent.

Alkaline degradation of 0.26 g. of the sulfone (III) in 10 ml. of 1 *N* potassium hydroxide and 2 ml. of water did not occur to any appreciable extent in 48 hr. at 25° because there was no observable change in rotation. However, when the solution was heated on a steam bath, the observed rotation in a 1-dm. tube changed overnight from $\alpha^{20}D$ −0.29° to −1.05° (constant). Paper chromatographic examination showed a spot of R_{gal} 3.2 identical with that of 1,6-anhydro-β-D-glucopyranose (VI). The solution was deionized and concentrated to a sirup that crystallized slowly; recrystallized from ethanol, the product melted at 178°, a value not depressed when the compound was mixed with 1,6-anhydro-β-D-glucopyranose.

Some Reactions of 6-*O*-Acetyl-β-D-glucopyranosyl *p*-Tolyl Sulfone (V). With Periodate.—The monoacetate (V), when oxidized with sodium metaperiodate overnight at 25°, consumed 2.02 moles of oxidant (determined by the Smith–Willeford ion-exchange technique[23]) and liberated 0.9 mole of formic acid per mole of compound. No formaldehyde could be detected by the chromotropic acid method.

Acetylation of V (0.9 g.) in 10 ml. of acetic anhydride and 15 ml. of pyridine for 2 days at 25°, followed by pouring the mixture into ice–water, yielded a white, crystalline precipitate. The product was recrystallized from ethanol to give 0.83 g. of prismatic needles, m.p. 150–151°, with no depression when mixed with authentic tetra-*O*-acetyl-β-D-glucopyranosyl *p*-tolyl sulfone (II).

Deacetylation of V with methanolic barium methoxide yielded β-D-glucopyranosyl *p*-tolyl sulfone (III), identified by melting point, mixture melting point, and R_{gal} 2.55. **Deacetylation with sodium borohydride** occurred when the monoacetate (V) was left with an excess of methanolic sodium borohydride overnight; the product, isolated in the usual manner and recrystallized from ethyl acetate, was identified as the free sulfone (III) by melting point and mixture melting point 151–152° and R_{gal} 2.55.

Reductive desulfurization of 1 g. of the sulfone monoacetate (V) with 12 g. of Raney nickel by refluxing in 40 ml. of ethanol for 12 hr. yielded a sirup. Paper chromatographic examination showed the presence of two substances, the one of R_{gal} 2.2 believed to be polygalitol and the other, in larger proportion, of R_{gal} 3.8 believed to be polygalitol 6-acetate because it gave a positive test when sprayed with alkaline hydroxylamine followed by ferric chloride.[24] The sirupy mixture, upon deacetylation with methanolic barium methoxide, yielded the expected 1,5-anhydro-D-glucitol (polygalitol, VII).

***o*-Tolyl Tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (VIII).**—This substance was prepared in 47% yield by the condensation of tetra-*O*-acetyl-α-D-glucopyranosyl bromide and *o*-toluenethiol according to the procedure described by Purves.[25] The broad needles obtained by recrystallization from ethanol melted at 104–105° and showed $[\alpha]^{20}D$ −17.2° (*c* 1, chloroform) in good agreement with the m.p. 104–106° and $[\alpha]D$ −16.4° reported by Černý, Zachystalová, and Pacák[26]; those authors had prepared it by the arylation of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucose with diazotized *o*-toluidine.

Tetra-*O*-acetyl-β-D-glucopyranosyl *o*-Tolyl Sulfone (IX).—Oxidation of 4.0 g. of VIII with 8 ml. of 30% hydrogen peroxide in 40 ml. of glacial acetic acid for 10 days at 25°, followed by dilution of the mixture with water and recrystallization from ethanol, afforded 2.85 g. of the sulfone acetate (IX) as white needles, m.p. 170–171°, $[\alpha]^{20}D$ −27.2° (c 1, chloroform). Deacetylation with barium methoxide failed to give a crystalline sulfone.

Anal. Calcd. for $C_{21}H_{26}O_{11}S$: C, 51.85; H, 5.39; S, 6.6; OAc, 35.4. Found: C, 51.90; H, 5.28; S, 6.7; OAc, 35.8.

***o*-Tolyl 1-Thio-β-D-glucopyranoside (X).**—The catalytic deacetylation of 25 g. of VIII furnished, after recrystallization from ethyl acetate, 13.3 g. of the thioglucoside (X) as fine needles, m.p. 149–150°, $[\alpha]^{20}D$ −57.8° (*c* 1, pyridine).

Anal. Calcd. for $C_{13}H_{18}O_5S$: C, 54.53; H, 6.34; S, 11.2. Found: C, 55.00; H, 6.62; S, 11.0.

Tetra-*O*-acetyl-β-D-glucopyranosyl *p*-Bromophenyl Sulfone (XI).—Oxidation of *p*-bromophenyl tetra-*O*-acetyl-β-D-glucopyranoside[3] with hydrogen peroxide in glacial acetic acid gave a 97% yield of the sulfone tetraacetate. Recrystallization from ethanol afforded long needles with m.p. 169–170° and $[\alpha]^{20}D$ −31.8° (*c* 2.5, chloroform).

Anal. Calcd. for $C_{20}H_{24}BrO_{11}S$: C, 43.57; H, 4.20; Br, 14.49; S, 5.8; OAc, 31.2. Found: C, 43.80; H, 4.32; Br, 14.21; S, 5.8; OAc, 30.8.

***p*-Bromophenyl β-D-Glucopyranosyl Sulfone (XII).**—Deacetylation of XI gave the free sulfone (XII); recrystallized from ethyl acetate in long fine needles, it melted at 166–167° dec. and showed $[\alpha]^{20}D$ −28.0° (*c* 0.8, pyridine), R_{glu} 2.9, λ_{max}^{MeOH} 234 mμ (ε 17,400).

Anal. Calcd. for $C_{12}H_{15}BrO_7S$: C, 37.61; H, 3.95; Br, 20.85; S, 8.4. Found: C, 37.83; H, 4.07; Br, 20.86; S, 8.1.

6-*O*-Acetyl-β-D-glucopyranosyl *p*-Bromophenyl Sulfone (XIII).—Oxidation of 1.6 g. of *p*-bromophenyl 1-thio-β-D-glucopyranoside[3] with 30% hydrogen peroxide in glacial acetic acid for 10 days resulted in a nearly quantitative yield of the sulfone 6-acetate (XIII). Recrystallized from ethanol, the fine, white needles showed m.p. 180–181° (followed by charring), $[\alpha]^{20}D$ −3.0° (*c* 0.7, pyridine), R_{glu} 3.1, λ_{max}^{MeOH} 234 mμ (ε 19,500).

(23) M. A. Smith and B. R. Willeford, Jr., *Anal. Chem.*, **26**, 751 (1954). Earlier, W. A. Bonner and R. W. Drisko [*J. Am. Chem. Soc.*, **70**, 2435 (1948); **73**, 3699 (1951)] had attempted to determine the ring structure of their sulfones by standard periodate procedures, but ran into difficulty because the end point in the final titration, with a starch indicator, faded rapidly. They were able to circumvent that difficulty by extracting the oxidation mixture with ethyl acetate to remove the dialdehyde before adding arsenite and making the final titration with iodine. The spectrophotometric method for the determination of periodate consumed [G. O. Aspinall and R. J. Ferrier, *Chem. Ind.* (London), 1216 (1957)] was unsatisfactory because the maximum of light absorption due to the periodate ion (223 mμ) is very close to that found for the *p*-tolyl sulfone moiety (228 mμ).

(24) M. Abdel-Akher and F. Smith, *J. Am. Chem. Soc.*, **73**, 5859 (1951).

(25) C. B. Purves, *ibid.*, **51**, 3619 (1929).

(26) M. Černý, D. Zachystalová, and J. Pacák, *Collection Czech. Chem. Commun.*, **26**, 2206 (1961).

Periodate oxidation of this sulfone monoacetate liberated 0.8 mole of formic acid and the consumption of oxidant (determined by the direct method, with a fading end point) amounted to 1.7 moles per mole of compound. No formaldehyde was detected with the dimedon reagent.

Anal. Calcd. for $C_{14}H_{17}BrO_8S$: C, 39.54; H, 4.03; Br, 18.79; S, 7.5; OAc, 10.1. Found: C, 39.49; H, 4.15; Br, 18.70; S, 7.5; OAc, 10.2.

p-Tolyl Tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (XIV).—Condensation of tetra-*O*-acetyl-α-D-galactopyranosyl bromide with *p*-toluenethiol in the usual manner gave about a 90% yield of crude product. Upon recrystallization from ethanol, the needles of XIV showed m.p. 116–117° and $[\alpha]^{20}D$ +6.0° (*c* 1, chloroform).

Anal. Calcd. for $C_{21}H_{26}O_9S$: C, 55.50; H, 5.77; S, 7.1. Found: C, 55.65; H, 5.87; S, 7.0.

Tetra-*O*-acetyl-β-D-galactopyranosyl *p*-Tolyl Sulfone (XV).—Oxidation of 3.7 g. of the thiogalactoside acetate (XIV) with hydrogen peroxide in glacial acetic acid led to the sulfone tetraacetate (XV). The product was recrystallized from aqueous ethanol as fine needles (2.8 g.), m.p. 133–134°, $[\alpha]^{20}D$ −20.3° (*c* 0.8, chloroform).

Anal. Calcd. for $C_{21}H_{26}O_{11}S$: C, 51.85; H, 5.39; S, 6.6; OAc, 35.4. Found: C, 51.63; H, 5.51; S, 6.7; OAc, 35.1.

β-D-Galactopyranosyl *p*-Tolyl Sulfone (XVI).—Deacetylation of the acetylated sulfone (XV) gave the free sulfone (XVI); recrystallized from isopropyl alcohol as acicular prisms, it melted at 166–167° (followed by charring) and showed $[\alpha]^{20}D$ −16.7° (*c* 1, pyridine), λ_{max}^{MeOH} 225 mμ (ε 14,200).

Anal. Calcd. for $C_{13}H_{18}O_7S$: C, 49.05; H, 5.70; S, 10.1. Found: C, 48.89; H, 5.85; S, 10.1.

p-Tolyl 1-Thio-β-D-galactopyranoside (XVII).—Deacetylation of the thiogalactoside tetraacetate (XIV) gave the free thiogalactoside (XVII): the long needles obtained by crystallization from water showed m.p. 142–143° and $[\alpha]^{20}D$ −55.8° (*c* 1.2, pyridine).

Anal. Calcd. for $C_{13}H_{18}O_5S$: C, 54.53; H, 6.34; S, 11.2. Found: C, 54.33; H, 6.25; S, 11.3.

o-Tolyl Tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (XVIII).—Condensation of tetra-*O*-acetyl-α-D-galactopyranosyl bromide with *o*-toluenethiol gave a 51% yield of XVIII after one recrystallization from ethanol as prismatic needles, m.p. 98–99°, and $[\alpha]^{20}D$ ±0.0° (*c* 1, chloroform).

Anal. Calcd. for $C_{21}H_{26}O_9S$: C, 55.50; H, 5.77; S, 7.1; OAc, 37.9. Found: C, 55.63; H, 5.82; S, 7.0; OAc, 37.5.

Tetra-*O*-acetyl-β-D-galactopyranosyl *o*-Tolyl Sulfone (XIX).—Oxidation of the thiogalactoside tetraacetate (XVIII) with hydrogen peroxide in glacial acetic acid gave the sulfone tetraacetate (XIX) as small, prismatic needles from aqueous ethanol, with m.p. 90–91° and $[\alpha]^{20}D$ −19.2° (*c* 1.1, chloroform). Deacetylation of XIX failed to give a crystalline product.

Anal. Calcd. for $C_{21}H_{26}O_{11}S$: C, 51.85; H, 5.39; S, 6.6; OAc, 35.4. Found: C, 51.63; H, 5.53; S, 6.8; OAc, 35.6.

o-Tolyl 1-Thio-β-D-galactopyranoside (XX).—Deacetylation of XVIII gave crystalline XX; the compound crystallized from ethyl acetate as feathery needles that melted at 148–149° and showed $[\alpha]^{20}D$ −49.7° (*c* 0.1, pyridine).

Anal. Calcd. for $C_{13}H_{18}O_5S$: C, 54.53; H, 6.34; S, 11.2. Found: C, 54.61; H, 6.40; S, 11.3.

Thioglycosides That Did Not Give Crystalline 6-*O*-Acetylglycosyl Aryl Sulfones.—The three new thioglycosides reported in this paper (X, XVII, and XX) and the following five old ones[3] failed to yield crystalline 6-acetates when oxidized with 30% hydrogen peroxide in glacial acetic acid: phenyl, *p*-acetylphenyl, *p*-chlorophenyl, 2,5-dichlorophenyl, and *N*-benzyl-*N*-methyl-*p*-aminophenyl β-D-glucopyranosides.

Oxidation of Thioglycosides with Peroxypropionic Acid.—One gram of *p*-tolyl 1-thio-β-D-glucopyranoside (IV) was dissolved in 20 ml. of boiling isopropyl alcohol and to the hot solution was added 7 ml. of carefully redistilled 3.5 *N* peroxypropionic acid.[27] The reaction mixture was left at 25° overnight and then another 7 ml. of oxidant was added. After 1 hr. the solution was concentrated *in vacuo* to a thick sirup; dilution with ethyl acetate yielded crystalline material that was identified by its R_f value and by melting point and mixture melting point as β-D-glucopyranosyl *p*-tolyl sulfone (III).

In a variation of this procedure, 1 g. of *p*-tolyl 1-thio-β-D-galactopyranoside (XVII) was dissolved in 7 ml. of dimethylformamide and 13 ml. of dioxane and then 6.5 ml. of 6 *N* peroxypropionic acid was added. After 1 hr. at 25° the mixture was heated on the steam bath, an additional 5 ml. of oxidant was added, and heating was continued for 0.5 hr. Concentration *in vacuo* left a semicrystalline residue from which some sirupy material was removed by extraction with ethyl ether. The residue, on recrystallization from hot isopropyl alcohol, afforded 0.5 g. of acicular prisms with m.p. and m.m.p. 166–167° (followed by charring) and $[\alpha]^{20}D$ −16.7° (*c* 1, pyridine); the product was thus identified as β-D-galactopyranosyl *p*-tolyl sulfone (XVI), and the C, H, and S analyses were in accord.

Infrared Data.—The infrared spectra were obtained with a Perkin-Elmer recording infrared spectrophotometer Model 21. Since no infrared data on glycosyl sulfones and their acetates seem to have been reported previously, we have listed the principal absorption bands of some representative compounds below. Nujol mulls were used unless otherwise noted. When chloroform, carbon disulfide, or pyridine was used as a solvent, the absorption bands listed were so strong that they could not be attributed, except perhaps in very small part, to the solvent used. It will be observed that all sulfones have one or more absorption bands near 1325 (the mean absorption frequency attributed to asymmetric SO_2 stretching vibrations in C–SO_2–C compounds[28]) and 1140 cm.$^{-1}$ (the mean absorption frequency attributed to symmetric SO_2 stretching vibrations in C–SO_2–C compounds[28]). The principal ester carbonyl absorption band appears, as expected, between 1745 and 1760 cm.$^{-1}$ for all sulfide and sulfone tetraacetates. In the two sulfone 6-acetates (V and XIII), however, this band appeared at 1690 and 1695 cm.$^{-1}$, respectively, when measured in Nujol mulls but shifted to 1740 and 1750 cm.$^{-1}$, respectively, when measured in pyridine.

p-Tolyl 1-thio-β-D-glucopyranoside (IV): 3280, 1106, 1084, 1044, 1033, 1020, 990, 810, and 800 cm.$^{-1}$.

p-Bromophenyl 1-thio-β-D-glucopyranoside[3]: 3570, 3250, 1107, 1087, 1078, 1064, 1045, 1033, 1010, 990, 817, and 797 cm.$^{-1}$.

β-D-Glucopyranosyl *p*-tolyl sulfone (III): 3500, 3350, 1640, 1602, 1355, 1335, 1305, 1295 (sh), 1288, 1257, 1193, 1144 (sh), 1133, 1117, 1098, 1083, 1055, 1041, 1015, 1002, 878, 841, 811, 705, and 653 cm.$^{-1}$.

p-Bromophenyl β-D-glucopyranosyl sulfone (XII): 3520, 3370, 1580, 1360, 1307, 1290, 1278, 1147, 1137, 1118, 1102, 1083, 1067, 1060, 1044, 1008, 880, 841, 820, 732, and 703 cm.$^{-1}$.

β-D-Galactopyranosyl *p*-tolyl sulfone (XVI): 3450, 3240, 1318, 1306, 1276, 1260, 1145, 1123, 1093, 1081, 1062, and 1037 cm.$^{-1}$.

p-Tolyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (I): 1750, 1298, 1250 (sh), 1228, 1104, 1083, 1042, 983, 918, 820, and 809 cm.$^{-1}$.

Tetra-*O*-acetyl-β-D-glucopyranosyl *p*-tolyl sulfone (II): 1745, 1323, 1263 (sh), 1243, 1224, 1211, 1154, 1107, 1085, 1063, and 1036 cm.$^{-1}$.

Compound II in potassium bromide pellet: 3400 (H_2O?),[29] 1760, 1630 (H_2O?),[29] 1600, 1432, 1368, 1323, 1228, 1152, 1083, 1058, and 1034 cm.$^{-1}$.

Compound II in chloroform: 1755, 1600, 1365, 1325, 1305, 1143, 1124, 1084, 1058, 1032, and 834 cm.$^{-1}$.

Compound II in carbon disulfide: 1760, 1363, 1334, 1235, 1215, 1147, 1085, 1061, 1033, and 810 cm.$^{-1}$.

Compound II in pyridine: 3370 (H_2O?),[29] 1755, 1660, 1363, 1323, 1220 (?), and 1083 cm.$^{-1}$.

Tetra-*O*-acetyl-β-D-glucopyranosyl *p*-bromophenyl sulfone (XI): 1755, 1342, 1330, 1243, 1226, 1153, 1115, 1063, 1036, 1008, 807, and 745 cm.$^{-1}$.

Compound XI in chloroform: 1760, 1580, 1388 (sh), 1368, 1343, 1152, 1130, 1084, 1068, 1035, and 1012 cm.$^{-1}$.

6-*O*-Acetyl-β-D-glucopyranosyl *p*-tolyl sulfone (V): 3390, 1690, 1600, 1344, 1328, 1285, 1255, 1150, 1110, 1088, 1050, 1022, 987, 922, 808, 704, and 673 cm.$^{-1}$.

Compound V in pyridine: 3140, 1740, 1320, 1235, 1112, 1082, and 1045 cm.$^{-1}$.

6-*O*-Acetyl-β-D-glucopyranosyl *p*-bromophenyl sulfone (XIII): 3400, 1695, 1350, 1333, 1315, 1295, 1287, 1273, 1255, 1155, 1143, 1112, 1092, 1082, 1069, 1049, 1013, 817, and 743 cm.$^{-1}$.

(27) D. L. MacDonald, *Methods Carbohydrate Chem.*, **1**, 73 (1962).

(28) L. J. Bellamy, "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, p. 49.

(29) Spectra obtained in potassium bromide pellets and in pyridine solution may show absorption bands near 3400 and 1630 cm.$^{-1}$; these are attributable to the presence of water and occur frequently unless special precautions are taken for the rigorous exclusion of moisture.

Compound XIII in pyridine: 3150, 1750, 1385, 1365, 1335, 1275, 1235, 1083, and 1050 cm.$^{-1}$.

Nuclear Magnetic Resonance Data.—The n.m.r. spectra were recorded on a Varian Model A-60 spectrometer; pyridine was used as the solvent and tetramethylsilane as the internal reference. We are indebted to Dr. John D. Stevens of this laboratory for the following interpretation.

Nuclear magnetic resonance spectra confirmed that the hydroxyl group on C-6 was acetylated in the two sulfone monoacetates (V and XIII). The spectrum for β-D-glucopyranosyl *p*-tolyl sulfone (III) showed signals at τ 7.83 (aromatic methyl group), at 5.3 to 6.1 (broad band due to protons on C-2 to C-6), and at 4.83 (doublet, spacing 9.0 c.p.s.). The doublet at τ 4.83 arises from the anomeric hydrogen atom. Since the spacing for this doublet is typical of 1,2 diaxially oriented hydrogen atoms on a six-membered ring,[30] this observation verifies the β-D-glucopyranosidic linkage in the sulfone. A similar spectrum was obtained for the *p*-bromophenyl β-D-glucopyranosyl sulfone (XII, doublet at τ 4.77, spacing 8.6 c.p.s.). 6-*O*-Acetyl-β-D-glucopyranosyl *p*-tolyl sulfone (V) showed signals at τ 8.13 (acetyl group), 7.75 (aromatic methyl group), a series of broad peaks between 5.25 and 6.13, and a doublet (spacing 9.2 c.p.s.) at 4.89. The low-field doublet in the spectrum of this compound is attributed to the anomeric hydrogen atom and the absence of any signals downfield from this proton is strong evidence for the absence of an acetoxy group on C-2, C-3, or C-4. [For comparison, the spectrum of methyl tetra-*O*-acetyl-β-D-glucopyranoside in pyridine solution showed protons on C-2, C-3, and C-4 at τ 4.3 to 4.6 and the anomeric hydrogen at 5.2 (spacing 7.5 c.p.s.)[31]] For tetra-*O*-acetyl-β-D-glucopyranosyl *p*-tolyl sulfone (II), signals with intensity corresponding to two protons occurred at τ 4.0 to 4.47 and another group of signals with two-proton intensity occurred at 4.5 to 4.97; thus, the signals due to protons on C-1 to C-4 all occur at τ-values less than 5. Similarly, no peaks occurred downfield from the doublet at τ 4.83 (spacing 9.0 c.p.s.) due to the anomeric hydrogen atom in the n.m.r. spectrum of 6-*O*-acetyl-β-D-glucopyranosyl *p*-bromophenyl sulfone (XIII).

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(30) R. U. Lemieux, R. K. Kullnig, H. F. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(31) N. Mori, S. Omura, O. Yamamoto, T. Suzuki, and Y. Tsuzuki [*Bull. Chem. Soc. Japan*, **36**, 1047 (1963)] have shown that for methyl tetra-*O*-acetyl-β-D-glycopyranosides in chloroform solution the signals due to the anomeric hydrogen appear at higher field than those due to protons on C-2 to C-4.

Preparation of 6-Acetamido-1,2,3,4-tetra-O-acetyl-6-deoxy-L-idothiapyranose[1]

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Reaction of 5,6-anhydro-3-O-benzyl-1,2-O-isopropylidene-D-glucofuranose (I) with benzylmercaptide ion afforded 3-O-benzyl-6-S-benzyl-1,2-O-isopropylidene-6-thio-D-glucofuranose (II) that, with thionyl chloride, yielded 3-O-benzyl-5-S-benzyl-6-chloro-6-deoxy-1,2-O-isopropylidene-5-thio-L-idofuranose (IV) *via* the benzylepisulfonium ion (VIII). Reaction of IV with sodium azide gave the 6-azido-5-benzylthio sugar (VII) that was reduced to the 6-amino-5-benzylthio derivative (V), easily converted to the N-acetate (VI). Reduction of V or VI with sodium and liquid ammonia afforded the 6-amino-5-thiol (IX) and the 6-acetamido-5-thiol (X), respectively. Acid hydrolysis of the isopropylidene group resulted in the formation of a thiapyranose sugar, that was acetylated to the pentaacetate (XII), one anomer of which was isolated as a crystalline solid.

Since 1961 a number of articles have appeared describing sugars that contain sulfur[2] or nitrogen[3] as the heterocyclic atom of the sugar ring. In studying the relative abilities of thiol, hydroxyl, and amino groups to interact with C-1 to form a cyclic sugar it will be advantageous to have a number of sugars containing these groups properly situated for potential cyclization. This manuscript reports the preparation of a derivative (XII) of 6-amino-6-deoxy-5-thio-L-idose, such a sugar. The pentaacetate (XII) is also a derivative of a vicinal aminomercapto sugar which is of interest for comparison with other such compounds which have recently been prepared.[4]

The conversion of 1,2:5,6-di-O-isopropylidene-D-glucofuranose to 5,6-anhydro-3-O-benzyl-1,2-O-isopropylidene-D-glucofuranose (I) was carried out using the sequence described by Meyer and Reichstein.[5] Reaction of the epoxide (I) with sodium benzyl mercaptide afforded the 6-benzylthio sugar (II) (Chart I) as an oil purified by chromatography over silica gel. Previously it had been determined that treatment of I with sodium hydroxide gave 3-O-benzyl-1,2-O-isopropylidene-D-glucofuranose predominantly, if not exclusively,[5] indicating nucleophilic attack at C-6. Similar 5,6-anhydro sugars have been shown to undergo nucleophilic attack by ammonia at C-6[6]; structure II is written on the basis of these considerations. The benzylthio sugar (II) was characterized as the crystalline phenylurethan (III) and was converted to the crystalline chloro sugar (IV) by treatment with thionyl chloride. The structure of IV was assigned on the assumption of opening of an episulfonium ion intermediate (VIII, formed by the way of the chlorosulfite of II) at C-6[5,6] and on the basis of n.m.r. information. Thus, the C-6 methylene group of IV appeared as a four-peak multiplet centered at γ 6.45 as compared

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(2) (a) J. C. P. Schwarz and K. C. Yule, *Proc. Chem. Soc.*, 417 (1961); (b) T. J. Adley and L. N. Owen, *ibid.*, 418 (1961); (c) R. L. Whistler, M. S. Feather, and D. L. Ingles, *J. Am. Chem. Soc.*, **84**, 122 (1962); (d) E. J. Reist, D. E. Gueffroy, and L. Goodman, *ibid.*, **85**, 3715 (1963).

(3) (a) J. K. N. Jones and J. C. Turner, *J. Chem. Soc.*, 4699 (1962); (b) H. Paulsen, *Angew. Chem., Intern. Ed. Engl.*, **1**, 597 (1962).

(4) (a) L. Goodman and J. E. Christensen, *J. Am. Chem. Soc.*, **83**, 3823 (1961); (b) J. E. Christensen and L. Goodman, *ibid.*, **83**, 3827 (1961).

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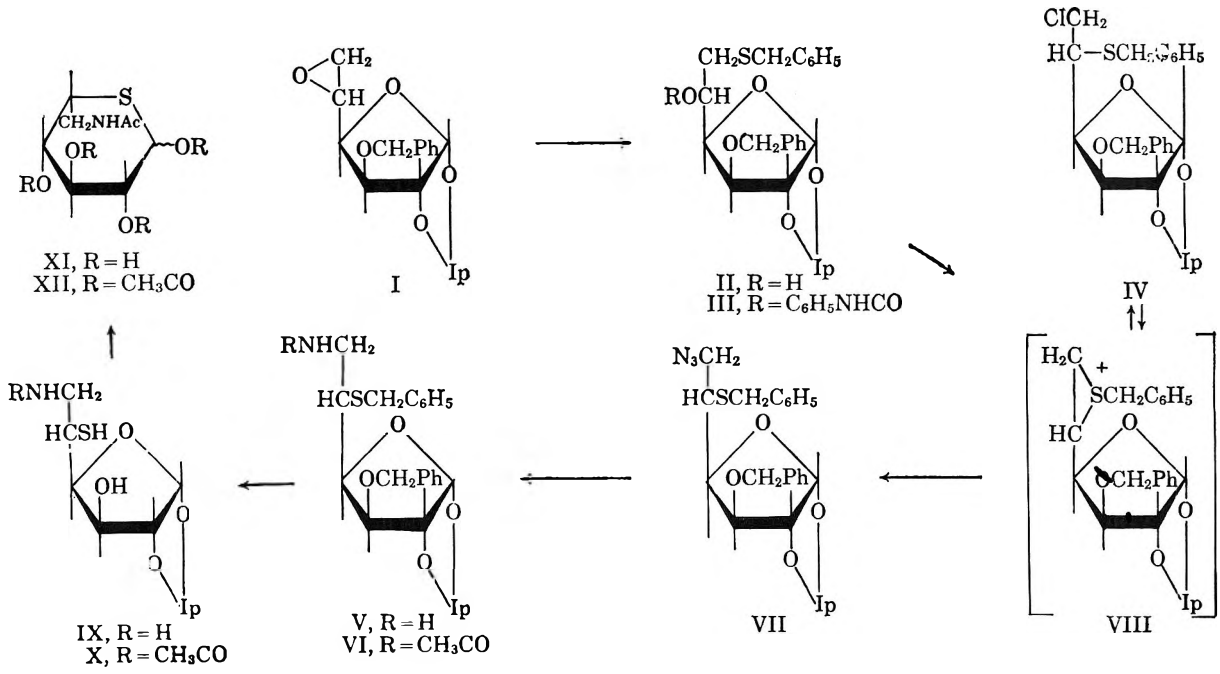
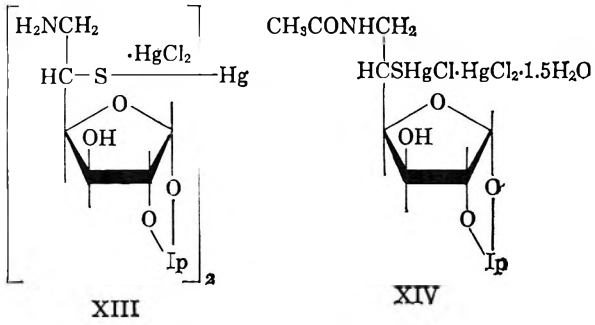
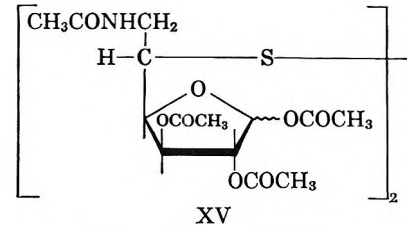
CHART I



to the C-6 methylene of III at γ 7.18; the position of the C-6 protons in IV as compared to that in III is logical when the deshielding ability of a chlorine is compared with that of a benzylthio group. Reaction of IV with sodium azide in 2-methoxyethanol gave a good yield of the azide (VII) that was reduced with sodium borohydride in isopropyl alcohol[7] to the crystalline amine (V) also characterized as the N-acetate (VI). The position of the amine group at C-6 is assumed on the basis of reaction *via* the ion VIII and opening of VIII at C-6. Reduction of either V or VI with sodium in liquid ammonia gave thiols that were isolated as complex mercaptides with mercuric chloride. The derivative from V was analyzed as the bismercurial XIII, that from VI as the chloromercuri derivative XIV. Similar complex mercaptides have been noted



in other work with mercaptoamino sugars.[4a,8] The regeneration of the free thiols from XIII and XIV with hydrogen sulfide, either in methanolic or aqueous hydrogen chloride to remove the isopropylidene group, gave solids that did not analyze well for the expected thiapyranose sugar (XI, or its methyl glycoside when methanolic hydrogen chloride was employed). It was found in later work that the isopropylidene group was unexpectedly resistant to acid hydrolysis and the presence of some deblocked compound may have been responsible for the poor analytical results. In the most favorable case the mercaptide (XIV) was treated with hydrogen sulfide in aqueous hydrochloride acid; then the removal of the isopropylidene group was completed with hot hydrochloric acid. The product of the reaction, presumably XI, was acetylated to give a low yield of a sharply melting, nitroprusside-negative, crystalline compound, probably one of the pure anomers of XII. The compound showed no infrared S-acetate absorption and its n.m.r. spectrum showed the presence of five acetyl groups, thus eliminating the furanose disulfide (XV) as a possible structure. The specific



rotation of crystalline XII, +54.5°, as compared with that of the mother liquors from crystallization of XII, −29.5°, suggests that crystalline XII is 6-acetamido-1,2,3,4-tetra-O-acetyl-6-deoxy-β-L-idothiapyranoside. The analysis of compound XII was not satisfactory according to normal analytical standards. However, the n.m.r. spectrum clearly showed the presence of about 0.4 benzene protons (benzene was one of the recrystallizing solvents); correction of the calculated values for the appropriate amount of benzene then gave completely acceptable analytical figures for solvated XII.

Experimental[9]

3-O-Benzyl-6-S-benzyl-1,2-O-isopropylidene-6-thio-D-glucofuranose (II) and Its Phenylurethan (III).—A solution of 20.53 g.

(7) P. A. S. Smith, J. H. Hall, and R. O. Kan, *J. Am. Chem. Soc.*, **84**, 485 (1962).

(8) J. E. Christensen and L. Goodman, *J. Org. Chem.*, **28**, 2995 (1963).

(9) Melting points are uncorrected and were obtained with the Fisher-Johns apparatus. Optical rotations were determined in chloroform at the sodium D line unless otherwise noted. The n.m.r. spectra were obtained with the A-60 instrument or the V-4311 spectrometer operated at 60 Mc. and were run in deuteriochloroform. Magnesium sulfate was the drying agent employed. The silica gel used in chromatography was purchased from Gallard-Schlesinger Chemical Manufacturing Corp., Garden City, N. Y.

(70.2 mmoles) of the crude epoxide (I),[5] 3.85 g. (71.2 mmoles) of sodium methoxide, 8.88 g. (71.5 mmoles) of benzylmercaptan, and 200 ml. of methanol was heated at reflux under nitrogen for 18 hr., then was cooled and adjusted to pH 7 with glacial acetic acid. The mixture was concentrated *in vacuo* to about half its volume, then was poured into 400 ml. of ice–water. The aqueous mixture was extracted with four 50-ml. portions of dichloromethane; the combined extracts were washed with 100 ml. of water, decolorized with Norit, and dried, then evaporated *in vacuo* leaving 25.6 g. of an amber sirup. This was applied to a silica gel column (90–200 mesh, 36 × 260 mm.), and elution with 500 ml. of benzene removed 9.6 g. of an oil that, according to its infrared spectrum, contained considerable dibenzyl disulfide. Further elution with benzene containing 4% ethyl acetate (800 ml.) gave 13.3 g. (45.7%) of a sirup whose infrared spectrum compared well with the analytical sample of II (see below) and which was suitable for use in subsequent work. Finally elution with 400 ml. of ethyl acetate afforded 2.5 g. of a sirup whose infrared spectrum showed too little benzylthio absorptions. The low yield of II is probably a reflection of the quality of I used; extensive decomposition accompanied efforts to purify I by distillation so that crude I was used in most of the work.

From another run, a portion of the product was acetylated with acetic anhydride and pyridine and the isolated acetate, a sirup, was deacetylated with a catalytic amount of sodium methoxide in methanol, affording II as a sirup with $n^{18}D$ 1.5663.

Anal. Calcd. for $C_{23}H_{28}O_5S$: C, 66.3; H, 6.78; S, 7.70. Found: C, 65.8, 65.9; H, 7.11, 7.18; S, 7.67.

A mixture of 0.50 g. (1.20 mmoles) of II, 0.22 g. (1.85 mmoles) of phenyl isocyanate and a drop of triethylamine, protected against moisture, was heated on the steam bath for 2.25 hr., then was extracted with three 5-ml. portions of petroleum ether (b.p. 30–60°). The sirup remaining after the petroleum ether treatment was a foamy solid that was recrystallized from 3 ml. of isopropyl alcohol giving 0.070 g. (11%) of solid, m.p. 110–133°. A second recrystallization from 2 ml. of isopropyl alcohol afforded 0.040 g. of the analytical sample, m.p. 138–139°, λ_{max}^{Nujol} 2.97 (NH) and 5.85 μ (urethan C=O). The n.m.r. spectrum showed resonances at γ 3.63 (NH singlet), 4.19 (C-1 doublet, J = 3.5 c.p.s.), 4.74 (C-5, one proton multiplet), 6.31 (benzylthio singlet), 7.18 (C-6, 2 proton multiplet), 8.54 and 8.72 (isopropylidene methyls).

Anal. Calcd. for $C_{30}H_{33}NO_6S$: C, 67.3; H, 6.21; N, 2.62; S, 5.99. Found: C, 67.1; H, 5.99; N, 2.59; S, 5.90.

3-O-Benzyl-5-S-benzyl-6-chloro-6-deoxy-1,2-O-isopropylidene-5-thio-L-idofuranose (IV).—A mixture of 15.2 g. (36.4 mmoles) of II, 17 ml. of thionyl chloride, and 150 ml. of dichloromethane was heated at reflux, with exclusion of moisture, for 1.5 hr., then poured cautiously with stirring into 900 ml. of cold (0°) saturated aqueous sodium carbonate. The layers were separated and the aqueous phase was extracted with two 100-ml. portions of dichloromethane. The combined organic solutions were washed with two 100-ml. portions of water, then dried and evaporated *in vacuo*, affording 14.7 g. (93%) of pale amber sirup whose infrared spectrum showed no –OH absorption. The sirup crystallized on standing. A portion (0.41 g.) was recrystallized from 5 ml. of isopropyl alcohol yielding 0.29 g. of needles, m.p. 62–65°. A second identical recrystallization afforded 0.18 g. of the analytical sample, m.p. 61.5–64.0°, $[\alpha]^{24}$ –70.8° (1%). The n.m.r. spectrum showed resonances at γ 4.13 (C-1 doublet, J = 3.5 c.p.s.), 6.11 (benzylthio singlet), 6.45 (C-6, 2 proton quartet), 6.85 (C-5, one proton multiplet), 8.58 and 8.73 (isopropylidene methyls).

Anal. Calcd. for $C_{23}H_{27}ClO_4S$: C, 63.5; H, 6.26; Cl, 8.15; S, 7.37. Found: C, 63.9; H, 6.64; Cl, 7.96; S, 7.36.

6-Azido-3-O-benzyl-5-S-benzyl-6-deoxy-1,2-O-isopropylidene-5-thio-L-idofuranose (VII).—A stirred mixture of 2.26 g. (5.20 mmoles) of the chloro sugar (IV), 8.5 g. (0.13 mole) of sodium azide, and 60 ml. of 95% aqueous 2-methoxyethanol was heated, under nitrogen, at 105–110° for 2 hr., then cooled, and evaporated *in vacuo*. The solid residue was partitioned between 100 ml. of dichloromethane and 150 ml. of water. The aqueous layer was extracted with two 50-ml. portions of dichloromethane, and the combined organic solutions were washed with 100 ml. of saturated aqueous sodium chloride solution, then dried. The filtrated solution was evaporated *in vacuo*, leaving 2.14 g. of a golden sirup. The sirup was extracted with 25 ml. of Skellysolve B (b.p. 62–70°), leaving a small residue. Evaporation of the Skellysolve B extract afforded 2.05 g. (90%) of a yellow sirup; λ_{max}^{film} 4.78 (N_3), 13.0, 13.56, and 14.27 μ (phenyl). Analysis was obtained on a product prepared as above.

Anal. Calcd. for $C_{23}H_{27}N_3O_4S$: C, 62.6; H, 6.16; N, 9.52; S, 7.28. Found: C, 62.5, 62.7; H, 6.41, 6.58; N, 9.82; S, 7.72.

6-Amino-3-O-benzyl-5-S-benzyl-6-deoxy-1,2-O-isopropylidene-5-thio-L-idofuranose (V) and Its N-Acetate (VI).—A stirred mixture of 3.68 g. (8.32 mmoles) of VII (as the crude sirup), 1.3 g. (34 mmoles) of sodium borohydride, and 30 ml. of isopropyl alcohol was heated at reflux for 40 hr., then cooled, and evaporated *in vacuo*. The residue was dissolved in 20 ml. of water, and the solution was extracted with 30 ml. of dichloromethane. The organic layer was washed with two 20-ml. portions of water, dried, and evaporated *in vacuo*, affording 3.38 g. (98%) of sirup. Crystallization from 30 ml. of Skellysolve C (b.p. 88–99°) afforded 2.0 g. (58%) of white crystals, m.p. 103–112°. An analytical sample was obtained from a reduction of VII with lithium aluminum hydride. After recrystallization from isopropyl alcohol it had m.p. 111–113°, $[\alpha]^{33}$ –115° (1%).

Anal. Calcd. for $C_{23}H_{29}NO_4S$: C, 66.5; H, 7.04; N, 3.37; S, 7.72. Found: C, 66.4; H, 7.31; N, 3.55; S, 7.99.

Acetylation of 0.40 g. (0.963 mmole) of V with 2 ml. of acetic anhydride and 0.30 g. of anhydrous sodium acetate at 55° for 3.5 hr. gave, after decomposition with 30 ml. of ice–water, 0.50 g. (114%) of white solid, m.p. 98–113°. Two recrystallizations from benzene–petroleum ether (b.p. 30–60°) gave 0.30 g. (68%) of white needles, m.p. 123–125°; λ_{max}^{Nujol} 2.99 (NH) and 6.05 μ (amide C=O); $[\alpha]^{22}$ –64° (*c* 1, methanol).

Anal. Calcd. for $C_{25}H_{31}NO_5S$: C, 65.6; H, 6.83; N, 3.06; S, 7.01. Found: C, 65.1; H, 6.52; N, 3.05; S, 7.23.

6-Amino-6-deoxy-1,2-O-isopropylidene-5-thio-L-idofuranose (IX) and Its Mercaptide (XIII).—To a stirred solution of 0.50 g. (21.7 mg.-atoms) of clean, dry sodium in 22 ml. of liquid ammonia was added dropwise a solution of 1.72 g. (4.14 mmoles) of the amine (V) in 7 ml. of 1,2-dimethoxyethane. The resulting solution was stirred for 30 min., then was treated with solid ammonium chloride until the blue color had disappeared. The ammonia was carefully evaporated, the residue was dissolved in 30 ml. of water, and the solution was adjusted to pH 6 with glacial acetic acid. Extraction of the solution with two 30-ml. portions of dichloromethane removed bibenzyl; then the solution was continuously extracted with chloroform for 18 hr., yielding 0.24 g. (25%) of white nitroprusside-positive solid. Continuous extraction for 48 hr. more with chloroform afforded 0.19 g. (20%) of the solid. The first crop was stirred with ether and filtered giving a white solid, m.p. 88–109°; λ_{max}^{Nujol} 3.1–3.3, 3.6–4.1, and 6.3 μ (broad absorptions, usually characteristic of amine salts).

Anal. Calcd. for $C_9H_{17}NO_4S$: C, 46.0; H, 7.28; N, 5.96; S, 13.6. Found: C, 44.4; H, 7.27; N, 5.92; S, 13.7.

When the aqueous solution containing the product from sodium and liquid ammonia treatment of 1.50 g. of V was treated with excess saturated aqueous mercuric chloride, a precipitate was formed. This was dried and triturated thoroughly with dichloromethane to remove any bibenzyl, giving 1.93 g. (44%) of white solid whose analysis is in accord with structure XIII.

Anal. Calcd. for $C_{18}H_{32}Cl_4Hg_3N_2O_8S_2$: C, 17.8; H, 2.66; Cl, 11.7; N, 2.31; S, 5.29. Found: C, 17.5; H, 3.03; Cl, 11.6; N, 2.09; S, 5.29.

Treatment of the mercaptide (XIII) with hydrogen sulfide either in methanol or water containing hydrogen chloride gave widely melting solids whose analytical figures did not agree with those for any logical structure.

6-Acetamido-6-deoxy-1,2-O-Isopropylidene-5-thio-L-idofuranose (X) and Its Mercaptide (XIV).—The amide (VI), 2.67 g. (5.84 mmoles), was treated with sodium and liquid ammonia using the procedure described for the similar treatment of V. The aqueous solution of the residue from evaporation of the ammonia was treated with excess aqueous mercuric chloride, affording 4.10 g. (90%) of cream-colored solid. From a previous run a similar solid, m.p. 123–125°, was obtained whose analysis was in accord with that for structure XIV.

Anal. Calcd. for $C_{11}H_{18}Cl_3Hg_2NO_5S \cdot 1.5H_2O$: C, 16.3; H, 2.61; Cl, 13.1; S, 3.95. Found: C, 16.2; H, 2.84; Cl, 12.9; S, 4.01.

The mercaptide (XIV), 4.10 g., was suspended in 40 ml. of cold (0°) water and the suspension was treated with hydrogen sulfide for 30 min. The suspension was filtered through Celite and the pH of the filtrate was adjusted to 5–6 with Amberlite IR 45 resin. After being filtered, the solution was evaporated

in vacuo and the residue was triturated with several portions of dry ether then maintained at 1 mm., leaving 0.75 g. (52%) of a hygroscopic, nitroprusside-positive foam which darkened on standing; λ_{max}^{film} 3.0 (OH, NH), 3.90 (SH), and 6.0–6.1 μ (amide C=O).

Anal. Calcd. for $C_{11}H_{19}NO_5S$: C, 47.6; H, 6.91; N, 5.05; S, 11.6. Found: C, 45.7; H, 6.93; N, 5.60; S, 11.8.

6-Acetamido-1,2,3,4-tetra-O-acetyl-6-deoxy-L-idothiapyranose (XII).—The mercaptide (XIV), 4.23 g. (5.40 mmoles), suspended in 40 ml. of 0.1 *N* hydrochloric acid, was treated with hydrogen sulfide as described for the preparation of IX. After the filtration through Celite, the filtrate was stirred at room temperature for 1.5 hr., then neutralized, and evaporated, yielding 0.75 g. of a foam that gave a positive reducing sugar test and a positive nitroprusside test; its infrared spectrum indicated the presence of the isopropylidene group, however. The foam was stirred in 0.1 *N* hydrochloric acid overnight, then neutralized, and evaporated, giving 0.53 g. of a glass whose n.m.r. spectrum in deuterium oxide showed the presence of about 60–70% of the original isopropylidene group. Finally, the material in 20 ml. of 0.5 *N* hydrochloric acid was stirred at 40–45° for 3.5 hr., then neutralized, and evaporated, yielding 0.41 g. of sirup whose n.m.r. spectrum showed the essential absence of the isopropylidene group.

The sirup, 0.35 g., was treated with 5 ml. of dry pyridine and the solution was decanted from some insoluble material, chilled to 0°, and 5 ml. of acetic anhydride was added. The mixture was maintained at 5° for 18 hr. and at room temperature for 2 hr., then was poured into 50 ml. of ice–water. The solution was neutralized with solid sodium carbonate, and extracted with two 20-ml. portions of dichloromethane; the extracts were washed with 20 ml. of water and dried. Evaporation left 0.26 g. of yellow sirup which crystallized on standing. It was recrystallized three times from benzene–petroleum ether (b.p. 30–60°), affording 0.065 g. of crystals, m.p. 165–166°; $[\alpha]^{24}$ +54.5° (1%); λ_{max}^{Nujol} 2.99, 3.02 and 6.42 (NH), and 5.68 (O-acetyl C=O), 6.02 μ (amide C=O); there was no appreciable absorption near 5.90 μ, suggestive of an S-acetyl carbonyl, nor near 7.40 μ, suggestive of the methyl group of the S-acetate. The n.m.r. spectrum showed absorptions at γ 2.71 (benzene solvent, 0.36 protons), 3.85 (C-1 doublet, J = 3.5 c.p.s.), 7.83, 7.91, 7.96, and 8.01 (CH_3CO protons totaling 15 protons).

Anal. Calcd. for $C_{16}H_{23}NO_9S \cdot 0.06C_6H_6$: C, 47.9; H, 5.74; N, 3.42; S, 7.84. Found: C, 48.1; H, 5.87; N, 3.45; S, 7.60.

The mother liquors from the recrystallizations were combined and evaporated *in vacuo* leaving a sirup, $[\alpha]^{25}$ −29.5° (1.1%), whose infrared spectrum was similar to that of the crystalline solid and demonstrated the same functional groups.

Acknowledgment.—The authors wish to thank Dr. Peter Lim and his group for the infrared, n.m.r., and optical rotation data, and Mr. O. P. Crews and staff for the large-scale preparation of certain intermediates.

2-Deoxy Sugars. VII. 2-Deoxy-D-allose (2-Deoxy-D-*ribo*-hexose) *via* the Fischer–Sowden Nitromethane Synthesis[1]

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Condensation of nitromethane with D-ribose (**1**) leads to a sirupy mixture of the nitrohexitols (**2** and **3**), which on acetylation yielded the corresponding epimeric acetylated derivatives **4** and **5**, the latter of which was crystalline. Both **4** and **5** were separately deacetylated by acid hydrolysis to regenerate the nitrohexitols (**2** and **3**), each of which underwent the Nef reaction to give D-allose (**6**) and D-altrose (**7**), respectively, thus establishing the structure of the crystalline acetylated nitrohexitol (**5**) as 2,3,4,5,6-penta-*O*-acetyl-1-deoxy-1-nitro-D-altritol. Elimination of a molecule of acetic acid from **5** gave the acetylated nitrohexene (**8**), which underwent reduction of the double bond to give the sirupy 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-D-*ribo*-hexitol (**9**). Alkaline hydrolysis of **9**, followed by the Nef reaction, gave 2-deoxy-D-allose (2-deoxy-D-*ribo*-hexose) (**11**) in 20% yield. Alternately, the acetylated deoxynitrohexitol (**9**) could be deacetylated by aqueous acid giving crystalline 1,2-dideoxy-1-nitro-D-*ribo*-hexitol (**10**), which underwent the Nef reaction to give 2-deoxy-D-allose (**11**) in 38% yield. Yields of **11** by both the alkaline and acid procedure are based on the hexene (**8**).

2-Deoxy-D-allose (2-deoxy-D-*ribo*-hexose) (**11**) has not been reported to occur naturally, but may be obtained by the hydrolysis of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexoside[4] for which an improved preparation in four steps, starting with methyl α-D-glucopyranoside, has been reported.[5] Our interest in preparing both cardenolides[6] and nucleosides containing as the carbohydrate component 2-deoxy-D-allopyranose (2-deoxy-D-*ribo*-hexopyranose) prompted us to investigate an alternate and perhaps more economical procedure for synthesizing the hexose (**11**).

In a variation of their nitromethane synthesis for lengthening the carbon chain of aldoses, Sowden and Fischer described[7] a general method for producing 2-deoxy sugars, and were successful in converting D-arabinose to 2-deoxy-D-*arabino*-hexose (2-deoxyglucose). In the same paper D-ribose (**1**) was treated similarly; in this case, however, the synthesis was not carried beyond the preparation and isolation of the intermediary 3,4,5,6-tetra-*O*-acetyl-1-nitro-D-*ribo*-hexene-1 (**8**). Our own work, which is presently described, is concerned with a re-examination of the conversion of D-ribose (**1**) to the acetylated hexene (**8**) as well as with the transformation of the latter to 2-deoxy-D-allose (**11**).

Condensation of D-ribose (**1**) with nitromethane and removal of the sodium from the sodium salts of the nitro alcohols by an ion-exchange resin gave a sirupy mixture of the free, epimeric nitro alcohols **2** and **3**, from which neither epimer could be obtained in crystalline form. Whereas Sowden and Fischer, on acetylating the sirup containing **2** and **3**, obtained only a sirupy mixture of the acetylated nitro alcohols **4** and **5**[7] we were able to secure crystalline 2,3,4,5,6-penta-*O*-acetyl-1-deoxy-1-nitro-D-altritol (**5**) in 19% yield based on D-ribose (**1**). In an effort to determine

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(2) To whom all inquiries regarding this paper should be addressed.

(3) This work was taken from a dissertation to be submitted to the Graduate School of Georgetown University in partial fulfillment of the degree of Doctor of Philosophy in Chemistry.

(4) W. W. Zorbach and T. A. Payne, *J. Am. Chem. Soc.*, **80**, 5564 (1958).

(5) D. A. Prins, *ibid.*, **70**, 3955 (1948).

(6) W. W. Zorbach and W. Buhler, *Ann. Chem.*, **670**, 116 (1963).

(7) J. C. Sowden and H. O. L. Fischer, *J. Am. Chem. Soc.*, **69**, 1048 (1947).

whether **5** had the *allo* or *altro* configuration, we considered means for deacetylating the material prior to conversion *via* the Nef reaction[8] to either D-allose (**6**) or D-altrose (**7**). Attempts to deacetylate **5** in methanol using either ammonia or small amounts of sodium methoxide failed, but when the material was refluxed with 1 *N* hydrochloric acid, deacetylation took place as evidenced by conversion of the resulting sirupy nitro alcohol to D-altrose (**7**). Under these conditions **7** was the sole carbohydrate product as disclosed by paper chromatograms, and was further characterized by conversion to the known dibenzyl dithioacetal (**7a**)[9] and to its *p*-nitrophenylhydrazone (**7b**), not hitherto described. When the acetylated nitro alcohol **5** was deacetylated under more acidic conditions and then subjected to the Nef reaction, a small amount of another carbohydrate material appeared on the chromatograms along with D-altrose (**7**). The artifact is most likely D-ribose (**1**), because it has an R_f value coincident with that of authentic **1** and gives the same coloration as does D-ribose when treated with aniline hydrogen phthalate reagent.[10]

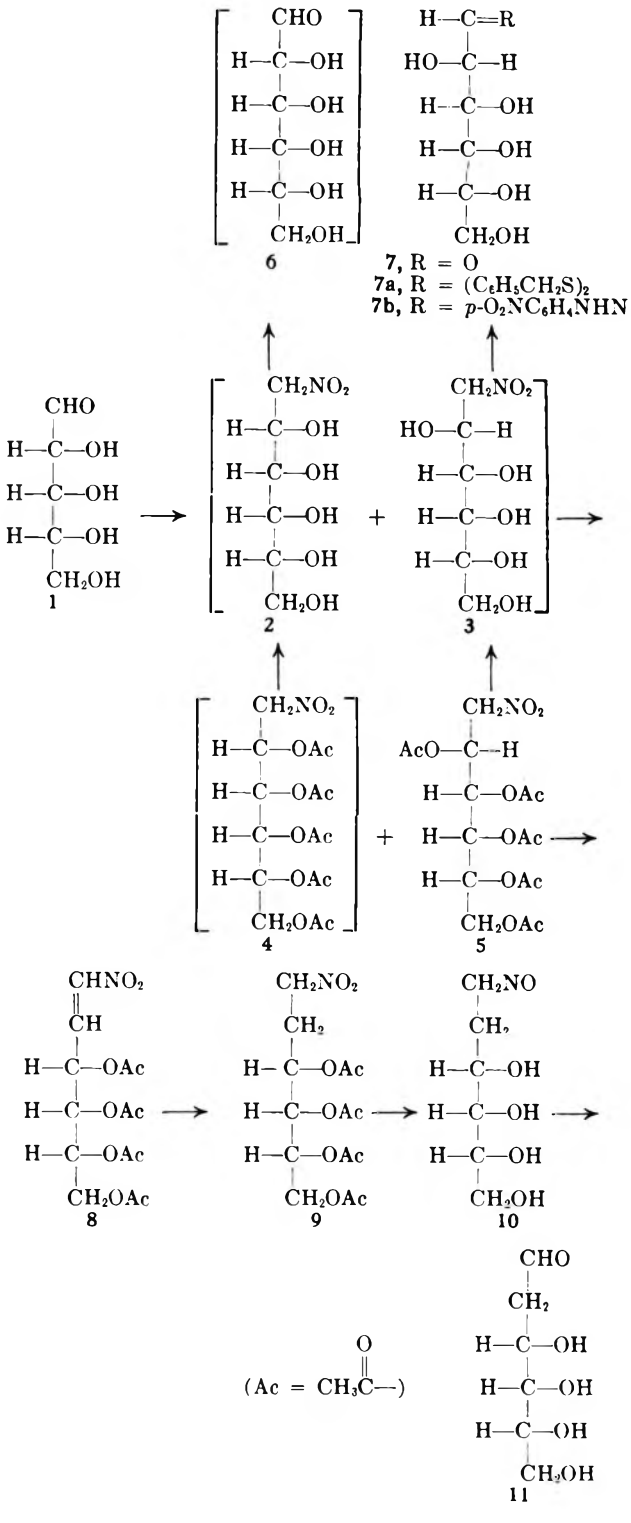
The acetylated nitroaltritol (**5**) readily lost 1 mole of acetic acid by refluxing with sodium bicarbonate in benzene[11] to give the known acetylated nitrohexene (**8**)[7] in 59% yield. In order to increase the total yield of the hexene (**8**) we turned to an examination of the filtrate which remained after exhaustive removal of the crystalline acetylated nitroaltritol (**5**) from the sirupy acetylation mixture. The filtrate was reduced to a sirup and was deacetylated under the same conditions given for **5** (*vide supra*), and without further purification was subjected to the Nef reaction. Paper chromatograms disclosed a single carbohydrate material, having an R_f value the same as that for authentic D-allose (**6**), demonstrating for practical purposes a complete separation of **4** from **5**. Unfortunately, repeated attempts to secure additional, crystalline hexene (**8**) from the sirupy acetylated nitroallitol (**4**) failed.

Hydrogenation of the nitrohexene (**8**) using freshly prepared palladium black[12] gave the acetylated 2-deoxynitrohexitol (**9**) which could not be obtained in crystalline form. Without further purification the sirupy material was treated with excess sodium hydroxide and the resulting solution was added to moderately concentrated sulfuric acid, giving 2-deoxy-D-allose (2-deoxy-D-*ribo*-hexose) (**11**) in 20% yield based on the hexene (**8**) (see Chart I).

Alternately, the acetylated hexitol (**9**) was deacetylated employing 1 *N* hydrochloric acid and, under these conditions, the intermediary nitrohexitol (**10**), not isolable through the alkaline procedure, was secured in crystalline form in 79% yield (based on **8**). To our knowledge this is the first reported instance in which a 2-deoxynitrohexitol has been isolated in crystalline form. In a separate experiment **9** was deacetylated in the same manner and the resulting crude hexitol (**10**), without further purification, was subjected to the Nef reaction giving 2-deoxy-D-allose (**11**) in 38% yield based on the hexene (**8**) demonstrating the superiority of this method for converting an acetylated nitro alcohol to the corresponding aldose.

The acid-catalyzed deacetylation of the three acetylated nitro alcohols **4, 5,** and **9** appears to take place smoothly without bringing about other changes in the molecule. It is to be noted that, whereas the epimeric nitro alcohols **2** and **3** could not be separated by fractional crystallization, the acetylated derivatives **4**

CHART I



(8) J. U. Nef, *Ann. Chem.*, **280**, 263 (1894).

(9) N. K. Richtmyer and C. S. Hudson, *J. Am. Chem. Soc.*, **57**, 1720 (1935).

(10) S. M. Partridge, *Nature*, **164**, 443 (1949). The author states that the reagent gives a bright red coloration with pentoses whereas, with hexoses and hexuronic acids, varying shades of brown and green are obtained. In our hands, D-ribose (**1**) gave a distinctly red coloration, while the color developed by both D-allose (**6**) and D-altrose (**7**) was brown.

(11) E. Schmidt and G. Rutz, *Ber.*, **61**, 2142 (1928).

(12) J. Tausz and N. von Putnoky, *ibid.*, **52**, 1576 (1919).

and **5** were readily separated and, through acid hydrolysis, a resolution of **2** and **3** was effected. This procedure may have considerable utility in selected cases of the nitromethane synthesis of aldoses where not only a resolution of the epimeric nitro alcohols arising from the nitromethane condensation cannot be effected, but also where separation of the epimeric aldoses at the end may be beset by difficulties.

Experimental

All melting points were determined using a Kofler hot stage. Unless otherwise indicated, all paper chromatograms were carried out by an ascending technique, employing butanol–pyridine–water (6:4:3). Reducing, carbohydrate materials were detected with aniline hydrogen phthalate reagent.[10]

2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-nitro-D-altritol (5).—The condensation of nitromethane with 50 g. (0.33 mole) of D-ribose (**1**) and deionization of the resulting sodium salts to give 44.5 g. (63%) of a sirupy mixture of the nitrohexitols (**2** and **3**) was carried out under essentially the same conditions given[7] by Sowden and Fischer for D-arabinose. Acetylation of the 44.5 g. of sirup was accomplished by dissolving it in 445 ml. of acetic anhydride, followed by the addition of 6 drops of concentrated sulfuric acid. After heating in a boiling water bath for 3.5 hr., the mixture was added over a period of 45 min. to 3 l. of ice–water containing crushed ice, and was then set aside in a refrigerator overnight. The supernatant liquid was decanted from the semisolid mass that had collected on the bottom and, after rinsing with cold water, the material was dissolved in 300 ml. of chloroform and was transferred to a separatory funnel. After shaking with 100 ml. of water, the chloroform extract was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The sirupy residue was further dried under a reduced pressure of 0.1 mm. at 40°, giving 82.5 g. of crude, noncrystalline **4** and **5**. The sirup was redissolved in 275 ml. of chloroform and was repeatedly decolorized with Darco G-60 until a pale, amber-colored solution was obtained. The solution was then evaporated to a thin sirup whereupon the bulk of the mass crystallized. Seed crystals were taken, and the material was redissolved in a minimum amount of absolute ethanol at 50°. After seeding, crystallization began without delay and, after standing overnight, there was obtained 23.7 g. of crude product, melting at 125–129°. By carefully working up the liquors an additional 3.0 g. of material was secured, bringing the total yield to 26.7 g. (30%). Recrystallization from absolute ethanol gave pure 2,3,4,5,6-penta-*O*-acetyl-1-deoxy-1-nitro-D-altritol (**5**), m.p. 132–133°, $[\alpha]^{24}D$ +47.2° (*c* 1.00, $CHCl_3$).

Anal. Calcd. for $C_{16}H_{23}O_{12}N$: C, 45.59; H, 5.50; N, 3.32. Found: C, 45.41; H, 5.61; N, 3.35.

Conversion of 2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-nitro-D-altritol (5) to D-altrose (7).—To 1.57 g. (3.7 mmoles) of **5** was added 26 ml. of 1 *N* hydrochloric acid and the mixture was refluxed for 75 min. After cooling and diluting with water to 40 ml., the mixture was neutralized with an excess of silver carbonate. Decolorization and evaporation of the filtrate gave 649 mg. (82%) of sirupy nitroaltritol (**3**) which was treated in turn with 5 ml. of 2 *N* sodium hydroxide and 8 ml. of 40% (v./v.) aqueous sulfuric acid. The material was worked up by essentially the same procedure given[7] for 2-deoxy-D-*arabino*-hexose and in this manner there was obtained 524 mg. (78%) of sirupy D-altrose (**7**). When chromatographed on paper, the material gave a single spot, coincident in position (R_f 0.45) with authentic **7**.

D-Altrose Dibenzyl Dithioacetal (7a).—The entire sirupy material obtained in the preceding preparation was treated with 1.25 ml. of toluenethiol and 0.9 ml. of concentrated hydrochloric acid. After stirring for 7 hr. a little crushed ice was added, with stirring continued for an additional 3 hr. The solid which had formed was filtered by suction and was washed with a small quantity each of ethanol and dry ether. The material was dissolved in 4 ml. of hot, absolute ethanol and the solution was poured into 100 ml. of water heated to 95°. After standing for 4 hr., the separated crystals were filtered and washed and, after drying for 2 days in a vacuum desiccator over potassium hydroxide, there was obtained pure D-altrose dibenzyl dithioacetal (**7a**), m.p. 121–122°, $[\alpha]^{23}D$ +37.3° (c 1.00, pyridine). For comparison purposes, a sample of **7a** was prepared from authentic D-altrose by a method described[9] by Richtmyer and Hudson, and had m.p. 121–122° and $[\alpha]^{20}D$ +38.9°.

D-Altrose *p*-Nitrophenylhydrazone (7b). A. From Authentic D-Altrose (7).—To a mixture of 500 mg. (2.8 mmoles) of D-altrose (**7**) in 5 ml. of methanol was added 425 mg. of *p*-nitrophenylhydrazine. After refluxing for 1.5 hr. the mixture was cooled to room temperature and an additional 3 ml. of methanol was added. The separated material was filtered by suction and was washed with 5 ml. of methanol, giving 757 mg. (91%) of yellow needles, m.p. 186–188°. Recrystallization from absolute ethanol gave pure hydrazone (**7b**), m.p. 188–190°.

Anal. Calcd. for $C_{12}H_{17}O_7N_3$: C, 45.74; H, 5.39; N, 13.33. Found: C, 45.81; H, 5.63; N, 13.35.

B. From D-Altrose (7) Prepared from the Acetylated Nitroaltritol (5).—A sample of 1.57 g. of **5** was deacetylated with 1 *N* hydrochloric acid and subjected to the Nef reaction in the same manner given previously (*vide supra*), resulting in 488 mg. of sirupy D-altrose (**7**) which was dissolved in 5 ml. of methanol. To this solution was added 390 mg. of *p*-nitrophenylhydrazine and the mixture was refluxed for 1.5 hr. After refrigerating for 6 hr. the separated material was filtered and amounted to 200 mg., m.p. 145–148°. Two recrystallizations from absolute ethanol gave pure D-altrose *p*-nitrophenylhydrazone (**7b**), m.p. 188–190°. No depression in the melting point was observed when admixed with a specimen of **7b** obtained in the preceding preparation.

Formation of D-Allose (6).—After removal of the crystalline acetylated nitroaltritol (**5**) from the acetylation mixture containing both **4** and **5**, the combined filtrates were evaporated *in vacuo* and the residue was dried under high vacuum. A portion of the sirup weighing 1.19 g. was deacetylated and the resulting sirupy nitroallitol (**2**) was subjected to the Nef reaction in the same manner as that described for converting **5** to D-altrose (**7**). The D-allose (**6**) thus formed did not crystallize, but when chromatographed on paper gave a single spot coincident in position with a sample of authentic **6** (R_f 0.35). The hexose (**6**) was not further characterized.

3,4,5,6-Tetra-*O*-acetyl-1-nitro-D-*ribo*-hexene-1 (8).—To a solution of 12.0 g. (0.029 mole) of the acetylated nitroaltritol (**5**), m.p. 125–129°, in 240 ml. of dry benzene was added 12 g. of sodium bicarbonate. After refluxing for 2.5 hr., the reaction mixture was filtered by suction and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in dry ether and was decolorized with Darco G-60. After filtering, the solution was boiled down to a small volume and was allowed to stand overnight, giving 6.1 g. (59%) of pure **8**, m.p. 86–87°, $[\alpha]^{25}D$ +17.1°[7] (c 1.00 $CHCl_3$).

Conversion of the Hexene (8) to 2-Deoxy-D-allose (11) (Alkaline Procedure).[7]—To a solution of 1 g. (2.8 mmoles) of the acetylated nitrohexene (**8**) in 105 ml. of absolute ethanol was added 0.11 g. of palladium black.[12] Hydrogenation was carried out in a Parr Hydrogenator (Series 3910) and was complete in 30 min. as evidenced by the uptake of 1 mole of hydrogen. After filtering the catalyst, the filtrate was evaporated *in vacuo*, giving 0.98 g. of a sirup from which crystalline material could not be obtained. Without further purification the sirup was dissolved in 35 ml. of 1 *N* sodium hydroxide and was allowed to stand for 1 hr. The solution was then added slowly with stirring to 12 ml. of 40% (v./v.) aqueous sulfuric acid and was neutralized with an excess of freshly prepared barium carbonate. The barium salts were removed by centrifugation and the combined, filtered decantate and washings was further deionized with Rexyn RG501(H-OH) ion-exchange resin (Fisher Scientific Co.). After filtering and washing, the filtrate was evaporated *in vacuo* at 50° and was dried under high vacuum for 1 hr. at the same temperature. The residue was dissolved in 3 ml. of absolute ethanol giving crude, crystalline material, which, when recrystallized twice from absolute ethanol, gave 90 mg. (20%) of pure 2-deoxy-D-allose (**11**), m.p. 140–142°, $[\alpha]^{24}D$ +57.5° (*c* 1.175, water). No depression in the melting point was observed when **11** was admixed with an authentic specimen.

1,2-Dideoxy-1-nitro-D-*ribo*-hexitol (10).—One gram (2.8 mmoles) of the hexene (**8**) was reduced in the same manner as described in the preceding preparation. To the resulting sirup was added 27 ml. of 1 *N* hydrochloric acid and the mixture was heated in a boiling water bath for 75 min. After diluting to 35 ml. with water and adding an excess of silver carbonate, the solution was filtered. The filtrate was further deionized using Rexyn RG501 (H-OH) ion-exchange resin and, after filtering, was evaporated *in vacuo* at 50° giving 506 mg. (93% based on **8**)

of material melting at 88–94°. In a subsequent experiment the crude material was decolorized once with Darco G-60 and was recrystallized twice from absolute ethanol giving pure **10**, m.p. 106–107°, $[\alpha]^{24}D$ +4.5° (*c* 0.10, water).

Anal. Calcd. for $C_6H_{13}O_6N$: C, 36.44; H, 6.71; N, 7.17. Found: C, 36.94; H, 6.50; N, 7.07.

Conversion of the Deoxynitrohexitol (10) to 2-Deoxy-D-allose (11).—The 506 mg. (2.6 mmoles) of crude hexitol (**10**) obtained in the preceding preparation was dissolved in 4 ml. of 2 *N* sodium hydroxide and the solution was added without delay to 4 ml. of a stirred, 40% (v./v.) aqueous solution of sulfuric acid. The product was worked up in the same manner as given for the preparation of **11** by the alkaline procedure (*vide supra*). After decolorizing with Darco G-60, the material was recrystallized once from absolute ethanol giving 170 mg. (40%) of 2-deoxy-D-allose (**11**), melting at 130–133°. Two additional recrystallizations raised the melting point of **11** to 140–142°.

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The Disproportionation of Some Chlorofluoroalkyl Nitroso Compounds[1]

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Fluorochloroalkyl nitroso compounds have been shown to disproportionate into nitro and chloro derivatives with the evolution of some nitrogen. A kinetic study of the decomposition of α- and β-chloro nitroso compounds has been made and a mechanism postulated.

The preparation of nitroso compounds by the addition of nitrosyl chloride to fluoroolefins usually results in the formation of some nitro and chloro derivatives of the olefin.

$$CF_2{=}CFCl \xrightarrow{NOCl} CF_2ClCFClNO + CF_2ClCFClNO_2 + CF_2ClCFCl_2 \quad (1)$$

For example, the addition of nitrosyl chloride to tetrafluoroethylene at 100° yielded a mixture of 1-chloro-2-nitrotetrafluoroethane and 1,2-dichlorotetrafluoroethane, but no nitroso compound.[2] It was postulated that the nitroso compound was formed initially and was subsequently oxidized by nitrosyl chloride to the nitro compound. Under milder conditions using catalysis, these two reactants yield primarily 1-chloro-2-nitrosotetrafluoroethane, but some of the corresponding nitro and chloro compounds are also obtained.[3] In this laboratory it was observed that certain fluorochloroalkyl nitroso compounds decomposed slowly on standing at room temperature. Furthermore, attempts to carry out reactions of these nitroso compounds with other materials by heating resulted in the formation of the corresponding nitro and chloro compounds[4] and very little else. Our observations suggested that disproportionation was occurring approximately according to the following equation.

$$2RNO \longrightarrow RNO_2 + RCl + 0.5N_2 \quad (2)$$

Equation 2 obviously does not balance and does not account completely for the products of the reaction, but it does describe the gross features of it. Our study was undertaken to learn more about this interesting reaction.

The only other data concerning the disproportionation of fluoroalkyl nitroso compounds have been obtained with perfluoroalkyl nitroso compounds. Haszeldine and co-workers have investigated rather thoroughly the reactions of nitrosotrifluoromethane, the thermal reactions of which follow quite different courses under different conditions. Irradiation of nitrosotrifluoromethane with ultraviolet light yields a dimer, $(CF_3)_2NONO$,[5] while heating nitrosotrifluoromethane over activated charcoal yields a mixture of nitrotrifluoromethane and hexafluoroazoxymethane[6] analogous to the reaction Bamberger reported for nitrosobenzene.[7] However, when nitrosotrifluoromethane is heated alone, a 48% yield of nitrotrifluoromethane is obtained along with the products of reaction of trifluoromethyl radicals with glass.[8] This last reaction was run under conditions similar to our experiments, the major difference being that theirs was a gas-phase reaction while ours was carried out in the liquid phase.

Andreades[9] has found that nitrosopentafluoroethane undergoes the following reaction when heated.

$$C_2F_5NO \longrightarrow CF_3CF_2N{=}CFCF_3 + C_2F_5NO_2 + C_2F_5ONO \rightleftharpoons CF_3COF + NOF \quad (3)$$

We postulate that the course of the thermal disproportionation of fluorochloroalkyl nitroso compounds is that shown in eq. 4, 5, and 6. Our arguments are based on the products of the reaction, the effect of added reagents (NO and NOCl), and the relative thermal stabilities of four chlorofluoroalkyl nitroso compounds.

The relative thermal stabilities of 1,2-dichloro-1-nitrosotrifluoroethane (I), 1,1-dichloro-1-nitrosotrifluoroethane (II), 1-chloro-1-nitrosotetrafluoroethane (III), and 1-chloro-2-nitrosotetrafluoroethane (IV) at 78.2° were measured. Compounds I and IV were made by

(1) Presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961.

(2) R. N. Haszeldine, *J. Chem. Soc.*, 2075 (1953).

(3) J. D. Park, A. P. Stefani, and J. R. Lacher, *J. Org. Chem.*, **26**, 4017 (1961).

(4) Throughout this paper the term chloro compound refers to the chlorofluorocarbon obtained by replacement of the nitroso group by chlorine.

(5) R. N. Haszeldine and B. J. H. Mattinson, *J. Chem. Soc.*, 1741 (1957).

(6) J. Jander and R. N. Haszeldine, *ibid.*, 919 (1954).

(7) E. Bamberger, *Ber.*, **33**, 1939 (1900).

(8) D. A. Barr, R. N. Haszeldine, and C. J. Willis, *J. Chem. Soc.*, 1351 (1961).

(9) S. Andreades, 2nd International Fluorine Symposium, Estes Park, Colo., July 17–20, 1962.

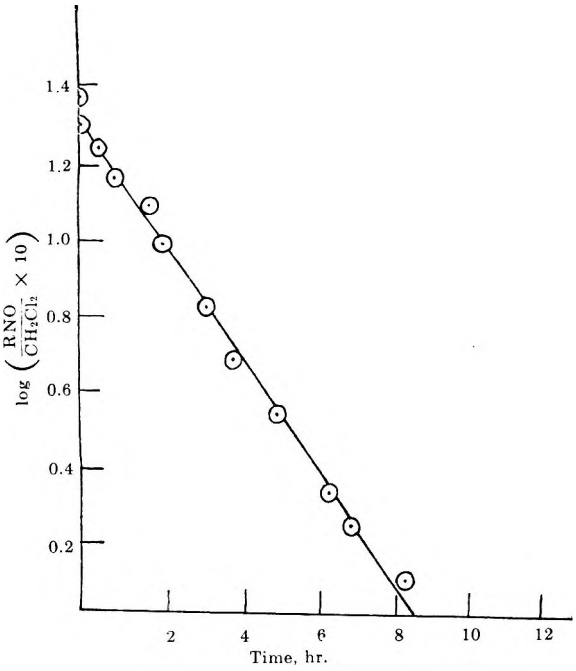

Fig. 1.—First-order plot: disproportionation of 1-nitroso-1,2-dichlorotrifluoroethane at 78.2°.

adding nitrosyl chloride to chlorotrifluoroethylene and tetrafluoroethylene, respectively.[10a] Compounds II and III were prepared by reacting the corresponding fluoroalkylmercury compound with nitrosyl chloride by a procedure to be discussed in a forthcoming publication.[10b] The thermal stabilities were determined by placing, in the vapors of refluxing 95% ethanol, sealed ampoules containing approximately equimolar amounts of nitroso compound and internal standard (methylene chloride for I and II, methyl bromide for III and IV). After a specified period of time the ampoules were cooled in Dry Ice–acetone and opened; a sample of their contents was injected into a vapor-phase chromatographic (v.p.c.) apparatus. From the v.p.c. curves it was possible to determine the rate of disappearance of nitroso compound and the quantities of nitro and chloro compound formed.

A first-order plot of the rate of disappearance of I is shown in Fig. 1. Comparable plots were obtained for compounds II, III, and IV, but with more scatter of points. The reaction was carried to >90% completion during which time the reaction medium changed from a mixture of roughly equimolar amounts of I and methylene chloride to a mixture of methylene chloride, 1,1,2-trichlorotrifluoroethane, 1,2-dichloro-1-nitrotrifluoroethane, and I. In spite of the change of solvent during the course of the reaction, the same first-order rate of disappearance was obtained throughout. Furthermore, when the reaction was carried out using carbon tetrachloride in place of methylene chloride, the same rate of disappearance of I, within experimental error, was observed. These results suggest that there is very little solvent effect in this reaction. Repeat runs with I in which the ratio of I to internal standard was varied by a factor of 2 gave essentially the same results.

(10) (a) A sample of IV was kindly furnished by Dr. E. C. Stump of Peninsular ChemResearch, Inc.; (b) P. Tarrant and D. E. O'Connor, *J. Org. Chem.*, **29**, 2012 (1964).

Compounds II, III, and IV exhibited similar behavior, although first-order plots of their rates of disproportionation showed more scatter. The data for each of the four compounds were subjected to first-order plots and from these plots half-lives were obtained for the purpose of comparing the four compounds. Since the data were obtained using quite concentrated solutions whose compositions changed significantly during the course of the reactions, no further significance was attached to the half-lives.

The products from the disproportionation of I are 1,2-dichloro-1-nitrotrifluoroethane (36%), 1,1,2-trichlorotrifluoroethane (34%), nitrogen (20%), nitric oxide, and a material, b.p. 51–53° (23 mm.), mol. wt. 416 ± 20, which was not identified.[11] The quantity of nitrogen evolved in the reaction was measured only once, and in a separate experiment from the rate determinations. The value obtained was a little over half the value predicted in the equations below.

$$CF_2ClCFClNO \longrightarrow CF_2ClCFCl\cdot + NO\cdot \quad (4)$$

$$CF_2ClCFClNO + NO\cdot \longrightarrow CF_2ClCFClNO_2 + 0.5N_2 \quad (5)$$

$$CF_2ClCFClNO + CF_2ClCFCl\cdot \longrightarrow CF_2ClCFCl_2 + CF_2ClCFNO \quad (6)$$

$$\downarrow$$

other products

Table I lists some of the data obtained in this study, the important aspects of which will be cited here for emphasis. (1) The three compounds containing an α-chlorine atom (I, II, and III) disproportionate at a significantly faster rate than does IV, which has no α-chlorine atom. (2) No chloro compound is obtained from IV, while with each of the three α-chloro compounds it is a major product. (3) The addition of nitric oxide greatly increases the rate of reaction of I and presumably would have a similar effect on the other nitroso compounds. (4) The addition of nitrosyl chloride increased the rate of disproportionation of I somewhat but not greatly, did not drastically change

TABLE I

SUMMARY OF THERMAL STABILITIES AND PRODUCT RATIOS FOR DISPROPORTIONATION OF NITROSO COMPOUNDS AT 78.2°

Compound	Relative half-life[a]	RCl–RNO_2[b]	RCl + RNO_2 average % of total product[b]
CF_3CCl_2NO (II)	1.3	2.1[c]	88[c]
$CF_2ClCFClNO$ (I)	1.95	0.9–0.95	70
$CF_3CFClNO$ (III)	4.0	1.1	62
CF_2ClCF_2NO (IV)	49	0.0	44
$CF_2ClCFClNO$ + NOCl	1.4	0.74	97
$CF_2ClCFClNO$ + NO	<0.25[d]	0.08[e]	*ca.* 100

[a] The constants for I and II were determined using CH_2Cl_2 as internal standard, III and IV in CH_3Br. When I was run with CCl_4 as internal standard, the half-life was found to be 1.98 thus indicating the absence of solvent effect. [b] The values contained in these columns are average values. [c] These values are gross approximations because of difficulties in measuring the areas under v.p.c. curves. [d] This value was not obtained by a first-order plot. It is based on the time required for more than half of 1.1 mmoles of I to react with 0.7 mmole of NO. [e] After 1 hr; the ratio was smaller during earlier parts of the run.

(11) An empirical formula of $C_2O_4Cl_3F_7N$ was calculated for this compound from elemental analysis results, but was not very accurate. This material has two strong, sharp bands at 5.49 and 5.62 μ in the infrared and it hydrolyzed very slowly in distilled water to yield an acidic solution. These data as well as a fluorine nuclear magnetic resonance spectrum suggest that the compound contains an acyl fluoride functional group.

the ratio RCl–RNO_2, but did increase the amount of RCl and RNO_2 in the product to almost 100%.

It appears that the disproportionation of I, II, and III are accommodated by the reaction scheme illustrated by eq. 4, 5, and 6.

The initial step in the reaction is probably the homolytic cleavage of the C–N bond as shown in eq. 4. The nitric oxide thus formed can then react with more of the nitroso compound to form the corresponding nitro compound and nitrogen as shown in eq. 5. The chlorofluoroalkyl radical formed in eq. 4 can react with more nitroso compound to form the chloro compound as shown in eq. 6. The radical formed by the process shown in eq. 6 probably goes on to form the $C_7Cl_3F_7NO_4$, the only other fluorine-containing product isolated from the reaction.

The presence of nitric oxide among the products is good evidence for a homolytic cleavage of the C–N bond. Evidence that nitric oxide is the oxidizing species was obtained by carrying out the reaction of I at 78.2° with nitric oxide. Under the conditions employed (NO–RNO = *ca.* 0.7:1.1), over half of the nitroso compound had been consumed in less than 15 min. indicating that I reacts readily with nitric oxide. Furthermore the nitro compound is formed in essentially 100% yield, the small amount of chloro compound formed being accounted for by some disproportionation according to the scheme postulated above. These facts strongly support the postulate that nitric oxide is the oxidizing agent.

The reaction of nitroso compounds with nitric oxide to form diazonium nitrates was reported by Bamberger[12] many years ago, and more recently Haszeldine and co-workers[8] postulated that a diazonium nitrate was an intermediate in the oxidation of nitrosotrifluoromethane by nitric oxide, the diazonium nitrate being formed by the reaction of the nitroso compound with two molecules of nitric oxide and subsequently reacting with a third molecule of nitric oxide to yield nitrotrifluoromethane, nitrogen, and nitrogen dioxide, analogous to eq. 7. Although they offered no direct evidence

$$CF_2ClCFClNO + 2NO\cdot \longrightarrow CF_2ClCFClN_2NO_3 \xrightarrow{NO} CF_2ClCFClNO_2 + N_2 + NO_2\cdot \quad (7)$$

for such an intermediate, it seems quite reasonable in view of Bamberger's findings. Hence, it seems likely that eq. 5 is more accurately represented as shown in eq. 7. The net reaction would not be changed, since the NO_2 radical formed could couple with a fluorochloroalkyl radical. The oxidation of nitrosomethane by nitric oxide has also been reported,[13] but no details were given.

Equation 6 is indicated by the fact that each of the three nitroso compounds containing an α-chlorine yields substantial quantities of the corresponding chloro compound (RCl), whereas the nitroso compound which contains no α-chlorine, *i.e.*, IV, yields no chloro compound. These data indicate that the chlorine in the RCl formed comes from the α-carbon of the nitroso compound, contrary to the recent postulate by Park and co-workers[5] that the initial steps in the disproportionation of I are the stepwise elimination of the nitroso group and chlorine from adjacent carbon atoms with formation of a fluoroolefin. If their postulate were true, then IV should give products similar to I, whereas III should behave quite differently. Actually, III behaved very much like I (similar thermal stability and similar product composition), whereas IV was quite different (formed no RCl and greater thermal stability).

That a chlorofluoroalkyl radical will abstract the α-chlorine but not the β-chlorine seems quite reasonable in view of the difference in resonance stabilization available to the two radicals.[14] The nitroso group attached to the radical-bearing carbon can stabilize the radical through the following resonance forms

$$CF_2ClC\dot{F}—\ddot{N}=\ddot{O}: \longleftrightarrow CF_2ClCF=\overset{+}{N}—\ddot{O}: \longleftrightarrow CF_2ClCF=\ddot{N}—\ddot{O}\cdot$$

while a radical formed on the β-carbon would receive no resonance stabilization by the nitroso group.

The fact that addition of nitrosyl chloride increases the combined yield of the nitro and chloro compounds from *ca.* 70 to *ca.* 100% and lowers the ratio of RCl–RNO_2 but does not alter the rate drastically lends further support to the proposed reaction path. The presence of nitrosyl chloride provides an alternative to reaction 6 for the chlorofluoroalkyl radical. Instead of abstracting a chlorine atom from a molecule of the nitroso compound, the chlorofluoroalkyl radical can abstract a chlorine atom from nitrosyl chloride. Thus, the reaction which produces the higher boiling unidentified product is essentially eliminated and all of the nitroso compound reacts to form the corresponding nitro and chloro compounds. The fact that an additional molecule of nitric oxide is produced when the alkyl radical reacts with nitrosyl chloride accounts for the decrease in the ratio of RCl–RNO_2. Ideally this ratio should be 0.5, but experimentally we observed a ratio of 0.74. It is, however, significantly less than the ratio observed for the disproportionation of the pure nitroso compound, which should be 1.0.

The results may be summarized as follows. Disproportionation as illustrated in eq. 2 occurs when there is an available source of chlorine atoms such as an α-chloro nitroso compound or nitrosyl chloride. When no source of chlorine atoms is available, dissociation occurs as shown in eq. 4 and oxidation occurs as shown in eq. 5, but the fluoroalkyl radical must react by some different course, perhaps to form the azomethines observed by Andreades.[11] This explains why certain fluoroalkyl nitroso compounds, *e.g.*, IV, react with nitrosyl chloride to yield the chloro as well as the nitro compound, while alone they form no chloro compound, whereas others, *e.g.*, I, II, and III, form both the chloro and the nitro compound in the presence or in the absence of nitrosyl chloride. Equations 4–6 account for the gross features of the reaction. Furthermore, it is reasonable to expect that any fluoroalkyl nitroso compound would react with nitrosyl chloride to yield both the nitro and chloro compounds.

(12) E. Bamberger, *Ber.*, **30**, 506 (1897).

(13) J. B. Levy, *Ind. Eng. Chem.*, **48**, 762 (1956).

(14) See C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, Chapter 6, for a discussion of this subject and for leading references.

Experimental[15]

Disproportionation of 1,2-Dichloro-1-nitrosotrifluoroethane.—An ampoule (25-mm. o.d., 3-mm. wall, *ca.* 140-ml. volume) was charged with 1,2-dichloro-1-nitrosotrifluoroethane (9 g., 0.05 mole) and was sealed under vacuum. The tube was heated at 75° for several hours until the blue color had faded. Then the tube was cooled in liquid nitrogen and was opened into the vacuum line. The pressure rose immediately indicating the presence of nitrogen, in 20% yield. The nitrogen was swept out and a molecular weight of the most volatile gas remaining was 31.1 (calculated for NO, 30.0). In addition, this colorless gas became brown when it was exposed to the air. The tube was then immersed in Dry Ice–acetone and the volatile material was pumped off. Then, an infrared spectrum of the remaining volatile material had bands at 5.52 and 5.59 μ, indicating the presence of nitrogen dioxide. A separate run was similarly made using 1,2-dichloro-1-nitrosotrifluoroethane (30 g., 0.16 mole). From this run was obtained 2.5 g. of material, b.p. 51–53° (23 mm.).

Anal. Calcd. for $C_2Cl_2F_3NO_4$: C, 20.9; H, 0.00; Cl, 26.5; F, 33.10; N, 3.48. Found: C, 19.52; H, 0.43; Cl, 27.3; F, 32.34; N, 3.40.

The molecular weight was 416 ± 20, determined cryoscopically. The nitro and chloro compounds were determined chromatographically during the rate studies described below. They were identified by comparing their retention times by v.p.c. with known samples.

Determination of the Thermal Stabilities of the Nitroso Compounds.—The relative rates of disproportionation at 78.2° of four chlorofluoroalkyl nitroso compounds were determined with a vapor-phase chromatographic column using an internal standard.

The nitroso compounds were purified by passing each of them through a vapor-phase chromatographic column packed with material prepared from 0.6 g. of dinonyl phthalate per gram of Johns Mansville "Chromosorb," 35–80-mesh size, and were subsequently stored at −78° until they were used.

Methylene chloride was used as an internal standard for the studies of the disproportionation of I and II and methyl bromide was used as an internal standard for the studies of III and IV. Carbon tetrachloride was also used as internal standard for I.

(15) Analyses were by Galbraith Laboratories, Knoxville, Tenn.

The nitroso compound and the internal standard were mixed in the desired ratio. Aliquot portions of approximately 0.1 ml. of the mixture were then transferred to glass tubes (5-mm. o.d., *ca.* 4-cm. length) which had previously been swept out with nitrogen. The tubes were sealed and were kept in Dry Ice–acetone until they were used. For the run in which the effect of added nitric oxide was determined, the tubes were filled in the usual manner, after which nitric oxide (*ca.* 0.7 mmole) was added and they were sealed under vacuum.

The disproportionations were carried out at 78.2 ± 0.1° by placing the tubes in the vapors of refluxing 95% ethanol for the desired length of time. When each tube was removed, it was cooled in Dry Ice–acetone and opened, and a sample of its contents was introduced into the vapor-phase chromatographic column. It was necessary to maintain the column at a temperature at which the rate of disproportionation of the nitroso compound was negligible. The temperatures chosen for the individual compounds were I, 60°; II, 45°; III, 35°; and IV, 35°.

The area under each curve was computed by multiplying the height of the peak by the width at the half-height point. This method was checked by accurately weighing a sample of methylene chloride and I, mixing them, and then determining their molar ratios from both their weights and from their areas under the curve. The results were ratio of CH_2Cl_2–I from weights—2.86, 1.26; from v.p.c.—2.84, 1.30. The differences in the ratios are probably due to weighing errors. Accurate weights of these materials were difficult to obtain because of their high volatility.

The major source of error was in transferring the aliquots to the individual tubes. In the case of I and II, the errors were not large, but with III and IV, which have boiling points of −5 and −4°, errors in transferring resulted in considerable scattering of the points.

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The Addition Reaction of Bromotrichloromethane to Compounds with Vinyl and Perfluorovinyl Groups

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The light-initiated reaction of bromotrichloromethane with olefins containing vinyl and trifluorovinyl groups has been studied. In cases where both groups are present in the molecule, the attack of trichloromethyl radical occurs preferentially on the methylene carbon. 1,4-Addition takes place with 1,1,2-trifluorobutadiene. In cases where a chlorine atom was located on a carbon atom adjacent to the carbon-bearing double bond, the chief product was generally not the 1:1 adduct but an olefin containing the trichloromethyl group. Some unusual dehydrohalogenations of the adducts are noted.

A number of reports have appeared in the literature[3] on the free-radical addition reaction of halo alkanes to olefins and fluorine-containing olefins. However, very little information has been published on the relative reactivity of vinyl and perfluorovinyl groups, or allyl and perfluoroallyl groups toward free-radical addition. In order to obtain information on their relative reactivities, we have carried out the sunlight-initiated reactions of bromotrichloromethane and compounds containing a vinyl or a perfluorovinyl group, or both of them either conjugated or separated. The addition reaction to 3,3-difluoroallyl bromide was also studied to compare the reactivity of fluorine-containing unsaturated groups in allylic structure with ordinary allyl groups.

Kharasch and his co-workers[4–6] obtained predominantly 1:1 adducts, 5-bromo-1,1,1,-trichloro-3-pentene (1,4-addition) and 3-bromo-5,5,5-trichloro-1-pentene (1,2-addition), by the peroxide-induced reaction of 1,3-butadiene and bromotrichloromethane. Recently Pyne[7] reported that only the 1,4-addition product

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(3) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 249.

(4) M. S. Kharasch, O. Reinmuth, and W. H. Urry, *J. Am. Chem. Soc.*, **69**, 1105 (1947).

(5) M. S. Kharasch and M. Sage, *J. Org. Chem.*, **14**, 537 (1949).

(6) M. S. Kharasch, E. Simon, and W. Nudenberg, *ibid.*, **18**, 328 (1953).

(7) W. J. Pyne, *ibid.*, **27**, 3483 (1962).

TABLE I

ADDITION OF CCl_3Br TO $CH_2=CHCFClCF_2Br$

Period of irradiation, days	Olefin g.	Olefin mole	Products: $CF_2BrCF=CHCH_2CCl_3$ (I) g.	(I) mole	(I) %	$CF_2BrCFClCHBrCH_2Cl$ (V) g.	(V) mole	(V) %	$CF_2BrCFClCHBrCH_2Br$ (VI) g.	(VI) mole	(VI) %	$CF_2BrCF=CHCHBrCCl_3$ (VII) g.	(VII) mole	(VII) %	$CF_2BrCFClCHBrCH_2CCl_3$ (VIII) g.	(VIII) mole	(VIII) %
2	64.5	0.29	26.2	0.086	30	28.5	0.084	29	3.6	0.009	3	4.1	0.011	4	29.7	0.071	24
10	61.0	0.27	6.3	0.020	7	30.3	0.089	33	10.0	0.026	10	17.3	0.045	17	30.2	0.072	27
26	74.9	0.34	1.4	0.005	2	39.0	0.115	34	12.1	0.032	9	27.3	0.071	21	38.8	0.092	27

was obtained in 76% yield using peroxide or ultraviolet irradiation.

Although 1,3-butadiene yielded about 70% of the 1:1 adduct (only 1,4-addition product) in our laboratory in the reaction with bromotrichloromethane when initiated by sunlight, 1,1,2-trifluoro-1,3-butadiene gave mostly white polymers with small amounts of telomers. Simple adducts of bromotrichloromethane to the butadiene would be $CCl_3CH_2CH=CFCF_2Br$ (I), $CCl_3CF_2CF=CHCH_2Br$ (I), $CCl_3CH_2CHBrCF=CF_2$ (III), and $CCl_3CF_2CFBrCH=CH_2$ (IV), depending upon the preference of CCl_3 radical attack for the two kinds of vinyl groups and the types of additions (1,4-addition or 1,2-addition).

It was confirmed that no 1,2-addition occurred, since the infrared spectrum of telomers showed only one absorption of carbon–carbon double bond at 5.87 μ, attributable to –CF=CH– bonds, and no appreciable absorptions near 5.6 and 6.1 μ, associated with $-CF=CF_2$ and $-CH=CH_2$, respectively, were noted. Further, the 1:1 adduct was isolated from the telomers and identified as I by comparison of its infrared spectrum with those of authentic samples, which were prepared as mentioned below. It seems, therefore, that the radical attacked on the $-CH=CH_2$ group preferentially rather than on the $-CF=CF_2$ group when these groups were conjugated in a substrate, and 1,4-addition prevailed as in the case of 1,3-butadiene.

To prepare the authentic samples of I and II, the addition reactions of bromotrichloromethane to 4-bromo-3-chloro-3,4,4-trifluoro-1-butene and 1,1,2-trifluoro-4-bromo-1-butene were carried out. The addition reaction of bromotrichloromethane to the former olefin, in which the molar ratio of the halomethane to olefin was about 5:1, yielded five products: $CF_2BrCF=CHCH_2CCl_3$ (I), $CF_2BrCFClCHBrCH_2Cl$ (V), $CF_2BrCFClCHBrCH_2Br$ (VI), $CF_2BrCF=CHCHBrCCl_3$ (VII), and $CF_2BrCFClCHBrCH_2CCl_3$ (VIII). Relative ratios of these products varied with the period of sunlight irradiation. The results are shown in Table I. The structures of the products were confirmed by their dehydrohalogenation or dehalogenation, infrared spectra, and analyses.

It is interesting that I was the chief product rather than adduct VIII using mild conditions. A few cases have been reported[8] of a loss of a neighboring halogen during free-radical additions to halo allyl compounds. Nesmeyanov and his co-worker[9] reported that the addition of bromotrichloromethane to 3,3,3-trichloropropene gave, instead of the expected $CCl_3CH_2CHBrCCl_3$, a mixture of $CCl_3CH_2CHClCCl_2Br$ and $CCl_3CH_2CH=CCl_2$. The olefin can presumably be formed by loss of chlorine from the radical $CCl_3\dot{C}HCH_2CCl_3$ and the bromide by attack on this olefin of the chlorine atom to give $CCl_3CH_2CHClC\dot{C}l_2$· which abstracts bromine from bromotrichloromethane. Kharasch and Sage[5] obtained $CCl_3CH_2CHBrCH_2CCl_3$ and $CH_2BrCHBrCH_2Br$ in the addition of bromotrichloromethane to allyl bromide. The formation of the former product was explained on the basis of β-elimination of bromine from an intermediate radical $CCl_3CH_2\dot{C}HCH_2Br$ to form $CCl_3CH_2CH=CH_2$, which was actually isolated in a run carried out in excess allyl bromide.

The mechanism suggested by Kharasch, *et al.*, for the addition of bromotrichloromethane to allyl bromide may be applied to the formation of five products mentioned above as follows.

$$CCl_3Br \xrightarrow{h\nu} CCl_3\cdot + Br\cdot \quad (1)$$

$$CF_2BrCFClCH=CH_2 + CCl_3\cdot \longrightarrow CF_2BrCFCl\dot{C}HCH_2CCl_3 \quad (2)$$

$$CF_2BrCFCl\dot{C}HCH_2CCl_3 \longrightarrow CF_2BrCF=CHCH_2CCl_3\ (I) + Cl\cdot \quad (3)$$

$$CF_2BrCFClCH=CH_2 + Cl\cdot \longrightarrow CF_2BrCFCl\dot{C}HCH_2Cl \quad (4)$$

$$CF_2BrCFCl\dot{C}HCH_2Cl + CCl_3Br \longrightarrow CF_2BrCFClCHBrCH_2Cl\ (V) + CCl_3\cdot \quad (5)$$

$$CF_2BrCFCl\dot{C}HCH_2CCl_3 + CCl_3Br \longrightarrow CF_2BrCFClCHBrCH_2CCl_3\ (VIII) + CCl_3\cdot \quad (6)$$

$$CF_2BrCFClCH=CH_2 + Br\cdot \longrightarrow CF_2BrCFCl\dot{C}HCH_2Br \quad (7)$$

$$CF_2BrCFCl\dot{C}HCH_2Br + CCl_3Br \longrightarrow CF_2BrCFClCHBrCH_2Br\ (VI) + CCl_3\cdot \quad (8)$$

$$CF_2BrCF=CHCH_2CCl_3 + Br\cdot \longrightarrow CF_2BrCF=C\dot{C}HCCl_3 + HBr \quad (9)$$

$$CF_2BrCF=C\dot{C}HCCl_3 + CCl_3Br \longrightarrow CF_2BrCF=CHCHBrCCl_3\ (VII) + CCl_3\cdot \quad (10)$$

The data presented in Table I indicate that VII is formed at the expense of I and eq. 9 and 10 are consistent with this fact.

In supporting the above mechanisms, the addition of bromotrichloromethane to 1,1,2-trifluoro-4-bromo-1-butene, in which an intermediate radical formed has no neighboring chlorine or bromine atoms, yielded only a 1:1 adduct, $CH_2BrCH_2CFBrCF_2CCl_3$ (IX) in good yield with small amounts of $CH_2BrCH_2CFBrCF_2Br$ (X) and hexachloroethane, and no halo-2-pentene. An authentic sample of II was prepared by

$$CH_2BrCH_2CF=CF_2 + CCl_3\cdot \longrightarrow CH_2BrCH_2C\dot{F}CF_2CCl_3 \xrightarrow{CCl_3Br} CH_2BrCH_2CFBrCF_2CCl_3\ (IX) + CCl_3\cdot \longrightarrow CCl_3CCl_3$$

dehydrohalogenation of IX using potassium hydroxide in ethanol.

Easy loss of the neighboring halogen atom from the intermediate radical could be partly due to the steric effect, because both β-carbons have such bulky groups as $-CF_2Br$ and $-CCl_3$, and partly due to the more stable

(8) For example, C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y. 1957, p. 268.

(9) A. N. Nesmeyanov, R. K. Freidlina, and L. I. Zakharin, *Dokl. Akad. Nauk SSSR*, **81**, 199 (1951).

TABLE II

HALO HYDROCARBONS[a]

Compounds	B.p. (mm.), °C.	$n^{25}D$	d^{25}_4	Mp	C, %		H, %		F, %		Halogen, %[b]	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
XII, $CCl_3CF_2CFBrCH_2$-$CHBrCH_2CCl_3$	117–118 (1)	1.5200	2.002	79.0	78.8	16.21	16.27	0.97	1.18	11.18	11.19	54.69	54.84
VIII, $CF_2BrCFClCHBr$-CH_2CCl_3	106–107 (7)	1.4950	2.046	60.0	60.1	14.24	14.27	0.72	0.93	13.52	13.54	50.45	50.54
XIX, $CF_2BrCFClCClBr$-CH_2CCl_3	91–92 (1)	1.5195	2.172	64.9	63.8	13.16	13.40	0.44	0.68	12.49	12.15	54.41	54.07
IX, $CH_2BrCH_2CFBrCF_2$-CCl_3	109–109.5 (7)	1.4990	2.065	55.7	56.4	15.50	15.75	1.04	1.12	14.72	14.91	45.80	45.92
VI, $CF_2BrCFClCHBr$-CH_2Br	93 (12.5)	1.4970	2.332	48.5	48.2	12.53	12.44	0.79	0.85	14.87	15.04	37.01	37.29
X, $CF_2BrCFBrCH_2CH_2Br$	72.5–73 (12.5)	1.4794	2.265	43.7	43.7	13.76	13.89	1.16	1.22	16.34	16.17	68.74	68.88
V, $CF_2BrCFClCHBr$-CH_2Cl	85–86 (15)	1.4780	2.097	45.6	44.6	14.17	14.22	0.89	0.95	16.82	18.75	41.86	42.17
XVI, $CF_3CBr_2CH_2CBr$-$(CF_3)CH_2CCl_3$	88–89 (1)	1.4816	2.150	72.9	72.8	15.31	16.15	0.74	0.90	20.40	21.03	38.81	38.81
XV, $CF_3CBr_2CH_2CCl_3$	80 (9)	1.4860	2.136	50.5	50.2	12.86	12.79	0.54	0.63	15.27	15.54	47.50	47.26

[a] Analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. [b] Calculated as Cl.

allylic structure of the product. Since the dehalogenation on the β-carbon of the intermediate radical was observed only in the CCl_3 radical attack on the olefin and not in chlorine radical attack (eq. 4), the steric effect would probably be the chief cause of radical dehalogenation. Additional evidence supporting the steric effect is that, in the addition of bromotrichloromethane to a more crowded olefin, $CF_2BrCFClCCl=CH_2$, predominant products were the unsaturated compound and $CF_2BrCFlCCClBrCH_2Cl$ with a small amount of 1:1 adduct.

In the addition reaction of bromotrichloromethane to 1,1,2-trifluoro-1,4-pentadiene, it was observed that the CCl_3 radical attacked the vinyl group first, then the perfluorovinyl group. Thus, a mixture of bromotrichloromethane and 1,1,2-trifluoro-1,4-pentadiene gave, in good yield, predominantly $CF_2=CFCH_2CHBrCH_2CCl_3$ (XI) with $CCl_3CF_2CFBrCH_2CHBrCH_2CCl_3$ (XII) under sunlight irradiation for 6 days. Irradiation for 11 days produced the latter adduct predominantly and in 25 days of irradiation XII was the only adduct obtained. The vinyl group seems also to be more reactive than the perfluorovinyl group for free-radical addition in an unsaturated compound with the two kinds of vinyl groups isolated from each other by a methylene group.

Another example which showed the lessened reactivity of the perfluorovinyl group toward free-radical addition is the addition of bromotrichloromethane to 3,3-difluoroallyl bromide. As is mentioned above, Kharasch and co-worker[3] obtained the product, $CCl_3CH_2CHBrCH_2CCl_3$, from allyl bromide. In the case of 3,3-difluoroallyl bromide, however, the main products were $CF_2=CHCBr_3$ (XIII) and $CF_2=CHCBrCCl_3$ (XIV), the $CF_2=CH-$ group being intact after reaction. The formation of these products could be explained by preferential dissociation[10] of C–Br bond of 3,3-difluoroallyl bromide under sunlight irradiation, or by debromination with CCl_3 radical to give the 3,3-difluoroallyl radical. The allyl radical formed, then, would attack bromotrichloromethane. Since allylic hydrogens of the 1,1-difluoro-4,4,4-trichloro-1-butene formed are rather reactive, the free-radical displacement of hydrogen by bromine atom would follow to yield XIV.

$$CF_2=CHCH_2\cdot + CCl_3Br \longrightarrow CF_2=CHCH_2CCl_3 + Br\cdot$$

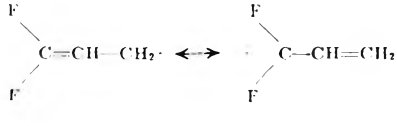
The addition reaction of bromotrichloromethane and 2-bromo-3,3,3-trifluoro-1-propene gave mainly the expected 1:1 adduct (XV) with small amounts of 2:1 adduct (XVI).

In order to prove the assigned structures of addition products, dehydrohalogenation and dehalogenation were carried out using ethanolic potassium hydroxide and zinc dust in ethanol, respectively. The dehydrohalogenation of $CH_2BrCH_2CFBrCF_2CCl_3$ (IX) can give two olefins, $CH_2BrCH=CFCF_2CCl_3$ (II) and $CH_2=CHCFBrCF_2CCl_3$. Actually the halo-2-pentene was obtained almost exclusively, the infrared spectrum of which exhibited a sharp absorption band at 5.93 μ, attributable to $-CF=CH-$ bond. When the reaction was carried out with excess potassium hydroxide, the predominant product was $C_2H_5OCH_2CH=CFCF_2CCl_3$ (XVII) which showed an absorption band at 5.91 μ for the $-CF=CH-$ group. The dehydrohalogenation of $CH_2BrCH_2CFBrCF_2Br$ (X) also yielded mainly $CH_2BrCH=CFCF_2Br$ (XVIII) with small amounts of $CH_2=CHCFBrCF_2Br$.

The formation of halo-2-pentene rather than halo-1-pentene could be explained by the steric effect of bulky groups and the stable allylic structure formation. In connection with the latter reasoning, the dehydrohalogenation of $CF_2BrCH_2CH_2Br$ was found to yield $CF_2=CHCH_2Br$ predominantly.[11]

An attempt to dehydrohalogenate $CF_2=CFCH_2CHBrCH_2CCl_3$ (XI) to get the halohexadiene or halohexatriene failed. The attack of ethoxide seemed to occur on the $-CF=CF_2$ group preferentially rather than

(10) The following resonance would stabilize the radical formed.



(11) P. Tarrant, A. M. Lovelace, and M. R. Lilyquist [*J. Am. Chem. Soc.*, **77**, 2783 (1955)] reported that dehydrohalogenation of $CF_2BrCH_2CH_2Br$ with aqueous potassium hydroxide gave mainly $CF_2BrCH=CH_2$. Therefore, the choice of solvent seems to be an important factor.

TABLE III

HALO OLEFINS[a]

Compounds	B.p. (mm.), °C.	$n^{25}D$	d^{25}_4	MD Calcd.	MD Found	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	F, % Calcd.	F, % Found	Halogen, %[b] Calcd.	Halogen, %[b] Found
XI, CF_2=$CFCH_2CHBrCH_2CCl_3$	96–97 (15)	1.4720	1.726	52.1	52.0	22.49	22.21	1.57	1.66	17.79	17.83	44.25	44.50
I, CF_2BrCF=$CHCH_2CCl_3$	77–78 (15)	1.4592	1.740	47.4	48.1	19.60	20.07	0.99	1.35	18.61	18.82	46.30	46.55
XX, CF_2BrCF=$CClCH_2CCl_4$	102–103 (14)	1.4887	1.917	51.9	51.3	17.62	16.24	0.59	0.68	16.73	17.09	52.02	50.39
II, CH_2BrCH=$CFCF_2CCl_4$	88–89 (14)	1.4720	1.767	47.4	48.4	19.60	19.49	0.99	1.18	18.61	19.50	46.30	45.63
VII, CF_2BrCF=$CHCHBrCCl_3$	102–103 (15)	1.4971	2.025	55.2	55.7	15.58	15.71	0.52	0.69	14.80	15.11	46.02	46.21
XVIII, CF_2BrCF=$CHCH_2Br$	132 (760)	1.4596	1.999	36.0	36.6	17.92	18.17	1.13	1.12	21.28	21.15	59.67	59.35
XVII, $C_2H_5OCH_2CH$=$CFCF_2CCl_3$	93–94 (16)	1.4345	1.402	50.5	50.4	30.95	30.72	2.97	2.87	21.00	21.39	39.19	39.47
XIV, CF_2=$CHCBr_2CCl_3$	109 (25)	1.4958	2.039	50.5	50.6	13.59	13.92	0.29	0.50	10.76	11.00	50.19	49.89
XIII, CF_2=$CHCBr_3$	77–78 (27)	1.5010	2.343	39.0	39.6	11.44	11.79	0.32	0.97	12.07	11.02	76.16	79.28

[a] Analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. [b] Calculated as Cl.

on the hydrogen of the adjacent carbon, yielding high boiling viscous liquid products which were not identified.

Dehalogenation of $CF_2BrClFClCHBrCH_2CCl_3$ (VIII), which could possibly give the halo-1-pentene and halo-2-pentene (I), gave predominantly halo-2-pentene. This result may be also explained by the same reasoning as the case of dehydrohalogenation.

The physical properties and results of analyses of the new compounds are listed in Tables II and III.

Experimental[12]

Materials.—1,1,2-Trifluoro-1,3-butadiene and 1,1,2-trifluoro-1,4-pentadiene were prepared by dehalogenation of 4-bromo-3-chloro-3,4,4-trifluoro-1-butene and 1,4-dibromo-2,5-dichloro-1,1,2 trifluoropentane with zinc dust in ethanol.[13] 4-Bromo-3-chloro-3,4,4-trifluoro-1-butene and 1,1,2-trifluoro-4-bromo-1-butene were obtained from Peninsular ChemResearch, Inc. 3,3-Difluoroallyl bromide was made by dehydrohalogenation of 1,3-dibromo-1,1-difluoropropane[14] with ethanolic potassium hydroxide.

Addition Reactions of Bromotrichloromethane to 1,1,2-Trifluoro-1,3-butadiene.—A mixture of 68 g. (0.34 mole) of bromotrichloromethane and 8 g. (0.07 mole) of 1,1,2-trifluoro-1,3-butadiene was sealed in a glass tube and irradiated by sunlight for 2 days. The white polymer which formed during the irradiation was filtered and washed with methanol in a Soxhlet extractor for 15 hr. and dried. Five grams of polymer was obtained. Distillation of the filtrate at reduced pressure gave 0.5 g. of 1:1 adduct (b.p. 77–85° at 12 mm.) and 3.5 g. of higher telomers (viscous liquid). The infrared spectrum of the 1:1 adduct (I) was superimposable with that of 1-bromo-1,1,2-trifluoro-5,5,5-trichloro-2-penene, prepared from other methods such as dehalogenation of 1,3-dibromo-1,1,2-trifluoro-2,5,5,5-tetrachloropentane (VIII) or addition of bromotrichloromethane to 4-bromo-3-chloro-3,4,4-trifluoro-1-butene.

Addition Reactions of Bromotrichloromethane to 4-Bromo-3-chloro-3,4,4-trifluoro-1-butene.—A mixture of 291 g. (1.47 moles) of bromotrichloromethane and 64.5 g. (0.29 mole) of 4-bromo-3-chloro-3,4,4-trifluoro-1-butene was added to a 200-ml. flask with a stopper and put under sunlight irradiation for 2 days. Fractional distillation of the irradiation products at reduced pressure, after the removal of unchanged bromotrichloromethane and olefin, gave five main products. From the gas chromatograms of each fraction, the yields of products were calculated. The results were shown in Table I. Additional runs were made by the same procedure.

(12) All temperature readings are uncorrected. Analyses were by Galbraith Laboratories, Knoxville, Tenn.

(13) P. Tarrant and E. G. Gilman, *J. Am. Chem. Soc.*, **76**, 5423 (1954).

(14) P. Tarrant and A. M. Lovelace, *ibid.*, **76**, 3466 (1954).

Addition Reaction of Bromotrichloromethane to 4-Bromo-2,3-dichloro-3,4,4-trifluoro-1-butene.—Irradiation of a mixture of 236 g. (1.19 moles) of bromotrichloromethane and 49 g. (0.19 mole) of 4-bromo-2,3-dichloro-3,4,4-trifluoro-1-butene for 26 days yielded 34.7 g. (0.10 mole, 53% yield) of CF_2BrCF=$CClCH_2CCl_3$ (XX), b.p. 101–103° (12 mm.), 24 g. (0.06 mole, 34% yield) of $CF_2BrCFClCClBrCH_2Cl$, b.p. 93–97 (6 mm.), and 3.5 g. (0.008 mole, 4% yield) of $CF_2BrCFClCClBrCH_2CCl_3$ (XIX), b.p. 90–92° (1 mm.).

Addition Reaction of Bromotrichloromethane to 1,1,2-Trifluoro-4-bromo-1-butene.—A mixture of 199 g. (1.00 mole) of bromotrichloromethane and 33 g. (0.17 mole) of 1,1,2-trifluoro-4-bromo-1-butene was added to a 200-ml. flask and irradiated by sunlight for 22 days. After the removal of unchanged bromotrichloromethane and olefin, fractional distillation of products gave about 3 g. of hexachloroethane which sublimed on a condenser, 6.4 g. (0.018 mole, 11% yield) of 1,2,4-tribromo-1,1,2-trifluorobutane (X), b.p. 68° (11 mm.), 53.4 g. (0.14 mole, 81% yield) of 3,5-dibromo-1,1,1-trichloro-2,2,3-trifluoropentane, b.p. 109–109.5° (7 mm.), and 2.4 g. of viscous liquid residue. The structure of 1,2,4-tribromo-1,1,2-trifluorobutane was confirmed by comparison of its infrared spectrum with that of an authentic sample prepared by bromine addition to 1,1,2-trifluoro-4-bromo-1-butene.

Addition Reactions of Bromotrichloromethane to 1,1,2-Trifluoro-1,4-pentadiene.—In a glass tube were sealed 112 g. (0.57 mole) of bromotrichloromethane and 11.7 g. (0.10 mole) of 1,1,2-trifluoro-1,4-pentadiene. The contents of the tube were irradiated by sunlight for 6 days. Fractional distillation of the reaction mixture under reduced pressure yielded 13.2 g. (0.041 mole, 43% yield) of 1,1,2-trifluoro-4-bromo-6,6,6-trichloro-1-hexane (XI), b.p. 96–97° (15 mm.), 17.8 g. (0.034 mole, 35% yield) of 1,1,1,7,7,7-hexachloro-2,2,3-trifluoro-3,5-dibromoheptane (XII), b.p. 117–118° (1 mm.), and 2 g. of residue. Using the same procedure, a mixture of 123 g. (0.62 mole) of bromotrichloromethane and 21.7 g. (0.18 mole) of 1,1,2-trifluoro-1,4-pentadiene under irradiation for 11 days gave 18.5 g. (0.058 mole, 32% yield) of the halohexene (XI) and 35.4 g. (0.068 mole, 38% yield) of the haloheptane (XII). Irradiation of a mixture of 54.8 g. (0.28 mole) of bromotrichloromethane and 7.5 g. (0.06 mole) of 1,1,2-trifluoro-1,4-pentadiene for 25 days gave exclusively XII, 27.6 g. (0.05 mole, 86% yield).

Addition Reaction of Bromotrichloromethane to 3,3-Difluoroallyl Bromide.—A mixture of 361 g. (1.82 moles) of bromotrichloromethane and 56 g. (0.36 mole) of 3-bromo-1,1-difluoropropene in a 200-ml. flask was irradiated for 10 days. Fractional distillation of products gave 48.4 g. (0.15 mole, 43% yield) of 1,1-difluoro-3,3,3-tribromo-2-propene (XIII), b.p. 76–78° (29 mm.), and 20 g. (0.06 mole, 16% yield) of 1,1-difluoro-3,3-dibromo-4,4,4-trichloro-1-butene (XIV), b.p. 109° (25 mm.), and 7 g. of residue.

Addition Reaction of Bromotrichloromethane to 2-Bromo-3,3,3-trifluoro-1-propene.—Irradiation of a mixture of 302 g. (1.52 moles) of bromotrichloromethane and 64.5 g. (0.37 mole) of 2-

bromo-3,3,3-trifluoro-1-propene for 13 days gave 52.3 g. (0.14 mole, 38% yield) of 1:1 adduct (XV), b.p. 86–88° (12 mm.), and 19.4 g. (0.035 mole, 10% yield) of 1:2 adduct (XVI), b.p. 86–89° (1 mm.).

Dehydrobromination of 1,3-Dibromo-5,5,5-trichloro-3,4,4-trifluoropentane (IX).—In a 300-ml. three-necked flask with a stirrer and reflux condenser was placed 81.5 g. (0.21 mole) of the halopentane. A solution of 34 g. (0.61 mole) of potassium hydroxide in 150 ml. of absolute ethanol was added dropwise for 40 min. and kept stirring for an additional 10 min. The cooled reaction mixture was suction filtered to remove the potassium bromide and water was added to the solution. The organic layer was separated, dried, and distilled to give 11 g. (0.036 mole, 17% yield) of a mixture of $CH_2BrCH{=}CHCF_2CCl_3$ (II) and $CH_2{=}CHCFBrCF_2CCl_3$, b.p. 88–90° (17 mm.), and 27.6 g. (0.10 mole, 48% yield) of $C_2H_5OCH_2CH{=}CFCF_2CCl_3$ (XVII), b.p. 93–94° (16 mm.), and viscous liquid residue, 9.8 g.

In the same procedure, a reaction of 99 g. (0.26 mole) of the halopentane with 21 g. (0.37 mole) of potassium hydroxide in 60 ml. of absolute ethanol gave 3.7 g. (0.01 mole, 5% yield) of $CH_2{=}CHCFBrCF_2CCl_3$, 37.4 g. (0.12 mole, 47% yield) of II, 6.3 g. (0.02 mole, 9% yield) of XVII, and 20.5 g. of unchanged halopentane.

Dehydrobromination of 1,2,4-Tribromo-1,1,2-trifluorobutane.—A reaction of 92 g. (0.26 mole) of the halobutane with 19 g. (0.34 mole) of potassium hydroxide in 100 ml. of absolute ethanol gave 31.6 g. (0.12 mole, 46% yield) of $CH_2BrCH{=}CFCF_2Br$, b.p. 51–52° (70 mm.), 10.6 g. of a mixture of two compounds, b.p. 70–72° (67 mm.), and 8 g. of unchanged halobutane.

Dehalogenation of 1,3-Dibromo-2,5,5,5-tetrachloro-1,1,2-trifluoropentane.—To 15 g. (0.23 mole) of zinc dust in 100 ml. ethanol was added dropwise 49 g. (0.12 mole) of the halopentane for 1 hr. The reaction mixture was filtered and diluted hydrochloric acid was added to the filtrate. The organic layer was separated and dried. Fractionation gave 4 g. (0.013 mole, 11% yield) of $CF_2{=}CFCHBrCH_2CCl_3$, 9.4 g. (0.031 mole, 26% yield) of $CF_2BrCF{=}CHCH_2CCl_3$, b.p. 74–78° (14 mm.), and 14.6 g. of unchanged halopentane.

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The Synthesis and Reactions of β-Chloroacrylonitrile

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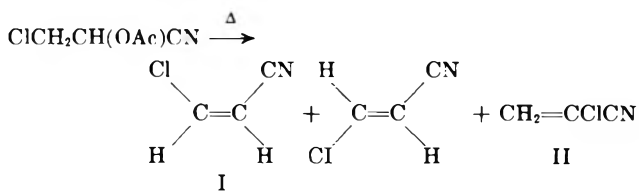
A mixture of *cis* and *trans* isomers of β-chloroacrylonitrile and α-chloroacrylonitrile is obtained by the pyrolysis of α-acetoxy-β-chloropropionitrile. The chlorine of β-chloroacrylonitrile is easily displaced by nucleophilic reagents enabling the compound to be used successfully as a cyanovinylating reagent. Reactions involving compounds containing nitrogen, sulfur, phosphorus, and carbon as the nucleophilic centers are described. Ethoxide ion and *p*-toluene sulfide ion react with *cis*- or *trans*-β-chloroacrylonitrile to give products of the same steric configuration as the starting material. In contrast, only one product, the *trans*-β-cyanovinylpiperidine, is obtained on cyanovinylation of piperidine with either the *cis*- or *trans*-β-chloroacrylonitrile. The mechanism of the cyanovinylation reaction is discussed.

In the last few years several investigators have shown increasing interest in the reactivity of vinyl halides both from a mechanistic and practical synthetic point of view. Vinyl halides which have β-electron-attracting substituents have been of particular interest because of the ease of replacement of the halogen atom by nucleophilic reagents.[1] The reactions of β-chloroacrylonitrile (I), a material of this structural type, have not been described in the literature.

Two methods for the preparation of I have been published. Dutcher[2] reported its synthesis by the addition of cyanogen chloride to acetylene; however, no physical or chemical properties were described. Gryszkiewicz-Trochimowski[3] described the synthesis of the *trans* isomer from the corresponding *trans* amide. A brief investigation of Dutcher's procedure revealed that only a very low yield of the hitherto unknown *cis* isomer was produced. We have found that I can be conveniently obtained by the pyrolysis of α-acetoxy-β-chloropropionitrile at 535°. Fractionation of the



pyrolysate gave equivalent amounts of the *cis* (b.p. 145–146°) and *trans* (b.p. 118°) isomers in 33% total yield along with a 28% yield of α-chloroacrylonitrile (II). The large amount of II obtained in the reaction is surprising. Acetate pyrolyses of this type are generally considered to proceed through an uncharged cyclic transition state; the chlorine rearrangement observed here suggests a unique mechanism involving charged species in the vapor phase.

The physical properties of *trans*-I obtained by pyrolysis were identical with those previously reported.[3] The *cis*-I obtained by the pyrolysis route was identical with the product of the cyanogen chloride–acetylene reaction.[2] In addition, the above assignments of configuration were substantiated by both infrared and nuclear magnetic resonance spectra (Table VI). The *trans* isomer exhibits a band at 935 cm.$^{-1}$ in the infrared which has been assigned to the *trans* in-phase, out-of-plane, carbon–hydrogen bending vibration.[4] The isomer to which we assign the *cis* configuration exhibits this vibrational band at 740 cm.$^{-1}$ as expected. The hydrogen–hydrogen coupling constants, 7.7 c.p.s.

(1) (a) D. E. Jones, R. O. Morris, C. A. Vernon, and R. F. M. White, *J. Chem. Soc.*, 2349 (1960); D. E. Jones and C. A. Vernon, *Nature*, **176**, 791 (1955); D. E. Jones, C. A. Vernon, and R. F. M. White, *Proc. Chem. Soc.*, 303 (1958); (b) F. Montanari, *Boll. Sci. Fac. chim. ind. Bologna*, **16**, 31, 140 (1958); (c) G. Modena, *et al.*, *Ric. sci. Suppl.*, **28**, 341 (1958); G. Modena, *et al.*, *Gazz. chim. ital.*, **89**, 854, 866, 878 (1959); (d) M. K. Kochetkov, *Usp. Khim.*, **24**, 32 (1955); (e) S. I. Miller and P. K. Yonan, *J. Am. Chem. Soc.*, **79**, 5831 (1957); (f) J. Erickson, U. S. Patent 2,433,742 (1947); (g) P. B. D. de LaMare, "Progress in Stereochemistry," Vol. 2, Academic Press, Inc., New York N. Y., 1958, p. 90; (h) W. E. Truce, *et al.*, *J. Am. Chem. Soc.*, **78**, 2743, 2748, 2752, 2756 (1949); (i) C. L. Dickenson, Jr., D. W. Wiley, and B. C. McKusick, *ibid.*, **82**, 6132 (1960).

(2) H. A. Dutcher, U. S. Patent 2,419,488 (1947).

(3) Gryszkiewicz-Trochimowski, *et al.*, *Bull. soc. chim. France*, 593 (1948).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 45.

TABLE I

NITROGEN CYANOVINYLATIONS

Nitrogen compound	β-Chloro-acrylonitrile	Yield, %	B.p. (m.m.) or [m.p.], °C. $n^{25}D$	Formula	Calcd., % / Found, % C	H	N
n-Butylamine[a,b]	*trans*	80	121 (0.2–0.25)	$C_7H_{12}N_2$	67.70	9.74	22.56
	cis	78	1.5085[j]		67.42	9.95	22.43
Di-*n*-propylamine[a]	*cis*	93	107–109° (0.3)	$C_9H_{12}N_2$	71.00	10.59	18.40
			1.5065		70.60	10.51	18.32
Diethylamine[a]	*trans*	90	85–87° (0.5)	$C_7H_{12}N_2$	67.70	9.74	22.56
	cis	90	1.5160		67.98	10.07	22.35
Dimethylamine[a]	*cis*	77	93–99° (0.6–1)	$C_5H_8N_2$	62.47	8.38	
			1.5308		62.40	8.54	
Piperidine[a]	*trans*	90	118–20° (0.5)	$C_8H_{12}N_2$	70.54	8.88	20.57
	cis[c]	88	[57–58°]		70.76	8.93	20.29
Cyclohexylamine[a,d]	*cis*	60	[164–166°]	$C_8H_{14}N_2$	72.03	9.39	18.65
					72.03	9.50	18.95
Aniline[e]	*trans*	78	[138–140°]	$C_{17}H_9N_3$	73.83	4.55	21.53
	cis	70			73.74	4.50	21.24
N-Ethylaniline[f]	*trans*	78	125–140° (0.1–0.2)	$C_{11}H_{12}N_2$			16.39
			1.6120				16.39
Phenylhydrazine[g]	*trans*	60	[80–85°]	$C_9H_9N_3$	67.90	5.69	26.39
					67.61	5.65	26.13
Pyridone[h]	*trans*	53	[55–56°]	$C_8H_6N_2O$	65.74	4.14	19.17
					65.56	4.40	19.22
Pyrrolidone[h]	*trans*	5	[54–55°]	$C_7H_9N_2O$	61.75	5.92	25.58
					61.69	6.04	25.33
Succinimide[i]	*cis*	25	[155–156.4°]	$C_7H_6N_2O_2$	55.99	4.03	18.66
					55.93	4.16	18.48

[a] Ether used as solvent for reaction; temp. 0–20°. [b] Yield and analyses on undistilled material; distillation accompanied by decomposition. [c] Recrystallized from ethylacetate–ligroin. Also obtained a 5% yield of 4-(piperidinomethylene)glutacononitrile. *Anal.* Calcd. for $C_{11}H_{13}N_3$: C, 70.46; H, 7.00; N, 22.44. Found: C, 70.41; H, 7.03; N, 22.65. [d] Recrystallized from benzene. [e] Ethanol was used as solvent for reaction; temp. 70°; product obtained was 4-(anilinomethylene)glutacononitrile. [f] Ethanol used as solvent. [g] Benzene used as solvent. [h] Reacted as sodium salt in 9:1 benzene–DMF solution. [i] Acetone used as solvent. [j] $n^{27}D$.

for *cis*-I and 14 c.p.s. for *trans*-I, observed in the n.m.r. spectra are also consistent with the proposed structures.[5]

Addition reactions at the nitrile and ethylenic linkages of I are comparable to those of acrylonitrile. For instance, *cis*-I was readily hydrolyzed with 85% sulfuric acid to the previously unknown *cis*-β-chloroacrylamide; however, an attempt at complete hydrolysis with 58% sulfuric acid gave only a low yield of *trans*-β-chloroacrylic acid.[6] The activity of I as a dienophile was demonstrated by the preparation of Diels–Alder adducts of *cis*-I with cyclopentadiene and hexachlorocyclopentadiene. Chlorination of β-chloroacrylonitrile has previously been shown to give 2,2,3,3-tetrachloropropionitrile.[7]

The facile displacement of halogen from I by nucleophilic reagents provides a method for the introduction of a cyanovinyl moiety. The reaction has wide applicability, as evidenced by cyanovinylations[8] of alcohols, phenols, thiols, amines, amides, imides, sulfinates, and active methylene compounds. The general reaction can be represented by the following, where BH is the nucleophilic reagent.

$$BH + ClCH{=}CHCN \longrightarrow BCH{=}CHCN + HCl$$

Nitrogen Cyanovinylations.—Both primary and secondary alkyl amines react rapidly with *cis*- and *trans*-I at relatively low temperatures (0–20°) to give cyanovinylamines (III) in good yields (Table I).

$$2R_1R_2NH + Cl{-}CH{=}CHCN \longrightarrow R_1R_2N{-}CH{=}CHCN + R_1R_2NH_2Cl$$

III

$R_1 = R_2 =$ alkyl or H

These weakly basic enamines dissolve in cold 5% hydrochloric acid solution with the evolution of heat. This is undoubtedly due to the hydrolysis to cyanoacetaldehyde[9] rather than simple salt formation, since the acidic solutions give a positive enol test with ferric chloride.[10] This test was negative with aqueous solutions even upon heating. Further, under the usual acidic conditions, the enamine was converted easily to the 2,4-dinitrophenylhydrazone of cyanoacetaldehyde. The N–H band at 3350 cm.$^{-1}$ shown by the secondary cyanovinylamines and their spectral similarities with the tertiary cyanovinylamines clearly indicate the absence of any of the tautomeric Schiff base form, $RN{=}CHCH_2CN$.

The reaction temperature required for the formation of quaternary cyanovinylammonium chlorides from tertiary amines varies to a considerable extent (Table II) depending on the structure of the amine. For instance, trimethylamine reacts readily at 0°, whereas triethylamine requires heating to 50° before reaction occurs at an appreciable rate. At reaction temperatures above 90°, the triethylcyanovinylammonium chloride (IV) initially produced decomposes *via* a Hoffmann-type degradation to form diethyl β-cyanovinylammonium chloride (V), the free amine (VI), and ethylene.

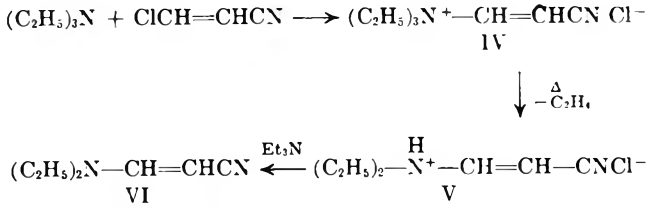
(5) C. N. Banwell and N. Sheppard, *Mol. Phys.*, **3**, 351 (1960).
(6) H. J. Backer and A. E. Beute, *Rec. trav. chim.*, **54**, 167 (1935).
(7) W. H. Jura and R. J. Gaul, *J. Am. Chem. Soc.*, **80**, 5402 (1958).
(8) By analogy with the term "cyanoethylation" for the incorporation of a cyanoethyl moiety, the incorporation of the cyanovinyl moiety can be called "cyanovinylation."
(9) C. Moureau and I. Lazannec, *Bull. soc. chim. France*, [3]**35**, 1179 (1906).
(10) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, New York, N. Y., 1958, p. 98.

TABLE II

REACTIONS OF TERTIARY AMINES AND β-CHLOROACRYLONITRILE

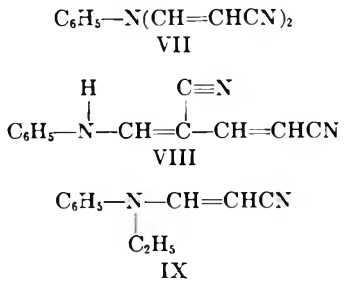
$$R_3N + ClCH{=}CHCN \rightarrow (R_3NCH{=}CHCN)^+Cl^-$$

Amine	β-ClAN	Temp., °C.	M.p., °C.	Yield, %	Formula	Calcd., % / Found, % —C—	—H—	—N—
Triethylamine	*cis*	50	138	90	$C_9H_{17}N_2Cl$	57.28	9.08	14.85
						57.09	9.27	15.03
Triethylamine	*cis*	0	158	90	$C_6H_{11}N_2Cl$			19.10
								19.18
Pyridine	*cis*	80	150–152	90	$C_8H_7N_2Cl$	57.67	4.24	16.82
						57.42	4.40	16.79



This elimination was first encountered in some of our earlier experiments in which triethylamine was used as a hydrogen chloride acceptor in an attempt to cyanovinylate nucleophiles of low reactivity at elevated temperatures. Distillation of the reaction mixtures afforded small amounts of VI, formed no doubt by the neutralization of V with unchanged triethylamine.

Aniline is much less reactive than the aliphatic amines and only a diadduct was obtained under various reaction conditions. There are two possible structures (VII and VIII), other than those which involve ring substitution, that can be written for this diadduct.

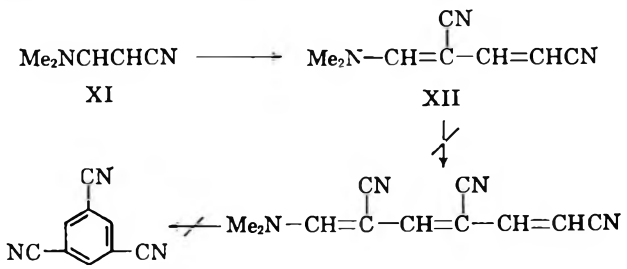


The infrared spectrum exhibited an N–H vibration (3300 cm.$^{-1}$) which is consistent with structure VIII. Efforts to obtain a similar diadduct with N-ethylaniline, where only one hydrogen is replaceable, were unsuccessful; only the monoadduct IX was formed. A comparison of the ultraviolet spectrum of IX (λ_{max} 285 mμ) with that of the diaddition product (λ_{max} 351 mμ) is revealing, since structures such as VII would be expected to have an absorption maximum near that of IX.

Interestingly, a small yield of a diadduct similar in structure to VIII, 4-(N-piperidinomethylene)glutacononitrile (X), was obtained along with the major product, β-cyanovinylpiperidine, when piperidine reacted with *cis*-I. However, compound X could be obtained much more conveniently from N-β-cyanovinylpiperidine by a procedure which appears to be of a general nature. This reaction was discovered in an attempt to prepare 1,3,5-tricyanobenzene from β-cyanovinyldimethylamine (XI) *via* Kochetkov's[11] procedure for obtaining 1,3,5-triacetylbenzene from β-aminovinyl methyl ketones.[12] These reactions may be mechanistically similar to the conversion of 1-butyne-3-one to 1,3,5-triacetylbenzene at room temperature in the presence of dimethylamine or pyridine acetate.[12]

When XI was heated in glacial acetic acid, a 45% yield of a yellow solid (XII) was obtained which decolorized both 2% aqueous permanganate solution and bromine in carbon tetrachloride. Dissolution in a large excess of 5% hydrochloric acid at 25° was slow.

In addition to its molecular weight and elemental analysis the spectral properties exhibited by the yellow solid are consistent with those of the previously unreported 4-(dimethylaminomethylene)glutacononitrile (XII). Catalytic hydrogenation indicated an equivalent weight of 48, in good agreement with the theoretical value of 49 based on the absorption of 3 moles of hydrogen (2 for the carbon double bond reduction and 1 for hydrogenolysis of the amino nitrogen–carbon bond). This diene could be considered as the first intermediate in the anticipated condensation leading to 1,3,5-tricyanobenzene.



This reaction path could also be proposed for Kochetkov's synthesis of triacetylbenzene; however, it is not readily apparent why our reaction did not lead to the aromatic structure.

Phenylhydrazine was monocyanovinylated in good yield; however, the position of cyanovinylation has not been established. Hydrazine reacted readily with I at 0° as evidenced by the formation of hydrazine hydrochloride in high yield; however, several attempts at isolation of the cyanovinyl product afforded only tars or led to explosive decomposition of the reaction mixture.

Succinimide was successfully cyanovinylated as its sodium salt or by the use of triethylamine as a hydrogen chloride acceptor. Amides, however, proved to be very difficult to cyanovinylate; tertiary amines did not catalyze the reaction, and treatment of the amide sodium salts with I led to the formation of tars. Only

(11) N. K. Kochetkov, *Izv. Akad. Nauk SSSR*, 991 (1953).

(12) R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," New York Academic Press, New York, N. Y., 1953, p. 159.

TABLE III
OXYGEN CYANOVINYLATIONS

Alcohol	β-Chloroacrylonitrile	Yield, %	B.p., °C. (mm.)	M.p., °C.	$n^{25}D$	Formula	Calcd., % / Found, % C	H	N
CH_3OH	*cis*	85	92–94 (27)		1.4540	C_4H_5NO	57.82 / 58.09	6.07 / 6.14	
C_2H_5OH	*cis*	90	85–87 (15)		1.4530	C_5H_7NO	61.84 / 61.91	7.22 / 7.04	14.42 / 14.77
C_2H_5OH	*trans*	91	76–78 (15)		1.4510	C_5H_7NO	60.84 / 61.64	7.27 / 7.21	14.42 / 14.49
C_6H_5OH[a]	*cis*	60	87–89 (2)	27–28		C_9H_7NO	74.46 / 73.99	4.86 / 4.81	9.55 / 9.47
$C_{10}H_5OH$[a]	*cis*	67		73–74		$C_{13}H_9NO$	80.00 / 79.98	4.65 / 4.88	7.19 / 7.25

[a] Dioxane used as solvent.

TABLE IV
ACETAL FORMATION FROM β-CHLOROACRYLONITRILE

$$RONa + Cl{-}CH{=}CH{-}CN \xrightarrow{ROH} (RO)_2CH{-}CH_2CN$$

Alcohol	β-Chloroacrylonitrile	B.p. (mm.), °C. $n^{25}D$	Yield, %	Formula	Calcd., % / Found, % C	H	N
CH_3OH	*cis* or *trans*	94–98 (25) 1.4124	56	$C_5H_9NO_2$	52.17 / 52.43	7.82 / 7.86	12.17 / 12.28
C_2H_5OH	*cis* or *trans*	57° (1) 1.4142	87	$C_7H_{13}NO_2$	58.72 / 59.95	9.15 / 9.01	9.78 / 9.84

cyclic amides such as 2-pyrrolidone or 2-pyridone appear to undergo cyanovinylation. Again tertiary amines were ineffective as catalyst and these amides were cyanovinylated as their sodium salts. A 5% yield of N-β-cyanovinylpyrrolidone and a 50% yield of N-β-cyanovinylpyridone were obtained. The strong basicity of the amide salts apparently limits this reaction, by favoring dehydrohalogenation of I to cyanoacetylene, which then can polymerize under the reaction conditions.[13]

Oxygen Cyanovinylations.—Cyanovinyl ethers were readily obtained in good yields on treatment of sodium alkoxides or phenoxides with an equivalent of I (Table III). Use of more than an equivalent of alkoxide will catalyze the addition of a second molecule of alcohol with acetal formation. This is a convenient method for making acetals of β-cyanoacetaldehyde (XIII, Table IV).[14]

$$RONa + Cl{-}CH{=}CH{-}CN \longrightarrow ROCH{=}CHCN + NaCl$$

$$ROCH{=}CHCN \xrightarrow{ROH,\ base} (RO)_2CHCH_2CN$$

XIII

Sulfur Cyanovinylations.—Alkyl and aryl mercaptans were readily cyanovinylated in the presence of triethylamine to yield the corresponding β-cyanovinyl thioethers. Ether was used as solvent so that the amine hydrochloride could be easily removed. β-Cyanovinyl aryl sulfones were easily obtained by the cyanovinylation of sodium aryl sulfinates. In general, these reactions required a higher temperature than those with the corresponding mercaptans. Sodium sulfide was dicyanovinylated as a suspension in ethano to yield β-cyanovinyl thioether.

$$Na_2S + 2ClCH{=}CHCN \longrightarrow S(CH{=}CHCN)_2 + 2NaCl$$

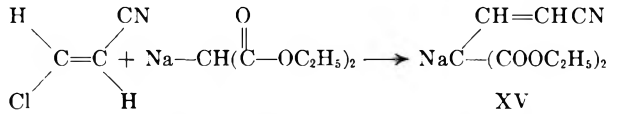
Reaction of sodium bisulfite with I yielded the disodium salt XIV.

$$3NaHSO_3 + ClCH{=}CHCN \longrightarrow (NaSO_3)_2CHCH_2CN + NaCl + H_2O + SO_2$$

XIV

Undoubtedly, the product resulted from addition of sodium bisulfite to the intermediate cyanovinyl compound. Attempts to isolate the mono sulfato intermediate were unsuccessful.

Carbon and Phosphorus Cyanovinylation.—The cyanovinylation of activated methylene compounds appears to be quite general as evidenced by the ease of reaction of diethyl sodiomalonate with I. The substitution product XV was easily isolated as its sodium salt when equivalent amounts of reactants were used.



XV

Cyanovinylphosphonates were easily obtained by the Arbuzov reaction of either *cis*- or *trans*-I with trialkyl phosphites; diethyl β-cyanovinyl phosphonate was also prepared from *cis*-I and diethyl phosphite in the presence of triethylamine, but this reaction proved difficult to repeat.

$$(RO)_3P + ClCH{=}CHCN \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}{-}CH{=}CHCN + RCl$$

R = alkyl

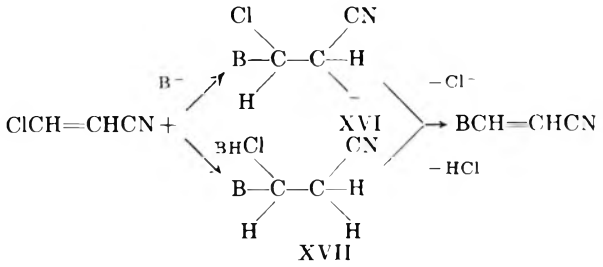
Mechanism.—The possible reaction mechanisms for substitution of halogen on a vinyl group containing an electron withdrawing moiety at the β-position have recently been examined by Vernon[15a] and may be assigned to either of two fundamental types: one, an "elimination–addition" mechanism

(13) S. Murahashi, *et al.*, *J. Chem. Soc. Japan*, **77**, 1689 (1956); **78**, 324, 327, 330 (1957).

(14) S. M. McElvain and R. L. Clarke, *J. Am. Chem. Soc.*, **69**, 2657 (1947).

$$ClCH{=}CHCN + B^- \longrightarrow HC{\equiv}C{-}CN + HB + Cl^- \longrightarrow BCH{=}CHCN$$

involving cyanoacetylene as a free intermediate (above), the other an addition–elimination mechanism.



With regard to this second mechanism, the nature of the addition product may vary from a carbanionic intermediate such as XVI to that of the uncharged adduct (XVII). If the reaction proceeded by an elimination–addition mechanism, with the production of cyanoacetylene, one would expect by the rule of *trans* addition that the product of the reaction would have the *cis* configuration.[15] If, on the other hand the reaction proceeds by an addition–elimination mechanism, the product or products would depend on the nature of the primary addition product. Vernon[1a] has shown by the use of deuterated solvent that the reaction of phenyl sulfide ion with *cis*- or *trans*-β-chlorocrotonates does not involve an intermediate such as XVII. The nature of the intermediate complex (XVI) may vary from one involving simultaneous bond formation of the nucleophile and bond breaking of the halogen (concerted mechanism), to one involving a true carbanion intermediate. The nature of the products will therefore depend on the degree of formation of the incipient carbanion. The more stable the carbanion or the greater its life, the greater the probability of rotation around the carbon–carbon bond. Elimination from such an intermediate can produce initially either a mixture of *cis* or *trans* isomers or a single isomer, which would be the thermodynamically more stable one. On the other hand, if the life is extremely short, retention of configuration would be expected.[1a] Thus, examination of the stereochemistry of the reaction products of β-chloroacrylonitrile might indicate which mechanism is operative. An investigation of I with several nucleophilic agents was made and the results are compiled in Table V.

TABLE V

REACTIONS OF VARIOUS NUCLEOPHILES WITH *cis*- AND *trans*-β-CHLOROACRYLONITRILE AT 0°

Isomer of I	Nucleophile	Isomer content of products, % *cis*	Isomer content of products, % *trans*
cis	EtO^-	95	<5
trans	EtO^-	<5	95
cis	$p\text{-}CH_3C_6H_4S^-$	95	<5
trans	$p\text{-}CH_3C_6H_4S^-$	10	90
cis	$C_5H_{11}N$	0	100
trans	$C_5H_{11}N$	0	100

Nucleophilic displacements by ethoxide or *p*-toluene sulfide ion resulted in a high retention of geometric configuration, but the reactions were not completely stereospecific. The configurations of the products were established by both infrared and n.m.r. spectra. The ratio of isomers was established by infrared analysis. It is interesting to note that the *cis*-β-cyanovinyl-*p*-tolyl thioether reaction proceeds with a higher degree of stereospecificity than that of its *trans* isomer. It is difficult to say with certainty that the *trans* thioether is formed in a lesser degree of stereospecificity than the *cis*, since the *trans* thioether may be the thermodynamically unstable isomer.[1a] It is clear with both ethoxide and *p*-toluene sulfide ion, because of high degree of retention of configuration of the products, that the reaction proceeds by the addition–elimination mechanism. Furthermore, the intermediate complex (XVI) must have an extremely short half life. Montanari[1b] recently showed that nucleophilic displacement by alkoxides and phenyl sulfide ion on β-chlorocrotonates proceeds by an addition–elimination mechanism; however, retention of configuration was only observed when phenyl sulfide ion was the nucleophile.

Only one product was obtained when piperidine was used as the nucleophilic reagent. Since our mechanism is solely based on the nature of the product, it was essential that we determine its structure. It is more difficult to assign structure on the basis of physical methods, as was done with the cyanovinyl ethers and cyanovinyl thioethers, when only one of the isomers is at hand. The infrared spectra of the cyanovinylamines have bands in the 960- and 720-cm.$^{-1}$ region. These two bands are very similar in intensity and wave length of absorption to those of the *trans*- and *cis*-β-ethoxyacrylonitriles, suggesting that a mixture was obtained. However, n.m.r. spectra and vapor-phase chromatographic analysis indicated that only one product was obtained. In addition, the vinyl hydrogen coupling constant in the n.m.r. spectrum[7] indicated that only the *trans* product was obtained (Table VI).

N-β-Cyanovinylpiperidine has been reported[13] and was prepared by the addition of piperidine to cyanoacetylene. This procedure was repeated and the product was identical with that obtained from either *cis*- or *trans*-I. If the rule of *trans* addition is applicable, the product should have the *cis* configuration; however, this extension of the *trans* rule might not necessarily be valid when the nucleophile is an amine.[16] We are inclined to favor the n.m.r. data, but cannot give adequate explanation for the 720-cm.$^{-1}$ band in the infrared spectrum.

Not only can the structure of the product shed light on the mechanism which is involved, but the relative reaction rates of the *cis*- and *trans*-β-chloroacrylonitrile should indicate which mechanism is operative. The rates of reaction of *cis*- and *trans*-I with piperidine were therefore determined (Table VII).

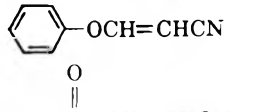
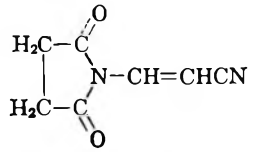
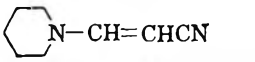
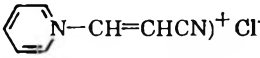
These kinetic results indicate that the elimination–addition mechanism is not in effect since, if it were, the *cis* isomer should undergo elimination much more rapidly than the *trans*.[15] It therefore may be concluded that, at least with neutral (uncharged) reagents, the reaction proceeds essentially in the same manner as that of anionic nucleophiles (addition–elimination). It is evident, moreover, particularly from the steric course of the reaction, that a difference exists in the

(15) W. E. Truce, *et al.*, *J. Am. Chem. Soc.*, **78**, 2743, 2748, 2752, 2756 (1949); A. Michael, *Ber.*, **34**, 4215 (1901); *J. prakt. chem.*, **52**, 344 (1895).

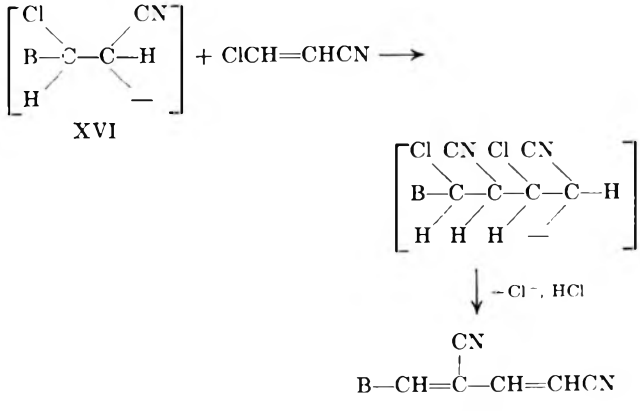
(16) E. A. Braude, *et al.*, *J. Chem. Soc.*, **45**, 948 (1946).

TABLE VI

SPECTRAL CHARACTERISTICS OF β-CYANOVINYL COMPOUNDS

	Product	β-Chloroacrylonitrile	Infrared spectra, cm.$^{-1}$ CN	C=C	C–H	Ultraviolet spectra mμ	ϵ_{max}	N.m.r. proton coupling constants, J_{HH}, c.p.s.
1	CH_3—S—CH=CHCN	*cis*	2235	1572	692	274	11,980	
2	*cis*-*p*-$CH_3C_6H_4$S—CH=CHCN	*cis*	2210	1555	715	281	16,700	11
3	*trans*-*p*-$CH_3C_6H_4$S—CH=CHCN	*trans*	2220	1590	935	273	28,700	14.8
				1585		218	shoulder	
4	$S(CH{=}CH{-}CN)_2$	*cis*	2210	1555		292	20,890	
5	*cis*-$CH_3OCH{=}CHCN$	*cis*	2235	1637	718	224	13,600	6.4
6	*cis*-$C_2H_5OCH{=}CHCN$	*cis*	2220	1637	725			6.5
7	*trans*-$C_2H_5OCH{=}CHCN$	*trans*	2220	1637	956	222	14,200	11.5
8		*cis*	2230	1650		240	15,700	
9	$(EtO)_2P(O)$—CH=CHCN	*cis*	2250	1615				
10	*cis*-*p*-CH_3—C_6H_5—$SO_2CH{=}CHCN$	*cis*	2235	1605				
11	*trans*-*p*-CH_3—C_6H_5—$SO_2CH{=}CHCN$	*trans*	2235	1605	958	205		
12	*cis*-$ClCH{=}CHCN$		2230	1610	740			7.7
13	*trans*-$ClCH{=}CHCN$		2230	1610	935			14.0
14		*cis*	2230	1640				
15	$Bu_2NHCH{=}CHCN$	*cis*	2200	1635				
16	Me_2N—CH=CHCN	*cis*	2200	1640		258	20,160	
17	Et_2N—CH=CHCN	*cis* or *trans*	2200	1640				13.6
18	*n*-Pr_2N—CH=CHCN	*cis*	2200	1640				13.8
19		*cis* or *trans*	2200	1640				11.5
20	$Me_2N{\cdot}CH{=}C(CN)CH{=}CHCN$		2200	1657		320	41,200	
				1605				
21	C_6H_5—NHCH=C(CN)CH=CHCN	*cis* or *trans*	2200	1665		351	43,500	
				1605				
22	$(Et_2NHCH{=}CHCN)^+Cl$	*cis*	2245	1655				
23		*cis*	2235	1635				
24	$(Me_3NCH{=}CHCN)^+Cl^-$	*cis*	2245	1650				
25	$(Et_3NCCH{=}CHCN)^+Cl^-$	*cis*	2245	1650				
26	C_6H_5—$N(C_2H_5)CH{=}CHCN$	*trans*	2200	1665		285		16
				1605				

half-life of the carbanion of the primary addition product (see preceding discussion). This is further exemplified in the case where aniline is the nucleophile and only a diadduct is obtained. Apparently here the carbanion (XVI) is stable enough to react further with another molecule of I as shown by the following.



XVI

The question arises as to a reason for the observed differences in the stability of the intermediate when amines are used as the nucleophiles. To determine whether the difference of the stereochemical course of the reaction with amines has any relation to the ionic charge of the nucleophilic species, the lithium salt of piperidine was treated with *trans*-I. Less than 1% of a product was obtained, which proved to be *trans*-β-cyanovinylpiperidine. Apparently the basicity of the material was too great, causing dehydrohalogenation and subsequent polymerization of the intermediate cyanoacetylene. However, Vernon[1a] has shown that nucleophilic atttack by a charged species such as ethoxide ion on *cis*- and *trans*-chlorocrotonates yields exclusively the *trans* product. From this we may conclude that the stability of the activated complex depends on the nucleophilic species as well as the activating group.

TABLE VII

REACTION OF β-CHLOROACRYLONITRILE AND PIPERIDINE IN METHANOL AT 0°

Reaction	Rate constant
cis-I + piperidine	2.00×10^{-2} sec.$^{-1}$ mole^{-1} l.
trans-I + piperidine	2.67×10^{-2} sec.$^{-1}$ mole^{-1} l.

Spectra.—Perhaps the most significant feature in the infrared spectra of the β-cyanovinylamines is the lowering of the nitrile band to 2200 cm.$^{-1}$ compared to the bands obtained with saturated nitriles (2250 cm.$^{-1}$) and with simple α,β-unsaturated[17] nitriles (*ca.* 2228 cm.$^{-1}$). This displacement is associated with a reduction in the triple bond character of the nitrile group and may be attributed to the contribution of the ionic resonance structure (XVIII) for the ground state of these molecules.[18-20] This pronounced frequency shift, which would not be expected to be operative in

$$>N-CH=CH-CN \longleftrightarrow \overset{+}{N}=CH-CH=C=\overset{-}{N}$$
XVIII

the case of α-cyanovinylamines, is compatible with the observed low basicity of these materials. The p electrons of the amino nitrogen, which are the seat of amine basicities, are here tied up by interaction within the system and are not readily available for coordination with acids.

Another characteristic of the spectra of the cyanovinylamines was the marked intensity of the double-bond vibration,[20] an effect which was encountered in most of the other cyanovinyl compounds, with the exception of the phosphonate ester. The ethylenic stretching frequencies for the amines were higher than those reported by Baldwin[20] for compounds which were similar except for the fact that the double bonds were tri- or tetrasubstituted. The ethylenic stretching frequency for the cyanovinyl thioethers was lowered considerably.

It is interesting that, in compounds in which the β-carbon of the carbon–carbon double bond is joined to an electron-attracting group, the nitrile group behaves spectroscopically like a simple unconjugated nitrile. This may be due to complete inhibition of resonance of the type shown in structure XVIII. The large bathochromic effects in the ultraviolet exerted by the amino, thio, and oxy auxochromes in conjugation with an α,β-unsaturated nitrile are readily apparent.[16] In this series of compounds the auxochromic power increases in the order O < N < S.

Experimental[21]

α-Acetoxy-β-chloropropionitrile.[22,23]—To 8000 g. of an aqueous solution of chloroacetaldehyde (pH adjusted to 7.5 ± 0.5 with solid sodium bicarbonate) was added 1580 g. of liquid hydrogen cyanide at a temperature of 0–9°. After the addition had been completed (2 hr.), the reaction mixture was allowed to stand overnight. Stabilization of the cyanohydrin for further treatment was accomplished by adjusting the pH to 2.5 or below with concentrated phosphoric acid. The hydrocyanic acid was removed *in vacuo* at 25° and the water was removed by continuous stripping (50° at 15 mm.). This procedure gave a 95% aqueous solution of chloroacetaldehyde cyanohydrin. Distillation of a 215-g. aliquot gave 193 g. (94%) of a colorless oil, b.p. 110° (3 mm.). Distillation of this material is hazardous since slight overheating may result in explosive decomposition of the cyanohydrin to chloroacetaldehyde and hydrogen cyanide.

A mixture of 1530 g. of acetic anhydride and 970 g. of a 95% aqueous solution of α-hydroxy-β-chloropropionitrile was held at 40° for 2 hr. and then at 100° for 3 hr. ($n^{25}D$ remained constant). The acetic acid was removed *in vacuo*. The acetic anhydride was stripped under 5-mm. pressure. Distillation of the residue gave 1200 g. (90%) of a colorless oil, b.p. 70° (215 mm.), $n^{25}D$ 1.4458.

β-Chloroacrylonitrile.—Into a glass tube packed with glass beads, heated to 535°, was fed 77 g. of α-acetoxy-β-chloropropionitrile over a 2-hr. interval (contact time = 10 sec.). Seventy grams of liquid product was collected in a trap at 25°. The crude product was poured into 100 ml. of water and sodium bicarbonate was added until the pH was 7.0. The mixture was extracted with 200 ml. of ether, the ether layer was dried over sodium sulfate, and the solvent was removed. Distillation of the residue gave 13 g. (28%) of α-chloroacrylonitrile and 15 g. (33%) of a 50:50 mixture of *cis*- and *trans*-β-chloroacrylonitrile. Distillation of the mixture provided pure *cis*- and *trans*-β-chloroacrylonitrile and α-chloroacrylonitrile. These compounds are potent lachrymators and vesicants, and should be handled accordingly. *cis*-I boiled at 145–146°, $n^{25}D$ 1.4560.

Anal. Calcd. for C_3H_2ClN: C, 41.17; H, 2.31. Found: C, 41.37; H, 2.60.

trans-I boiled at 118° and melted at 45°, $n^{25}D$ 1.4520.

Anal. Calcd. for C_3H_2ClN: C, 41.17; H, 2.31. Found: C, 41.27; H, 2.61.

α-Chloroacrylonitrile boiled at 88°, $n^{20}D$ 1.4297, $n^{25}D$ 1.4303.

***cis*-β-Chloroacrylamide.**—*cis*-β-Chloroacrylonitrile (87.5 g.) was added to 113.2 g. of 95.4% sulfuric acid and 14.6 g. of water. The reaction mixture was maintained at 85–90° during the addition and for an additional 90 min., first with an ice bath, and then with heating as the reaction subsided. The mixture was cooled to about 40° and poured into a stirred mixture of 400 g. of ice and 145 ml. of concentrated ammonium hydroxide. The temperature was held below 35° with external cooling. The precipitate was filtered, air-dried, and triturated with four 15-ml. portions of hot acetone. Evaporation of the acetone and recrystallization of the solid residue (67.5 g.) from ethyl acetate gave 51.5 g. of *cis*-β-chloroacrylamide, m.p. 111–112°.

Anal. Calcd. for C_3H_4ClNO: N, 13.27. Found: N, 13.11.

The known *trans* isomer melts at 143.5–145°.[3]

***trans*-β-Chloroacrylic Acid.**—Aqueous sulfuric acid (58%) was heated to 95° and *cis*-I was added over 35 min. The two-phase mixture was then heated under reflux for 11 hr., during which time hydrogen chloride was steadily evolved. The reaction mixture was cooled and shaken with 100 ml. of water and 100 ml. of chloroform. The organic phase was separated and extracted with a solution of 73 g. of potassium carbonate and 250 ml. of water. The alkaline solution was stirred with carbon black, filtered, acidified with hydrochloric acid, and extracted with four 50-ml. portions of chloroform. After drying with calcium sulfate, the chloroform was evaporated; recrystallization of the residue (12 g.) from 40 ml. of hexane gave 6.7 g. (13%) of *trans*-β-chloroacrylic acid melting at 84–86°, lit.[6] m.p. 85–86°.

2,2,3,3-Tetrachloropropionitrile.—*cis*-I (43.9 g., 0.5 mole) was placed in a 250-ml. three-necked flask equipped with a stirrer, thermometer, and Y-tube connected to a condenser and a gas dispersion tube. Benzoyl peroxide (0.1 g.) was added to the mixture and chlorine was passed through. A self-sustaining reaction ensued, with vigorous evolution of hydrogen chloride, which carried the temperature to 83°. The total gain in weight was 42.2 g. (theory 35.5 g.). The crude product was dissolved in ether and washed with water and 0.1 *M* sodium thiosulfate. After drying over calcium sulfate, the ethereal solution was vacuum stripped to give 66.7 g. (69.2%) of crude product. Fractional distillation afforded pure 2,2,3,3-tetrachloropropionitrile, b.p. 64–65° (10 mm.).

Anal. Calcd. for C_3HCl_4N: C, 18.68; H, 0.52; Cl, 73.54. Found: C, 18.65; H, 0.83; Cl, 73.56.

Cyanovinylation of Primary and Secondary Alkyl Amines (Table I).—The cyanovinylations of the amines in Table I were carried out according to the following procedure. β-Chloroacrylonitrile (0.1 mole) was added to a stirred solution of the amine (0.2 mole) in ether or in benzene. A precipitate formed almost immediately after the addition was started. The reaction mixture was allowed to stand until the reaction was completed. The mixture was then filtered to remove the amine hydrochloride, and the product was isolated by distillation or recrystallization.

Cyanovinylation of Tertiary Amines (Table II).—A solution comprising 0.1 mole each of β-chloroacrylonitrile and a tertiary amine was heated in an inert solvent such as anhydrous toluene

(17) J. Felton, *et al.*, *J. Chem. Soc.*, 2120 (1955).

(18) J. Weinstein and G. M. Wyman, *J. Org. Chem.*, **23**, 1519 (1958).

(19) J. P. Freeman and W. D. Emmons, *J. Am. Chem. Soc.*, **78**, 3405 (1956).

(20) S. Baldwin, *J. Org. Chem.*, **26**, 3288 (1961).

(21) Melting points are uncorrected.

(22) R. M. Nowak, U. S. Patent 2,915,549 (1959).

(23) J. Houben and E. Pfankuch, *Ber.*, **59B**, 2397 (1926).

or anhydrous ether. Upon cooling, the salt precipitated and was isolated by filtration and recrystallized from ethanol.

4-(Anilinomethylene)glutaconitrile.—In a flask equipped with a reflux condenser, 18.6 g. of aniline and 8.75 g. of *cis*- or *trans*-I were dissolved in ethanol. After heating for 24 hr. in refluxing ethanol, a yellow precipitate formed. The reaction mixture was slurried with 100 ml. of water and filtered to give 7.5 g. of a mustard-yellow product. Recrystallization of the solid from acetonitrile yielded 5.2 g. of material, m.p. 138–140°.

N-β-Cyanovinyl-N-ethylaniline.—N-Ethylaniline (36 g.) and 13.1 g. of *trans*-I were dissolved in 100 ml. of absolute ethanol. The mixture was heated for 24 hr. at 78°. Upon cooling, crystals of the amine hydrochloride formed. The solution was poured into 200 ml. of cold water and the organic phase was separated. The organic layer was removed, dried, and distilled. A forerun of N-ethylaniline was obtained (6.48 g.) before the cyanovinylamine fraction distilled. A total of 10.6 g. of the cyanovinylated amine was collected at 125–140° (0.1–0.2 mm.) as a viscous, clear liquid.

N-β-Cyanovinylsuccinimide (Table I).—To a solution consisting of 19.8 g. (0.2 mole) of succinimide and 20.2 g. (0.2 mole) of triethylamine in 100 ml. of acetone was added 17.5 g. (0.2 mole) of *cis*-I. After standing for several hours, the orange solution was filtered and the filtrate evaporated. A slushy residue remained, which was triturated with 150 ml. of water and then recrystallized from 175 ml. of ethanol, affording 5.5 g. (18.3%) of N-β-cyanovinyl succinimide, m.p. 155–156.4°.

N-β-Cyanovinylpyridone.—The sodium salt of 2-pyridone was prepared by the addition of 9.8 g. of 2-pyridone dissolved in a 10% solution of DMF in benzene to a mixture of 4.55 g. of sodium hydride dispersion in the 10% DMF–benzene solution. The salt was then added to a stirred solution of 8.75 g. of *trans*-I in 500 ml. of benzene. The addition was complete in 2 hr., and the resulting black solution was filtered to remove the sodium chloride, washed with 200 ml. of water, and dried over magnesium sulfate. Evaporation of the solvents left a brown crystalline material which was recrystallized from a water–acetone solution. Another recrystallization from methanol yielded 7.7 g. of the substitution product (53%), m.p. 55–56°.

N-β-Cyanovinylpyrrolidine.—The reaction was performed essentially as described above, yielding 5% of material, m.p. 54–55°.

β-Cyanovinyldiethylammonium Chloride (Table II).—*cis*-β-Chloroacrylonitrile (0.2 mole) and triethylamine were heated in a 70° oil bath. The temperature rose within a few minutes to 90°, and vigorous boiling started. The bath was removed and, when the boiling subsided, heat was reapplied (90°) for an additional 25 min., during which time the mixture became semisolid. After cooling, the liquid portion was decanted and the solid was washed repeatedly with acetone and ether. The light residue (15 g.) was dissolved in 300 ml. of anhydrous ethanol, decolorized, and reprecipitated into ether as fine off-white needles (5 g.). The purification was repeated and, after drying under vacuum (0.3 mm.), the product was submitted for analysis. The material was extremely hygroscopic.

Anal. Calcd. for $C_7H_{13}ClN_2$: N, 17.44. Found: N, 17.64.

β-Cyanovinylphenylhydrazine.—Into a suitable reaction vessel equipped with stirrer, reflux condenser, and thermometer were introduced 9.8 g. of phenylhydrazine and 50 g. of benzene. Subsequently, 8.7 g. of β-chloroacrylonitrile was added slowly over a period of 30 min., while the temperature of the reaction was held at 60° with stirring. The reaction mixture was held at this temperature for another 6 hr. At the end of this time, the reaction mixture was cooled, and phenylhydrazine hydrochloride was filtered off. Approximately one-half of the benzene was evaporated under reduced pressure. Crystallization of β-cyanovinylphenylhydrazine was induced by cooling. Filtration of the solid product from the benzene mother liquor resulted in a recovery of 6.5 g. of pale orange needles, m.p. 80–85°.

Oxygen Cyanovinylation (Table III).—The following procedure was used for cyanovinylation of alcohols and phenols. Phenols were cyanovinylated in ethanol.

A solution of 1.0 mole of the alkoxide in 100 ml. of the corresponding alcohol was added to a similar solution of 1.1 moles of the *cis*- or *trans*-I. The temperature of the reaction was kept below 20° by external cooling. On completion of addition, the contents of the flask were allowed to warm to room temperature and then neutralized with glacial acetic acid to a phenolphthalein end point. The sodium chloride which formed during the course of the reaction was removed by filtration. The solvents were stripped and the residue was distilled.

Acetal Formation (Table IV).—Example given is for the formation of β,β-diethoxypropionitrile from *trans*-I. This procedure was followed for other examples given in Table IV.

A solution of 17.4 g. of sodium ethoxide in 550 ml. of ethanol was added to a stirred solution of 21.9 g. of *trans*-I in 150 ml. of ethanol. The addition was complete in 45 min. and the reaction mixture was stirred for an additional 4 hr. The mixture was then neutralized with glacial acetic acid to a phenolphthalein end point. The precipitated sodium chloride was removed by filtration, and evaporation of the ethanol followed by distillation of the residual liquid yielded 28 g. of β,β-diethoxypropionitrile, b.p. 57° (1 mm.), $n^{25}D$ 1.4142.[14]

***cis*-β-Cyanovinyl Methyl Thioether.**—A benzene solution of *cis*-I (29.2 g.) and triethylamine (33.8 g.) was cooled to 0° and methyl mercaptan (16 g.) was bubbled in over a period of 75 min. After standing overnight at room temperature, the precipitate (41.3 g.) was removed by filtration and the filtrate was distilled, yielding 27.8 g. (84%) of β-cyanovinyl methyl thioether, b.p. 92–93° (10 mm.), $n^{25}D$ 1.5371.

Anal. Calcd. for C_4H_5NS: C, 48.45; H, 5.08; N, 14.13. Found: C, 48.67; H, 5.25; N, 13.89.

***trans*-β-Cyanovinyl *p*-Tolyl Thioether.**—*trans*-I (8.75 g.) was added to a stirred solution of *p*-thiocresol (12.4 g.) and triethylamine (10.1 g.) in 300 ml. of anhydrous ether. The temperature of the solution was kept below 20° during addition. Stirring was continued for 1 hr. after the addition was complete. The triethylamine hydrochloride was removed by filtration and the ether solution was washed successively with water, cold 2% sodium hydroxide, and a saturated sodium chloride solution. The solution was dried over anhydrous magnesium sulfate, and the ether was evaporated. Low-temperature recrystallization from petroleum ether (b.p. 30–60°)–ethanol mixture yielded 16.5 g. (94%) of *trans*-β-cyanovinyl *p*-tolyl thioether as a white low-melting solid, $n^{25}D$ 1.6065. This material contained 10% of the *cis* isomer, as indicated by its infrared spectrum. Distillation resulted in additional isomerization; the product had b.p. 115° (1 mm.).

Anal. Calcd. for $C_{10}H_9NS$: C, 68.57; H, 5.14; N, 8.00. Found: C, 68.88; H, 5.03; N, 8.16.

***cis*-β-Cyanovinyl *p*-Tolyl Thioether.**—Use of *cis*-I in the above procedure gave the corresponding *cis* product, b.p. 116–120° (2 mm.).

Anal. Calcd. for $C_{10}H_9NS$: C, 68.57; H, 5.14; N, 8.00. Found: C, 68.40; H, 5.07; N, 7.71.

β,β-Dicyanovinyl Thioether.—A solution of sodium sulfide monohydrate (48 g., 0.2 mole) in 350 ml. of 95% ethanol was added to a stirred ethanolic solution of β-chloroacrylonitrile (35 g., 0.4 mole). After standing overnight, the solution was filtered to remove sodium chloride (21 g.). The filtrate was concentrated to about 225 ml. and diluted to 900 ml. with ice–water. Filtration gave 15 g. (55%) of light yellow product which, after recrystallization from ethyl acetate–cyclohexane, melted at 141–142°. An additional recrystallization raised the melting point to 142.4–143.2°.

Anal. Calcd. for $C_6H_4N_2S$: C, 52.92; H, 2.96; N, 20.58. Found: C, 52.73; H, 2.95; N, 20.54.

2-Benzothiazolyl β-Cyanovinyl Thioether.—To a solution of 33.4 g. of mercaptobenzothiazole and 20.2 g. of triethylamine in 120 ml. of acetone, was added 17.5 g. of *cis*-I at 25–30°. Filtration, evaporation of the filtrate, and recrystallization of the residue from methylene chloride gave 36 g. (82%) of 2-benzothiazolyl β-cyanovinyl thioether, m.p. 105–107°.

Anal. Calcd. for $C_{10}H_6N_2S_2$: C, 55.05; H, 2.77; N, 12.83. Found: C, 55.03; H, 2.93; N, 13.07.

1,1-Ethanedisulfuric Acid 2-Cyano Disodium Salt.—A solution of 20.8 g. of sodium bisulfite in 400 ml. of water was added to a reaction vessel equipped with a reflux condenser and stirrer. To this solution, 8.75 g. of *cis*-I was added. The reaction mixture was heated to 80° and kept at this temperature for 24 hr. During the course of the reaction, the mixture became homogeneous. On cooling, the disodium salt precipitated with the addition of methanol. On filtration, the product was obtained in 92.5% yield.

Anal. Calcd. for $C_3H_3NNa_2O_6S_2$: C, 13.90; H, 1.17; N, 5.40. Found: C, 13.44; H, 1.47; N, 5.17.

β-Cyanovinyl *p*-Tolyl Sulfone.—A solution of *trans*-β-chloroacrylonitrile (17.5 g., 0.2 mole) in 50 ml. of ethanol was added to a stirred alcoholic solution of the sodium *p*-tolyl sulfinate (43 g., 0.2 mole) at reflux temperature in 15 min. After heating for an

additional hour, the mixture was cooled and filtered. The filtrate was concentrated to about 125 ml. on a rotary evaporator and crystallization was induced by cooling. Filtration gave 37 g. (89%) of the substitution product. This material was recrystallized from isobutyl alcohol for analysis; the product had m.p. 135–136°.

Anal. Calcd. for $C_{13}H_9NO_2S$: C, 58.10; H, 4.38; N, 6.77. Found: C, 58.28; H, 4.40; N, 6.61.

Use of the *cis*-I in the above procedure gave a 26% yield of solid, m.p. 73–85°. This was presumed to be a mixture of the *cis* and *trans* isomers.

Anal. Calcd. for $C_{13}H_9NO_2S$: C, 58.10; H, 4.38; N, 6.77. Found: C, 57.76; H, 4.41; N, 6.73.

O,O-Diethyl-β-cyanovinyl Phosphonate.—A solution of 24.9 g. of triethyl phosphite and 13.1 g. of a 50:50 mixture of *cis*- and *trans*-I was heated in an oil bath at 120. Ethyl chloride was evolved, and the heating was continued for 4 hr. Distillation yielded 18.7 g. (66%) of O,O-diethyl-β-cyanovinyl phosphonate boiling at 106° (1.5 mm.), $n^{25}D$ 1.4510.

Anal. Calcd. for $C_7H_{12}NO_3P$: C, 44.44; H, 6.40; N, 7.41. Found: C, 44.30; H, 6.53; N, 7.47.

O,O-Dibutyl-β-cyanovinyl Phosphonate.—A solution of 12.5 g. of tributyl phosphite and 5.36 g. of *cis*-I was placed in an oil bath. When the reaction mixture reached 127°, a volatile liquid distilled. Heating was continued until the temperature reached 154°, at which point the reaction was essentially complete, with 2.8 g. of butyl chloride distilled. Two redistillations of the residue gave 6.56 g. of O,O-dibutyl-β-cyanovinyl phosphonate, b.p. 119–120° (3 mm.), $n^{25}D$ 1.4505.

Anal. Calcd. for $C_{11}H_{20}NO_3P$: C, 53.87; H, 8.22; N, 5.71. Found: C, 54.05; H, 8.30; N, 5.44.

Carbon Cyanovinylation.—Sodium diethyl malonate (0.1 mole) made from 16 g. of diethyl malonate and 2.3 g. of sodium in ethanol was added slowly to 8.75 g. of *trans*-β-chloroacrylonitrile in ethanol. The temperature of the reaction flask was kept below 50°. During the course of the reaction, a solid material precipitated from solution. The solid was filtered, washed with water, and dried in an oven, yielding 12 g. of the sodium salt of the addition product (XV).

Anal. Calcd. for $C_{12}H_{12}NNaO_4$: C, 51.50; H, 5.19. Found: C, 51.33; H, 5.15.

5-Chlorobicyclo[2.2.1]hept-1-ene-4-carbonitrile.—Dicyclopentadiene (7.2 g.) and *cis*-I (0.5 g.) were sealed in a glass tube. The tube was kept at 150° for 24 hr. The contents were dissolved in hexane and the mixture was filtered. Crystallization occurred on cooling, and the precipitate was filtered, yielding 4.1 g. (24.5%) of the addition product, m.p. 96–97°.

Anal. Calcd. for C_8H_8ClN: C, 62.55; H, 5.25; N, 9.12. Found: C, 62.87; H, 5.51; N, 8.91.

1,3,4,5,6,7,7-Heptachloro-5-norbornene-2-carbonitrile.—Hexachlorocyclopentadiene (27.3 g.) and *cis*-β-chloroacrylonitrile (8.75 g.) were sealed in a glass tube. The tube was immersed in in an oil bath and kept at 180° for 24 hr. After opening the tube, the contents were slurried in petroleum ether (b.p. 30–60°) and filtered to remove any carbonaceous material. Crystallization, followed by filtration, yielded 18.6 g. (52%) of the addition product.

Anal. Calcd. for $C_8H_2Cl_7N$: Cl, 68.93; N, 3.88. Found: Cl, 68.62; N, 3.91.

4-Dialkyl Aminomethylene Glutacononitriles.—A solution of 0.1 mole of the β-cyanovinylalkylamine in 100 ml. of glacial acetic acid was heated at reflux for 30 min. The solution, on cooling, was poured into 100 ml. of water. The solid was filtered, dried, and recrystallized.

4-Piperidinomethylene glutacononitrile was obtained in 73% yield after crystallization from acetonitrile; it melted at 146–147° alone and when mixed with the product obtained from I and piperidine (*cf.* Table I, footnote *c*).

4-Dimethylaminomethyleneglutacononitrile was obtained in 40% yield after crystallization from methanol and had m.p. 121.5–122.5°.

Anal. Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.61; H, 6.01; N, 28.17.

Kinetics.—Kinetic measurements were carried out in an ice–water bath provided with an efficient stirrer. The solutions were precooled to 0° before mixing. Ten-milliliter aliquots were withdrawn at suitable intervals and rapidly poured into a dilute nitric acid solution. The reaction was followed by determining the amount of chloride ion present using the Volhard method. The concentration of the piperidine was made double that of the β-chloroacrylonitrile. The concentrations of the various solutions were *trans*-I, 0.01995 mole/l.; *cis*-I, 0.01997 mole/l.; KCNS, 0.01 mole/l.; piperidine, 0.1003 mole/l.; and $AgNO_3$, 0.005 mole/l.

The analytical data then were used to calculate the kinetic constants by graphical methods, using the customary formulas.[24]

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(24) S. Glasstone, "Textbook of Physical Chemistry," A. Van Nostrand Co., Inc., New York, N. Y., 1947, Chapter 13.

Hydroxycarbamonitriles from the Reaction of Amino Alcohols with Cyanogen Bromide[1]

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The reaction of cyanogen bromide with *trans*-2-amino-1,2,3,4-tetrahydro-1-naphthol or a *trans*-2-amino-*p*-menthan-1-ol affords crystalline 1-hydroxy-2-carbamonitriles which have been cyclized to the *trans*-2-amino-2-oxazolines. The reaction of *cis*-3-amino-2,2,4,4-tetramethyl-1-cyclobutanol with cyanogen bromide gives a hydroxycarbamonitrile which is not cyclized by either acid or base.

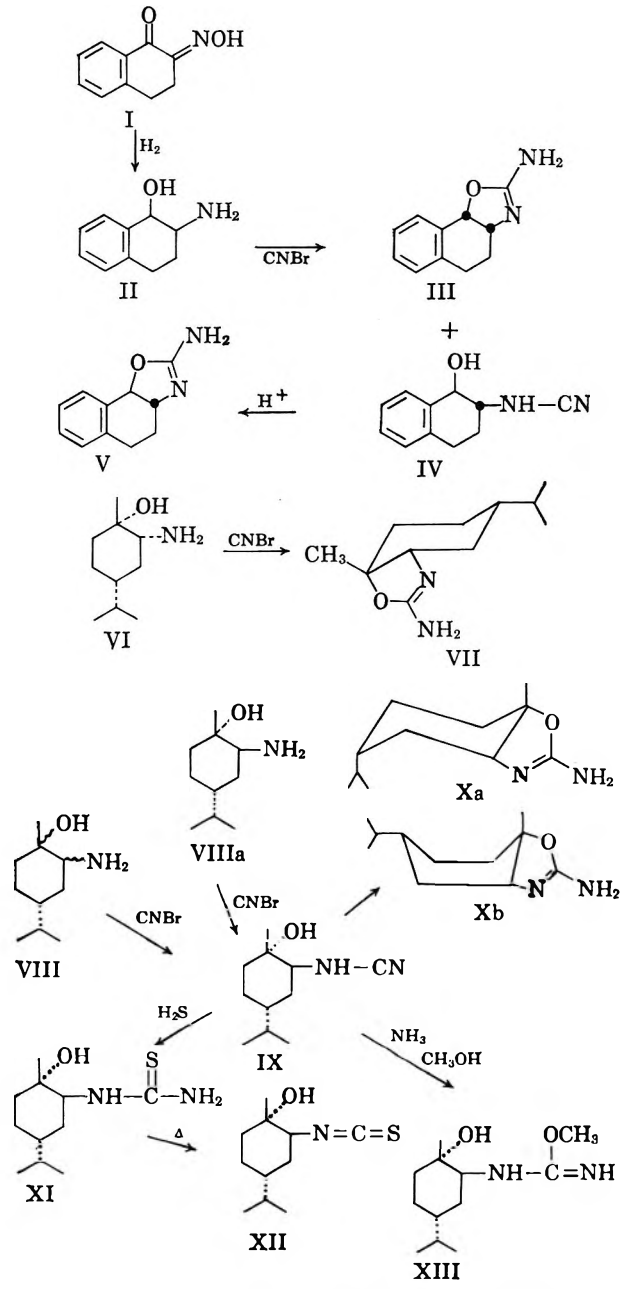
The preparation of 2-amino-2-oxazolines by reaction of 1,2-amino alcohols with cyanogen bromide has been previously described.[2] As has been reported,[2a,3,4] the intermediate hydroxycarbamonitriles (cyanamides) were found to cyclize spontaneously in every case and were not isolable. Meschino and Bond[5] have recently described the preparation of several 5-substituted 2-amino-5,6-dihydro-4H-1,3-oxazines by cyclization of 1,3-amino alcohols with cyanogen bromide. In contrast to the 1,2-amino alcohols, the intermediate hydroxy cyanamides could be isolated in most cases, and one such intermediate was characterized.

A further study of the reaction of several 1,2- and 1,3-amino alcohols with cyanogen bromide has led to the isolation and characterization of additional uncyclized hydroxy cyanamides from both series of compounds. In all cases these were derived from amino alcohols which were difficult to cyclize for steric reasons.

Low pressure hydrogenation of 3,4-dihydro-2-oximino-1-naphthalenone (I) gave a mixture of *cis*- and *trans*-1,2-amino alcohols II which was treated directly with cyanogen bromide.[2b] The reaction mixture was separated into a basic and a neutral fraction. From the basic fraction there was isolated a crystalline amino oxazoline. Since this compound was obtained by spontaneous cyclization of the intermediate hydroxycarbamonitrile, the *cis* structure III is assigned.[6] The neutral fraction afforded a crystalline hydroxy cyanamide to which the *trans* structure IV is assigned.[6] On treatment with hydrogen chloride in methylene chloride, IV provided the *trans*-2-amino-2-oxazoline (V). Although the yields of III and IV were low, they were found to be reproducible. (See Chart I.)

Several terpene-1,2-amino alcohols were found to react with cyanogen bromide in a manner similar to the tetrahydronaphthalene-1,2-amino alcohol (II). The configuration of the *cis*-2-amino-*p*-menthan-1-ol (VI) has been previously established by its preparation from a *trans*-*p*-menthane-1,2-diol of known configuration.[7] On reaction with cyanogen bromide, VI gave the *cis*-2-aminohexahydrobenzoxazole (VII) in 47% yield. The ease of formation of the conformationally favorable aminooxazoline VII and the absence of any uncyclized hydroxy cyanamide in the reaction product is further evidence for the *cis* configuration of the hydroxyl and amino groupings in VI.

CHART I



(1) Florida Agricultural Experiment Stations Journal Series No. 1841.

(2) (a) R. R. Wittekind, J. D. Rosenau, and G. I. Poos, *J. Org. Chem.*, **26**, 444 (1961); (b) G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszkowski, N. M. Kelley, and J. McGowin, *J. Med. Chem.*, **6**, 266 (1963).

(3) G. Fodor and K. Koczka, *J. Chem. Soc.*, 850 (1952).

(4) E. Fromm and R. Kapeller-Alder, *Ann.*, **467**, 240 (1928).

(5) J. A. Meschino and C. H. Bond, *J. Org. Chem.*, **28**, 3129 (1963).

(6) These structural assignments have been confirmed by n.m.r. studies of the isomeric aminooxazolines III and V. These data will be published separately by Dr. H. R. Almond, Jr., of McNeil Laboratories.

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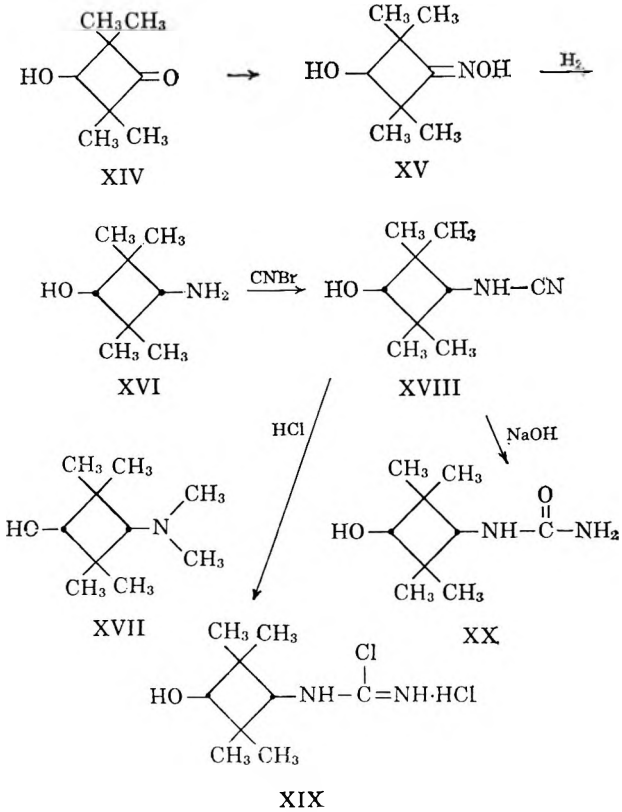
The mixed *trans*-amino alcohols VIII, prepared by the cleavage of *p*-menthane 1,2-epoxide with ammonia,[7] in contrast to VI gave a neutral reaction product with cyanogen bromide from which a single, crystalline hydroxy cyanamide IX was isolated in 59% yield. The remainder of the reaction product was a neutral, amorphous glass which showed strong C≡N absorption at 4.5 μ in the infrared. However, the *trans*-hydroxy cyanamide isomeric with IX could not be isolated.

The configuration of IX was established by its preparation in 80% yield from the reaction of the *trans*-2-amino-*p*-menthan-1-ol (VIIIa) with cyanogen bromide. The configuration of VIIIa has been previously established by its preparation from *trans*-*p*-menthane-1,2-diol of known stereochemistry.[7]

The failure of the hydroxy cyanamide IX to cyclize spontaneously is easily understood by an examination of possible chair and boat conformers Xa and Xb of the ring closed product. Both Xa and Xb have a number of unfavorable interactions. Despite this, hydroxy cyanamide IX was found to cyclize in 28% yield by heating in methanol containing clay boiling stones (Boilerezers). Apparently this cyclization was due to mild alkaline catalysis for it could be prevented by pretreatment of the boiling stones with dilute hydrochloric acid. Other weak bases such as sodium acetate gave much lower yields of X than those obtained using Boilerezers. The *trans*-hydroxy cyanamide IX did not cyclize under other basic reaction conditions.

Additions across the nitrile triple bond of IX occurred readily. In ethanolic triethanolamine, hydrogen sulfide added to give the crystalline hydroxythiourea XI in good yield (70%). On heating under vacuum, XI lost ammonia and was converted smoothly to the liquid isothiocyanate XII. Treatment of IX with methanolic ammonia resulted in the addition of methanol to afford the methylpseudourea XIII.



The reaction of *cis*-3-amino-2,2,4,4-tetramethyl-1-cyclobutanol (XVI) with cyanogen bromide was also studied. Amino alcohol XVI was prepared by catalytic hydrogenation of oxime XV which was prepared from ketol XIV[8] by partial catalytic hydrogenation of dimethylketene dimer. Evidence for the assignment of *cis* stereochemistry to amino alcohol XVI was obtained by conversion to the N,N-dimethyl derivative XVII (m.p. 129)°. Compound XVII is reported to melt at 129–130° while the corresponding *trans* isomer melts at 70–72°.[9]

The sole product from the reaction of aminocyclobutanol XVI and cyanogen bromide was the hydroxy cyanamide XVIII. On treatment with hydrogen chloride in tetrahydrofuran, XVIII gave the chloroformamidine hydrochloride XIX by addition to the nitrile bond. With strong aqueous alkali, XVIII was hydrolyzed to the cyclobutylurea XX in good yield. Thus, as would be expected, this 1,3-cyclobutyl system is resistant to cyclization for steric reasons.

Experimental

***cis*-2-Amino-3a,4,5,9b-tetrahydronaphth[2,1]oxazole (III) and *trans*-1-Hydroxy-1,2,3,4-tetrahydro-2-naphthalenecarbamonitrile (IV).**—A 10.0-g. sample (0.057 mole) of 3,4-dihydro-2-oximino-1-naphthalenone (I) was hydrogenated over 0.8 g. of platinum oxide in 200 ml. of absolute methanol on a Parr shaker. The theoretical amount of hydrogen was consumed in 10 min., and the reaction was stopped after an additional 10 min.

Under a stream of nitrogen, the reduction mixture was poured into a solution of 14 g. (0.171 mole) of sodium acetate in 50 ml. of water. After cooling to 0°, the mixture was treated with a solution of 6.6 g. (0.0627 mole) of cyanogen bromide in 50 ml. of methanol. The reaction mixture was stirred at 0° for 2.5 hr., made basic with aqueous ammonia, filtered, and concentrated *in vacuo* to remove the methanol. It then was diluted with water, acidified with dilute hydrochloric acid, and extracted three times with ether. From the ether extracts there was obtained 1.1 g. of neutral product. This material was recrystallized from acetone–benzene (Norit–Darco) to give 0.92 g. (8.6% from I) of IV, m.p. 111–114°; λ_{max}^{KBr} 2.98, 3.47, 4.54, 5.8 (w), 6.26 (w), 6.70, 6.88, and 6.96 μ.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.22; H, 6.53; N, 15.09, 15.23.

The acidic solution was made basic with sodium hydroxide and extracted with methylene chloride. The extracts afforded 3.5 g. of basic material. After two recrystallizations from benzene (Norit–Darco), there was obtained 1.23 g. (11.5%) of III, m.p. 150.5–153.5°; λ_{max}^{KBr} 2.93, 3.30, 3.42, 5.93, 6.25, 6.69, 6.88, 6.93, and 7.05 μ.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.20; H, 6.62; N, 15.16.

A sample of III was converted to its fumarate salt, m.p. 159–169° after recrystallization from ethanol; λ_{max}^{KBr} 3.45, 5.84, 6.60, 6.88 (w), 6.98 (w), and 7.38 μ.

Anal. Calcd. for $(C_{11}H_{12}N_2O)_3 \cdot (C_4H_4O_4)_2$: N, 10.52. Found: N, 10.59.

***trans*-2-Amino-3a,4,5,9b-tetrahydronaphth[2,1]oxazole (V) from *trans*-1-Hydroxy-1,2,3,4-tetrahydro-2-naphthalenecarbamonitrile (IV).**—A 0.175-g. sample of IV was dissolved in methylene chloride and treated with ethereal hydrogen chloride, affording 0.2 g. of amine salt; λ_{max}^{Nujol} 3.35, 3.45, 5.85, 6.25, 6.45, 6.7, 6.85, and 7.28 μ.

The salt was dissolved in 5% sodium hydroxide and extracted into methylene chloride. The extracts were dried and concentrated, and the base was twice recrystallized from methylene chloride–ether, giving 0.035 g. of V, m.p. 136–137.5°, m.p. 133.5–147° when mixture melted with III; λ_{max}^{KBr} 2.89, 3.2, 3.33, 3.41, 3.46, 5.86, 5.93, 6.08, 6.23, 6.67, 6.77, 6.85, and 7.03 μ. The infrared spectra of III and IV were clearly different.

(8) R. H. Hasek, E. V. Elam, J. C. Martin, and R. G. Nations, *J. Org. Chem.*, **26**, 700 (1961).

(9) R. H. Hasek and J. C. Martin, *ibid.*, **28**, 1468 (1963).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.67; H, 6.48; N, 14.95.

***cis*-2-Amino-5-isopropyl-7a-methyl-3a,4,5,6,7,7a-hexahydrobenzoxazole (VII).**—A suspension of 2.8 g. (0.070 mole) of crushed sodium hydroxide pellets in 90 ml. of dry benzene containing 11.8 g. (0.069 mole) of dissolved *cis*-2-amino-*p*-menthan-1-ol (VI) was stirred and cooled at 5° during the dropwise addition of a solution of 7.31 g. (0.069 mole) of cyanogen bromide in 40 ml. of dry benzene. The cooling bath then was removed and the mixture was stirred at room temperature for 16 hr. The precipitated salts were collected on a filter and the filter cake was washed twice with benzene and once with ether. Concentration of the filtrate under vacuum gave a viscous residue which rapidly crystallized (prisms). These crystals were collected on a filter and washed with cold petroleum ether (b.p. 30–60°). This procedure gave 6.34 g. (47%) of *cis*-2-amino-5-isopropyl-7a-methyl-3a,4,5,6,7,7a-hexahydrobenzoxazole (VII), m.p. 93–96.5°, which was soluble in most common organic solvents and dilute aqueous acids but was insoluble in water. Several recrystallizations from petroleum ether afforded a sample melting at 96.8–97.8°; $[\alpha]^{25}D$ +42.3° (*c* 10.0, acetone); λ_{max}^{KBr} 2.94, 3.39, 3.49, 5.88, 5.98, 6.21, 6.80, 6.88, 7.08, and 9.67 μ.

Anal. Calcd. for $C_{11}H_{20}N_2O$: C, 67.30; H, 10.27; N, 14.27. Found: C, 67.44; H, 9.76; N, 14.42.

The *trans*-1-Hydroxy-*p*-menthane-2-carbamonitrile (IX) from the Mixed *trans* Isomers of VIII.—A solution of 14 g. (0.082 mole) of mixed *trans*-2-amino-*p*-menthan-1-ols (VIII) and 21.8 g. (0.160 mole) of sodium acetate trihydrate in 100 ml. of methanol was stirred at 0–5° during the dropwise addition of a solution of 9.50 g. (0.089 mole) of cyanogen bromide in 50 ml. of methanol (20 min.). The clear solution then was stirred and allowed to warm to room temperature (55 min.). Twelve milliliters of ammonium hydroxide was added and most of the methanol was removed under vacuum. Four hundred milliliters of water was added and the product crystallized. The crystals were collected on a filter, washed with water, and recrystallized from ethanol–water solution. This procedure gave 9.5 g. (59%) of *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX), m.p. 154–156.6°, which was very sparingly soluble in water and soluble in most common organic solvents. A sample purified by repeated recrystallization from aqueous ethanol melted at 158.2–158.4°; $[\alpha]^{25}D$ +81.4° (*c* 10.0, ethanol); λ_{max}^{KBr} 2.98, 3.14, 3.36, 3.46, 4.48, 6.63, 6.79, 6.86, 8.28, and 9.79 μ.

Anal. Calcd. for $C_{11}H_{20}N_2O$: C, 67.30; H, 10.27; N, 14.27. Found: C, 67.56; H, 10.58; N, 13.96.

***trans*-1-Hydroxy-*p*-menthane-2-carbamonitrile (IX) from *trans*-2-Amino-*p*-menthan-1-ol[7] (VIIIa).**—A solution of 1.43 g. (0.0083 mole) of the pure *trans*-2-amino-*p*-menthan-1-ol (VIIIa) and 2.18 g. (0.016 mole) of sodium acetate trihydrate in 10 ml. of methanol was stirred at 0–5° during the dropwise addition of a solution of 0.95 g. (0.0090 mole) of cyanogen bromide in 5 ml. of methanol. The same reaction conditions described above were used and the product was isolated in the same manner. This procedure afforded 1.32 g. (80%) of the *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX), m.p. 154–155.5° which was identical in all respects, including infrared absorption, with a sample of IX prepared from VIII.

***trans*-2-Amino-5-isopropyl-7a-methyl-3a,4,5,6,7,7a-hexahydrobenzoxazole (X).**—One gram of *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX) was dissolved in 25 ml. of methanol and the solution was refluxed for 2 hr. with 5 g. of Boileezers.[10] The mixture was filtered and the filtrate was concentrated to dryness under vacuum. The basic, amorphous residue was converted to a picrate salt by treatment with excess picric acid in benzene–methanol solution. This procedure gave 0.62 g. (28%) of the crude picrate of X as yellow prisms, m.p. 146–152°. Two recrystallizations from benzene–methanol solution afforded 0.49 g., m.p. 154–155°.

Anal. Calcd. for $C_{17}H_{23}N_5O_8$: C, 48.00; H, 5.45; N, 16.46. Found: C, 47.75; H, 5.76; N, 15.86.

The free base X, regenerated from the picrate by treatment with dilute, aqueous sodium hydroxide followed by ether extraction, was an amorphous glass. This material was sublimed under vacuum to give a colorless glass which was a strong base soluble in ether and most organic solvents; $[\alpha]^{25}D$ +74.9° (*c* 8.0, acetone); $\lambda_{max}^{CCl_4}$ 2.89, 2.96, 3.37, 3.46, 5.88, 6.03, 6.28, 6.55, 6.82, 6.93, 7.29, 7.52, 9.14, and 9.70 μ.

(10) Supplied by Fisher Scientific Co.

1-(*trans*-1-Hydroxy-*p*-menth-2-yl)-2-thiourea (XI).—Twenty-four grams of *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX) was dissolved in a solution of 81 ml. of triethanolamine in 400 ml. of absolute ethanol. Hydrogen sulfide was bubbled into the solution for 2 hr. with stirring at a temperature of 50°. The solution was cooled to room temperature, again saturated with hydrogen sulfide, stoppered, and left at room temperature for 4 days. It was then concentrated under vacuum. The residual oil was dissolved in ether and the ether phase was washed three times with 6 *N* hydrochloric acid and finally with water until neutral. Removal of the ether under vacuum gave a colorless, solid residue which was dissolved in ethanol–water. The hot solution was treated with Darco-G60, filtered, and concentrated. When cooled, colorless needles of 1-(*trans*-1-hydroxy-*p*-menth-2-yl)-2-thiourea (XI) separated from the solution. This procedure afforded 21.5 g. (70%) of XI, m.p. 90–94°. A small sample, purified by repeated crystallizations from methanol–water solution, melted at 93–94.5° with bubbling and apparent decomposition; $[\alpha]^{25}D$ +70.9° (*c* 10, acetone); λ_{max}^{KBr} 3.02, 3.14, 3.38, 3.47, 6.09, 6.17, 6.43, 6.83, 7.03, 7.31, and 9.04 μ.

Anal. Calcd. for $C_{11}H_{22}N_2OS$: C, 57.34; H, 9.63; N, 12.16; S, 13.92. Found: C, 56.76; H, 9.76; N, 11.60; S, 13.69.

1-Hydroxy-*p*-menthane-2-isothiocyanate (XII).—Five grams of 1-(*trans*-1-hydroxy-*p*-menth-2-yl)-2-thiourea (XI) was vacuum distilled at 160–170° (0.5 mm.) over a very short path in order to avoid excessive heating. Two 25-ml. round-bottomed flasks connected by a short U tube were used. Decomposition proceeded smoothly with the evolution of ammonia and the isothiocyanate XII distilled as a colorless, slightly viscous liquid (3 g., 65%). After two redistillations, 1 g. of isothiocyanate was obtained which distilled at a pot temperature of 110–115° (0.25 mm.); $n^{25}D$ 1.5265; λ_{max}^{KBr} 2.86, 3.36, 3.45, 4.62, 4.75, 6.81, 7.28, and 8.30 μ.

Anal. Calcd. for $C_{11}H_{19}NOS$: C, 61.92; H, 8.98; N, 6.57; S, 15.03. Found: C, 62.38; H, 9.06; N, 6.44; S, 14.87.

2-Methyl-3-(*trans*-1-hydroxy-*p*-menth-2-yl)pseudourea (XIII).—Five grams of *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX) was dissolved in 100 ml. of 8% ammoniacal methanol. The resulting solution was stirred and heated at 110–120° in a bench-scale autoclave for 2 hr. and finally concentrated to dryness under vacuum. The colorless, oily product was dissolved in methanol–water and sufficient solid picric acid was added to make the solution strongly acidic. This procedure gave 5.7 g. (49%) of XIII picrate, m.p. 109–112°. On recrystallization from benzene–methanol solution, the picrate lost solvent of crystallization and crystallized as yellow needles, m.p. 133–135°. This anhydrous picrate showed a tendency to darken on exposure to light; λ_{max}^{KBr} 2.83, 2.93, 3.08, 3.24, 3.38, 5.91, 6.07, 6.36, 7.29, 7.45, and 8.92 μ.

Anal. Calcd. for $C_{18}H_{27}N_5O_9$: C, 47.26; H, 5.95; N, 15.31; CH_3O–, 6.77. Found: C, 47.37; H, 5.87; N, 15.15; CH_3O–, 7.57.

3-Hydroxy-2,2,4,4-tetramethylcyclobutanone (XIV).—A mixture of 20 g. (0.14 mole) of tetramethylcyclobutane-1,3-dione, 2 ml. of triethylamine, and 1.5 teaspoonfuls of nickel sponge catalyst[11] in 250 ml. of absolute ethyl alcohol was hydrogenated in a Parr shaker. The theoretical amount of hydrogen was taken up in 70 min. The mixture was filtered and the catalyst was washed with 50 ml. of ethyl alcohol. The combined solution was evaporated to afford 20 g. of crude product. After one recrystallization from water, 19 g. (95%) of 3-hydroxy-2,2,4-4-tetramethylcyclobutanone (XIV), m.p. 112–114° (lit.[8] m.p. 114°), was obtained; λ_{max}^{KBr} 2.97, 3.41, 3.52, 5.75, 9.05, 9.69, 9.84, and 12.02 μ.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.29; H, 9.90.

3-Hydroxy-2,2,4,4-tetramethylcyclobutanone Oxime (XV).—To a solution of 15.3 g. (0.125 mole) of the ketol (XIV) in 135 ml. of 50% ethyl alcohol was added 9.2 g. (0.13 mole) of hydroxylamine hydrochloride and a solution of 10.7 g. (0.13 mole) of sodium acetate in 35 ml. of water. The solution was heated on a steam bath for 5 min. and then stirred at room temperature for 12 hr. Water (100 ml.) was added and the mixture was stirred at room temperature overnight. The product was separated by filtration and recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°) to give 13.5 g. (68%) of the oxime XV, m.p. 147–152°; λ_{max}^{KBr} 3.11 and 5.94 μ.

(11) Supplied by Davison Chemical Co.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.98; H, 9.61; N, 8.73.

cis-3-Amino-2,2,4,4-tetramethyl-1-cyclobutanol (XVI).—A mixture of 10 g. (0.064 mole) of the oxime XV and 2 teaspoonfuls of nickel catalyst[11] in 100 ml. of absolute ethanol was hydrogenated on a Parr shaker. The reduction was rapid and within 20 min. the theoretical amount of hydrogen was taken up. The mixture was filtered and the solvent was distilled under diminished pressure to obtain 10 g. (theoretical yield) of crude XVI; $\lambda_{max}^{CHCl_3}$ 3.07, 6.24, 6.86, 8.93, and 9.5 μ.

Five grams (0.036 mole) of the free base XVI in anhydrous ether was converted to the corresponding amine hydrochloride by treating the solution with hydrogen chloride. After recrystallization from ethanol–ether, 4.5 g. (over-all 80%) of *cis*-amino alcohol XVI hydrochloride, m.p. 243–245° dec., was obtained; λ_{max}^{KBr} 3.03, 4.77, 6.14, 6.57, 7.45, 8.95, 9.58, and 9.95 μ.

Anal. Calcd. for $C_8H_{17}NO \cdot HCl$: C, 53.50; H, 10.11; N, 7.80. Found: C, 53.70; H, 10.25; N, 7.55.

cis-3-Dimethylamino-2,2,4,4-tetramethyl-1-cyclobutanol (XVII).—Thirty-seven grams (0.7 mole) of cold 88% formic acid was added to 20 g. (0.14 mole) of the *cis*-aminocyclobutanol XVI, and to the resulting clear solution was added 34 g. (0.42 mole) of 37% formaldehyde solution. The mixture was placed in an oil bath which had been heated to 100°. A vigorous evolution of carbon dioxide began after 3–5 min., at which time the reaction mixture was removed from the bath until the gas evolution notably subsided; then it was returned to the bath and heated at 100° for 18 hr. After the mixture was cooled, hydrochloric acid (30 ml. of concentrated hydrochloric acid in 70 ml. of distilled water) was added and the acidic solution was distilled under diminished pressure to remove the solvent. The resulting sirupy residue was dissolved in 80 ml. of water, made basic by the addition of 100 ml. of 30% sodium hydroxide, and extracted with three 150-ml. portions of ether and three 150-ml. portions of methylene chloride.

The combined solution was dried over anhydrous magnesium sulfate and the solvent was distilled under diminished pressure, giving 18 g. (75%) of *cis*-3-dimethylamino-2,2,4,4-tetramethyl-1-cyclobutanol (XVII), m.p. 115–118°. Recrystallization from hexane gave a sample melting at 129° (lit.[9] m.p. 129–130°); λ_{max}^{KBr} 3.16, 3.58, and 3.65 μ.

A 6.6-g. sample (0.038 mole) of the free base in anhydrous ether was converted to the corresponding amine hydrochloride by treating the solution with hydrogen chloride. After one recrystallization from ethanol–ether, 6.3 g. (over-all 64%) of *cis*-3-dimethylamino-2,2,4,4-tetramethyl-1-cyclobutanol hydrochloride, m.p. 292–293° dec., was obtained; λ_{max}^{KBr} 3.12, 3.50, 3.84, 6.76, 6.81, 7.43, 7.60, 8.15, 8.34, 8.75, and 8.94 μ.

Anal. Calcd. for $C_{10}H_{21}NO \cdot HCl$: C, 57.56; H, 10.20; N, 6.74. Found: C, 57.37; H, 10.30; N, 6.66.

cis-3-Hydroxy-2,2,4,4-tetramethyl-1-cyclobutylcarbamonitrile (XVIII).—To a solution of 5 g. (0.035 mole) of the 3-aminocyclobutanol XVI and 3.1 g. (0.037 mole) of sodium acetate in 50 ml. of 95% methanol was added, with cooling a solution of 3.9 g. (0.037 mole) of cyanogen bromide in 25 ml. of methanol. The resulting solution was allowed to stand at room temperature for 90 min. and the solvent was distilled under diminished pressure. A 75-ml. portion of water was added to the residue. The resulting white solid was filtered and recrystallized from benzene to give 3 g. (51%) of the hydroxycyclobutylcarbamonitrile XVIII, m.p. 164–166°; λ_{max}^{KBr} 2.96, 4.48, 8.45, and 9.07 μ.

Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.25, H, 9.59; N, 16.65. Found: C, 64.46; H, 9.75; N, 16.42.

Chloro-N-(*cis*-3-hydroxy-2,2,4,4-tetramethyl-1-cyclobutyl)-formamidine Hydrochloride (XIX).—A solution of 7.8 g. (0.046 mole) of *cis*-3-hydroxy-2,2,4,4 tetramethyl-1-cyclobutylcarbamonitrile (XVIII) in 80 ml. of anhydrous tetrahydrofuran was cooled in an ice bath. An excess of hydrogen chloride was dissolved in the solution and the resulting reaction mixture was allowed to stand at room temperature. The precipitated product was filtered and dried to give 7.5 g. (67%) of chloroformamidine hydrochloride (XIX), m.p. 162–164°; λ_{max}^{KBr} 2.93, 6.01, 6.19, 9.07, and 9.53 μ.

Anal. Calcd. for $C_9H_{17}ClN_2O \cdot HCl$: N, 11.61. Found: N, 11.58.

(*cis*-3-Hydroxy-2,2,4,4-tetramethyl-1-cyclobutyl)urea (XX).—A solution of 1 g. (0.006 mole) of *cis*-3-hydroxy-2,2,4,4-tetramethylcyclobutylcarbamonitrile (XVIII) in 80 ml. of 60% sodium hydroxide solution was allowed to stand at room temperature for 15 hr. The resulting white solid product was filtered and recrystallized from benzene–ethanol to give 0.7 g. (63%) of the hydroxycyclobutylurea XX, m.p. 183–184°; λ_{max}^{KBr} 2.95, 3.07, 6.02, 6.18, and 9.25 μ.

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 58.31; H, 9.91; N, 14.76.

Model Reactions for the Biosynthesis of Thyroxine. VI. Structural Requirements of Analogs of Diiodotyrosine in the Reaction with 4-Hydroxy-3,5-diiodophenylpyruvic Acid to Form Analogs of Thyroxine[1,2]

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To contribute to the understanding of the mechanism by which thyroxine is formed in good yield from 4-hydroxy-3,5-diiodophenylpyruvic acid (I) and 3,5-diiodotyrosine in the presence of oxygen, keto acid I was permitted to react in a similar fashion with a series of analogs of diiodotyrosine. The dependence of the formation of the corresponding analogs of thyroxine on various structural features of the analogs of diiodotyrosine used has been investigated.

The biosynthetic mechanism by which thyroxine is formed from diiodotyrosine has not yet been elucidated. A few years ago, Meltzer and Stanaback[4] reported that 4-hydroxy-3,5-diiodophenylpyruvic acid (I) couples with 3,5-diiodotyrosine [IIa, X = I; R = $CH_2CH(NH_2)COOH$] in the presence of oxygen at a neutral or slightly alkaline pH to form thyroxine rapidly and in good yield. Shiba and Cahnmann[5] extended the investigation to the preparation of radioactive products. They proved that the phenolic ring of the thyroxine [IIIa, X = I; R = $CH_2CH(NH_2)COOH$] formed is derived from 4-hydroxy-3,5-diiodophenylpyruvic acid (I), and the nonphenolic ring and its alanine side chain from 3,5-diiodotyrosine (IIa). More recently the same authors found that rattlesnake venom, in the presence of oxygen and of catalase, can convert diiodotyrosine

(1) Previous paper in this series, T. Shiba and H. J. Cahnmann, *J. Org. Chem.*, **29**, 1652 (1964); for first paper in this series see ref. 8.

(2) This paper has been presented at the 16th Annual Meeting of the Chemical Society of Japan, April, 1963, Tokyo, Japan.

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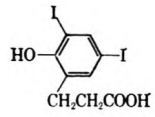
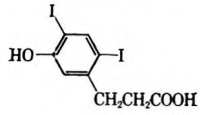
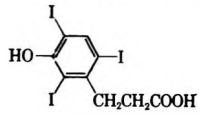
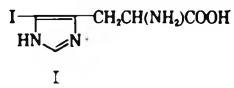
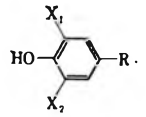
(4) R. I. Meltzer and R. J. Stanaback, *J. Org. Chem.*, **26**, 1977 (1961).

(5) T. Shiba and H. J. Cahnmann, *ibid.*, **27**, 1773 (1962).

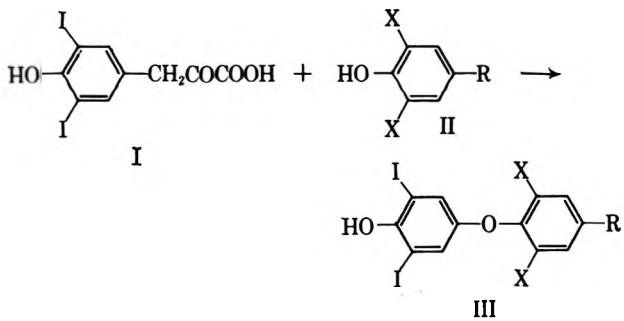
TABLE I

	Diiodotyrosine and its analogs			Thyroxine and its analogs	Yield, %	Analog of thyroxine					Other products
	X_1[a]	X_2[a]	R[a]			R_f[b]	Infrared bands, cm.$^{-1}$				
Group 1											
IIa	I	I	$-CH_2CH(NH_2)COOH$	IIIa	18	0.36	3470	1700	1245	913	IV
IIb	I	I	$-COOH$	IIIb	5	0.50	3500	1692	1236	916	IV, V
IIc	I	I	$-CH_2COOH$	IIIc	9	0.51	3400	1700	1246	919	IV
IId	I	I	$-CH_2CH_2COOH$	IIId	10	0.50	3440	1703	1233	913	IV
IIe	I	I	$-CH_2CH_2CH_2COOH$	IIIe	4	0.48	3400	1689	1235	912	IV
IIf	I	I	$-CH_2CH(CH_3)COOH$	IIIf	4	0.59	3470	1702	1238	915	IV
IIg	I	I	$-CH_2CH(C_6H_5)COOH$	IIIg	Trace	0.60					IV
IIh	I	I	$-CH_2CH(OH)COOH$	IIIh	14	0.46	3450	1720	1234	915	IV
IIi	I	I	$-CH=CHCOOH$	IIIi	18	0.64	3450	1685	1240	918	IV
IIj	I	I	$-I$	IIIj							IV
Group 2											
IIk	Br	Br	$-CH_2CH_2COOH$	IIIk	13	0.46	3420	1700	1253	916	IV
IIl	Cl	Cl	$-CH_2CH_2COOH$	IIIl	16	0.45	3470	1698	1258	903	IV
IIm	H	I	$-CH_2CH_2COOH$	IIIm	Trace	0.56					IV
IIn	I	OMe	$-CH=CHCOOH$	IIIn	2	0.58	3520	1690	1280	906	IV
IIo	H	H	$-CH_2CH_2COOH$	IIIo							IV, IIIb
IIp	NO_2	NO_2	$-CH_2CH_2COOH$	IIIp							IV, IIIb
IIq	*t*-butyl	*t*-butyl	$-CH_2CH_2COOH$	IIIq							IV
Group 3											
VI				X	Trace	0.63					IV
VII				XI	1	0.42	3460	1706	1230	915	IV
VIII				XII	10[c]	0.62					IV
IX				XIV							IV, IIIb

I

[a] X_1, X_2, and R denote the substituents *ortho* and *para* to the phenolic group in  . [b] Paper chromatography in 1-butanol–ammonia (2 *N*) (upper phase), Toyo Roshi paper No. 51, ascending method. [c] Yield of XIII obtained by catalytic hydrogenation of the reaction products.

to thyroxine with the intermediary formation of 4-hydroxy-3,5-diiodophenylpyruvic acid (I).[6]



I II III

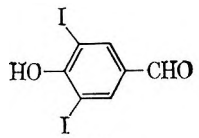
These findings suggest that the acid (I) may be an intermediate in the formation of thyroxine *in vivo*. We have, therefore, investigated the reaction of I with various analogs of diiodotyrosine to examine the structural requirements of these analogs in this reaction. The reaction was carried out according to the procedure of Shiba and Cahnmann.[5] The reaction mixture was extracted with 1-butanol after the addition of alkali. The butanol extract always contained 3,5-diiodobenzaldehyde (IV) in addition to the analog of thyroxine formed. When no analog of thyroxine was formed, a small amount of 3,5,3′,5′-tetraiodothyroformic acid (IIIb) was also present in the butanol extract. The results are shown in Table I. The analogs of thyroxine were identified by direct comparison with authentic samples[7] or by elemental analysis and through their spectroscopic and chromatographic properties.

The members of group 1 consisting of diiodotyrosine (IIa) and its side-chain analogs (IIb–IIj) were chosen to study the structural influence of the aliphatic side chain on this reaction. The formation of almost pure

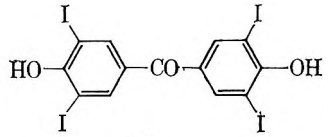
(6) T. Shiba and H. J. Cahnmann, *Biochim. Biophys. Acta*, **57**, 609 (1962).

(7) The synthesis will be published elsewhere.

thyroxine (IIIa) in 18% yield in this reaction could be confirmed. The reactions of IIb, IIc, and IId to form IIIb, IIIc, and IIId, respectively, were already mentioned, without experimental details, by Meltzer and Stanaback.[4] In the case of IIb, 4,4′-dihydroxy-3,5,-3′,5′-tetraiodobenzophenone (V) was isolated from the reaction mixture in 6% yield in addition to the analog IIIb of thyroxine. The structure of V was confirmed by conversion to 4,4′-dihydroxybenzophenone. The yields of the analogs of thyroxine obtained from IIb–IIg are almost the same as those obtained when these analogs of diiodotyrosine are incubated alone for several days.[8] In both cases the highest yield is obtained



IV



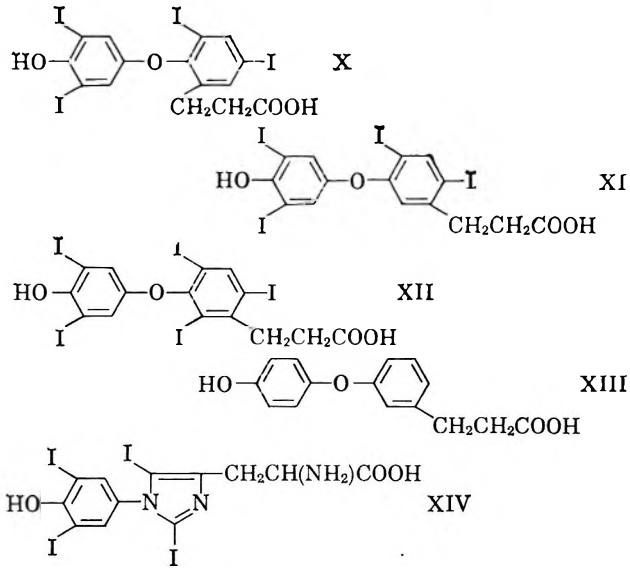
V

when the aliphatic side chain has the structure –C–C–COOH. Lengthening or shortening of this side chain as well as branching leads to poorer yields. However, in contrast to the incubation of IIa, IIh, and IIi in the absence of the keto acid I,[8] incubation of these compounds with the keto acid gave high yields of thyroxine or of the corresponding analog.

The influence of the substituents *ortho* to the phenolic hydroxyl was examined in group 2. The members of this group (IIk–IIq) are propionic or acrylic analogs of diiodotyrosine in which one or both iodine atoms are replaced with other substituents. Dibromo- and dichlorophloretic acid (IIk and IIl) gave the corresponding analogs of thyroxine in higher yield than diiodophloretic acid (IIb). The monoiodo derivatives IIm and IIn gave considerably lower yields than diiodophloretic acid, and the noniodinated derivatives IIo, IIp, and IIq yielded no analog of thyroxine at all. It seems therefore that the substitution of both *ortho* positions with halogen atoms greatly facilitates the formation of the corresponding thyronines. It should be noted, however, that Shiba and Cahnmann[1] obtained 3,3′,5′-triiodothyronine in good yield from 3-iodotyrosine and the keto acid I. The formation of IIIk, IIIl, IIIm, and IIIn provides additional evidence to support Shiba and Cahnmann's finding[5] that in this coupling reaction the phenolic ring of the iodinated thyronine formed is derived from I and the nonphenolic ring and its side chain from diiodotyrosine or its analogs.

Other structural requirements were examined with the members of group 3. The poor yields obtained in the reactions of the *ortho* and *meta* analogs (VI and VII) of diiodophloretic acid may be due to the fact that only one *ortho* position to the hydroxyl group is substituted with iodine. In contrast to triiodophenol (IIj), the triiodinated *meta* analog VIII yielded the corresponding analog (XII) of thyroxine in good yield. This analog could not be isolated in pure form and was therefore catalytically hydrogenated to form the crystalline *meta* analog (XIII) of thyropropionic acid. In a control run, thyropropionic acid was isolated in 10% yield by catalytic hydrogenation of the reaction products from IId. This shows that a shift of the propionic side chain in diiodophloretic acid from the *para* to the *meta* position does not affect the yield of the corresponding analog of thyroxine, if both *ortho* positions are substituted with iodine. Diiodohistidine (IX) which is known to be present in the thyroid gland[9] was also subjected to the reaction with the keto acid I, but the expected reaction product XIV could not be detected.

The results obtained in the reactions of the keto acid I with a series of analogs of diiodotyrosine permit the conclusion that the formation of the corresponding analog of thyroxine is favored by the following structural features of the analog of diiodotyrosine: (1) substitution of both *ortho* positions to the phenolic hydroxyl with halogen, (2) an aliphatic side chain of the type C–C–COOH in the *para* or *meta* position to the phenolic hydroxyl, (3) the presence of an amino group, a hydroxyl group, or a double bond in α-position to the carboxyl group of the side chain.



Experimental[10]

Preparation of Materials. 3-(3,5-Dichloro-4-hydroxyphenyl)-propionic Acid (IIl).—Dry chlorine gas was passed through a solution of 49.8 g. (0.3 mole) of phloretic acid[8] (IIo) in 500 ml. of acetic acid until the weight increase indicated the absorption of 1 mole equiv. of chlorine. When the reaction mixture was concentrated to 100 ml. under reduced pressure, crystals deposited which on recrystallization from chloroform gave 24.2 g (34%) of prisms, m.p. 108–110°.

Anal. Calcd. for $C_9H_8Cl_2O_3$: C, 45.99; H, 3.43. Found: C, 45.95; H, 3.47.

3-(4-Hydroxy-3-iodophenyl)propionic Acid (IIm).—To a solution of 15 g. (0.09 mole) of phloretic acid in 80 ml. of 20% aqueous methylamine was added a solution of 22.8 g. (0.18 g.-atom) of iodine and 23 g. of potassium iodide in 80 ml. of water. The reaction mixture was acidified with dilute hydrochloric acid to separate a liquid which solidified on standing. The solid was collected by filtration, dried, dissolved in chloroform and chromatographed on a column of 300 g. of silica gel. Elution with chloroform–ether (99:1) yielded diiodophloretic acid and elution with chloroform–ether (9:1) yielded 12 g. (55%) of IIm as prisms, m.p. 114–116°, lit.[11] m.p. 112–113°.

5-Iodovanillin.—To a solution of 14.2 g. (0.1 mole) of vanillin in 400 ml. of dilute hydrochloric acid (18%) was added at 50°

(8) T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **81**, 871 (1959).

(9) R. J. Block, R. H. Mandl, and S. Keller, *Arch. Biochem. Biophys.*, **75**, 508 (1958).

(10) Melting points were determined in capillary tubes and are uncorrected. The infrared spectra were determined in a Nippon Bunko recording spectrophotometer, Model IR-S. The ultraviolet spectra were determined in a Hitachi recording spectrophotometer, Model EPS-2. The microanalyses were made by Mr. J. Goda and his associates, of this faculty.

(11) Runeberg, *Acta Chem. Scand.*, **12**, 188 (1958).

16.2 g. (0.1 mole) of iodine monochloride in 20 ml. of concentrated hydrochloric acid, and the mixture was allowed to stand for 2 days. The crystals which formed were collected by filtration. On standing, the filtrate deposited additional crystals and the total yield was 21.6 g. (81%).

Recrystallization from dilute ethanol gave needles, m.p. 180–181°, lit. m.p.[12] 181–182°.

3-Methoxy-4-hydroxy-5-iodocinnamic Acid (IIn).—A mixture of 15 g. (54 mmoles) of 5-iodovanillin, 13.5 g. (165 mmoles) of anhydrous sodium acetate, and 44 ml. of acetic anhydride was refluxed for 4 hr. After standing overnight at room temperature, the reaction mixture was poured into 300 ml. of water and boiled for 1 min. The precipitate formed was collected by filtration and treated with a solution of 20 g. of sodium hydroxide in 300 ml. of water. The insoluble material was removed by extraction with ether. The aqueous solution was heated on a water bath for 30 min., then cooled, and acidified with dilute hydrochloric acid (18%). The precipitate formed was collected by filtration, washed with water, dried, and dissolved in ethanol. The insoluble material was removed by filtration. Concentration of the filtrate gave crystals which were recrystallized from acetone to give 6.6 g. (38%) of IIn as yellow prisms, m.p. 250–251° dec.; λ_{max}^{EtOH} 234 mμ (log ε 4.34), 244 (4.39), and 322 (4.31).

Anal. Calcd. for $C_{10}H_9IO_4$: C, 37.52; H, 2.83. Found: C, 37.89; H, 2.99.

4-Acetoxy-3,5-di-*t*-butylcinnamic Acid.—A mixture of 17.0 g. (0.07 mole) of 3,5-di-*t*-butyl-4-hydroxybenzaldehyde,[13,14] 14.2 g. (0.17 mole) of fused sodium acetate, and 40 ml. of acetic anhydride was refluxed for 24 hr. The reaction mixture was poured into ice and, after standing overnight, extracted with ether. The ethereal layer was extracted three times with 5% aqueous sodium carbonate. Acidification of the sodium carbonate solution with dilute hydrochloric acid yielded a precipitate which was recrystallized from benzene–cyclohexane to give 4.56 g. (20%) of the acid as needles, m.p. 233–235°. Further recrystallization raised the melting point to 237–238°.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.27; H, 8.02.

3-(4-Acetoxy-3,5-di-*t*-butylphenyl)propionic Acid.—To a solution of 2.0 g. of 4-acetoxy-3,5-di-*t*-butylcinnamic acid in 60 ml. of 10% sodium hydroxide aqueous solution was added at 90° 6 g. of Raney nickel alloy in portions with stirring over a period of 20 min. Stirring was continued for 1 hr., then the nickel was removed by filtration and the filtrate was poured into a mixture of concentrated hydrochloric acid and ice. The mixture was extracted with ether and the ether layer was dried and evaporated to a crystalline mass which, on recrystallization from benzene–cyclohexane, yielded 1.6 g. (80%) of crystals, m.p. 149–150°. On further recrystallization the melting point rose to 153–155°.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.00; H, 8.59.

3-(3,5-Di-*t*-butyl-4-hydroxyphenyl)propionic Acid (IIq).—A solution of 1.2 g. of 3-(4-acetoxy-3,5-di-*t*-butylphenyl)propionic acid in 30 ml. of a 2 *N* solution of sodium hydroxide in 1-butanol was refluxed for 2.5 hr. The mixture was evaporated to dryness under reduced pressure and the residue was acidified with dilute hydrochloric acid to yield a precipitate which was collected by filtration, dried, and recrystallized from benzene–cyclohexane to give 0.90 g. (87%) of IIq as needles, m.p. 171–173°. On further recrystallization, the melting point rose to 173–175°, lit. m.p. 172°[15] and 172–173°.[16]

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.28; H, 9.65.

Reaction of 4-Hydroxy-3,5-diiodophenylpyruvic Acid (I) with Analogs of 3,5-Diiodotyrosine. General Procedure.—The reactions were carried out by a slight modification of the procedure of Shiba and Cahnmann.[5] The analog of diiodotyrosine (4.63 mmoles) was dissolved in mixture of 50 ml. of 0.2 *M* borate buffer (pH 7.6), 17.5 ml. of 1 *N* sodium hydroxide and 17.5 ml. of a saturated aqueous solution of sodium sulfate. Enough 4 *N* hydrochloric acid was added to the solution to adjust the pH to 7.6. After the addition of 10 ml. of a 1% solution of *t*-butyl hydroperoxide in 1-butanol, the pH was again adjusted to 7.6. To the vigorously stirred mixture was added a solution of 2.59 g. (6.0 mmoles) of 4-hydroxy-3,5-diiodophenylpyruvic acid (I)[17] in 50-ml. of 1-butanol over a period of about 1 hr. During the addition oxygen was bubbled through the reaction mixture and the pH was kept constant at 7.6 by adding 2 *N* sodium hydroxide by means of an immersed thin polyethylene tubing. The rate of the addition of alkali was automatically controlled with a pH-Stat. Stirring and bubbling of oxygen were continued for about another hour.

After the addition of 30 ml. of 10 *N* sodium hydroxide the reaction mixture was shaken with 50 ml. of 1-butanol. The butanol layer was separated and the aqueous layer was extracted twice with 1-butanol. The combined butanol layers were washed with 150 ml. of 1 *N* sodium hydroxide, then with 100 ml. of water, and were evaporated under reduced pressure at room temperature. The residue was dissolved in 20 ml. of water and the solution was acidified with 4 *N* hydrochloric acid. The resulting precipitate (A) was analyzed by paper chromatography (Table I). Short-wave ultraviolet light was used for the detection of 4-hydroxy-3,5-diiodobenzaldehyde (IV), and diazotized N^1,N^1-diethylsulfanilamide[8] for the detection of all other compounds. Fractional recrystallization yielded the pure reaction products. The yield of the analogs of thyroxine was based on the analog of diiodotyrosine used.

Reaction with 3,5-Diiodo-L-tyrosine (IIa).—The precipitate A (0.83 g.) was treated with hot acetone. On filtration, 0.64 g. (18%) of thyroxine was obtained as an almost colorless solid, m.p. 218–220° dec., which showed a single spot on a paper chromatogram. The solid obtained by the concentration of the filtrate from A was found to consist mainly of 4-hydroxy-3,5-diiodobenzaldehyde (IV, infrared spectrum and by paper chromatogram).

Reaction with 4-Hydroxy-3,5-diiodobenzoic Acid (IIb).—The precipitate A (0.91 g.) was recrystallized from methanol to give 0.20 g. (6%) of 4,4′-dihydroxy-3,5,3′,5′-tetraiodobenzophenone (V) as colorless needles, m.p. 255° dec.; infrared spectrum (Nujol) 3600, 3400, 1622, 1572, and 1528 cm.$^{-1}$; λ_{max}^{EtOH} 209 mμ (log ε 4.53), 246.5 (4.50), and 372 (4.10).

Anal. Calcd. for $C_{13}H_6I_4O_3$: C, 21.75; H, 0.84; I, 70.75. Found: C, 21.85; H, 1.21; I, 70.31.

A solution of 0.15 g. of this substance in 20 ml. of ethanol was hydrogenated in the presence of 0.20 g. of 10% palladium–charcoal and 0.25 g. of anhydrous sodium acetate. After the absorption of hydrogen ceased (1 hr.), the catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was shaken with a mixture of ether and water. The ethereal layer was separated, dried, and evaporated. The residue was recrystallized from benzene, then from benzene–ethyl acetate to give 29 mg. of prisms, m.p. 213–214°; λ_{max}^{EtOH} 227 mμ (log ε 4.17) and 300 mμ (4.36).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.91; H, 5.06.

This substance was identified as 4,4′-dihydroxybenzophenone[18] by comparison with an authentic sample (infrared spectrum and mixture melting point).

The mother liquor obtained from the recrystallization of 4,4′-dihydroxy-3,5,3′,5′-tetraiodobenzophenone (V) gave after concentration pale yellow needles, which were recrystallized from ethyl acetate to yield 0.18 g. (5.3%) of colorless needles, m.p. 269–270° dec. The infrared spectrum was identical with that of an authentic sample of tetraiodothyroformic acid (IIIb).

From the mother liquor of the recrystallization of tetraiodothyroformic acid, crystals (0.49 g.) were obtained. The infrared spectrum and paper chromatogram showed that the crystals consisted of 4-hydroxy-3,5-diiodobenzaldehyde (IV) contaminated with tetraiodothyroformic acid (IIIb).

Reaction with 4-Hydroxy-3,5-diiodophenylacetic Acid (IIc).[8]—The precipitate A (0.55 g.) was recrystallized from benzene containing a small amount of ethanol to give 0.32 g. (9.2%) of colorless needles, m.p. 229–230°. The infrared spectrum was identical with that of an authentic sample of 3,5,3′,5′-tetraiodothyroacetic acid (IIIc).[8]

(12) G. D. Thorn and C. B. Purves, *Can. J. Chem.*, **32**, 373 (1954).

(13) (a) G. M. Coppinger and T. W. Campbell, *J. Am. Chem. Soc.*, **75**, 734 (1953); (b) L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957).

(14) The starting material, 2,6-di-*t*-butyl-4-methylphenol, for this preparation was kindly supplied by Koppers Co., Inc.

(15) S. Fujisaki, Japan Patent 11,030 (1960); *Chem. Abstr.*, **55**, 466 (1961).

(16) T. H. Coffield, H. H. Filbey, G. G. Ecke, and A. J. Kolka, *J. Am. Chem. Soc.*, **79**, 5019 (1957).

(17) Chemed, Inc., Odenton, Md.

(18) K. Nakagawa, S. Matsuura, and S. Baba, *J. Pharm. Soc. Japan*, **74**, 498 (1954).

Reaction with 3-(4-Hydroxy-3,5-diiodophenyl)propionic Acid (IId).[8]—Recrystallization of the precipitate A (0.52 g.) from benzene gave 0.35 g. (10%) of colorless needles, m.p. 213–215°, whose infrared spectrum was identical with that of an authentic sample of 3,5,3′,5′-tetraiodothyropropionic acid (IIId)[8]; λ_{max}^{EtOH} 216 mμ (log ε 4.68), 225 (4.69), 238 (4.52), 295 (3.62), and 303 (3.63).

Reaction with 4-(4-Hydroxy-3,5-diiodophenyl)butyric Acid (IIe).[8]—The precipitate A (0.53 g.) was recrystallized from benzene, then from ethyl acetate to give 0.17 g. (4.4%) of 3,5,3′,5′-tetraiodothyrobutyric acid (IIIe) as colorless needles, m.p. 200–202°, lit.[19] m.p. 195–196°; λ_{max}^{EtOH} 213 mμ (log ε 4.67), 226 (4.69), 238 (4.43), 295 (3.64), and 303 (3.63).

Anal. Calcd. for $C_{16}H_{12}I_4O_4$: C, 24.77; H, 1.56. Found: C, 24.94; H, 1.85.

From the mother liquor, 50 mg. of 4-hydroxy-3,3-diiodobenzaldehyde (IV) was isolated.

Reaction with 3-(4-Hydroxy-3,5-diiodophenyl)-2-methylpropionic Acid (IIf).[8]—Recrystallization of the precipitate A (0.67 g.) from benzene gave 80 mg. of 4-hydroxy-3,5-diiodobenzaldehyde (IV). The mother liquor, on slow evaporation, deposited a mixture of two kinds of crystals. Needle-shape crystals were picked up and recrystallized twice from benzene to give 0.14 g. (3.8%) of α-methyl-3,5,3′,5′-tetraiodothyropropionic acid (IIIf) as colorless needles, m.p. 193–195°; λ_{max}^{EtOH} 213 mμ (log ε 4.70), 226 (4.69), 237 (4.45), 295 (3.65), and 303 (3.66).

Anal. Calcd. for $C_{16}H_{12}I_4O_4$: C, 24.77; H, 1.56. Found: C, 24.77; H, 2.00.

Reaction with 3-(4-Hydroxy-3,5-diiodophenyl)-2-phenylpropionic Acid (IIg) (Iodoalphionic Acid).[20]—Recrystallization of the precipitate A (0.68 g.) from benzene gave 4-hydroxy-3,5-diiodobenzaldehyde (IV). The mother liquor, on slow evaporation, deposited crystals. The paper chromatogram and the infrared spectrum (1701, 1233, and 912 cm.$^{-1}$) of the crystals indicated that they consisted of a mixture of α-phenyl-3,5,3′,5′-tetraiodothyropropionic acid (IIIg) and of IV, but IIIg could not be isolated in pure form.

Reaction with 3-(4-Hydroxy-3,5-diiodophenyl)lactic Acid (IIh).[8]—Recrystallization of the precipitate A (0.67 g.) from a mixture of ethyl acetate, benzene, and petroleum ether gave 0.52 g. (14%) of 3,5,3′,5′-tetraiodothyrolactic acid (IIIh) as colorless needles, m.p. 201–203°, lit.[8] m.p. 207–208°. The infrared spectrum was identical with that of an authentic sample of IIIh[8]; λ_{max}^{EtOH} 214 mμ (log ε 4.70), 225 (4.70), 238 (4.45), 294 (3.64), and 302 (3.65).

Reaction with 4-Hydroxy-3,5-diiodocinnamic Acid (IIi).[8]—Recrystallization of the precipitate A (1.43 g.) from ethyl acetate gave 0.64 g. (18%) of 3,5,3′,5′-tetraiodothyroacrylic acid (IIIi) as colorless needles, m.p. 277–278° dec., lit.[21,22] m.p. 270° dec.; λ_{max}^{EtOH} 213 mμ (log ε 4.58), 247 (4.61), and 279 (4.37).

Anal. Calcd. for $C_{15}H_8I_4O_4$: C, 23.71; H, 1.05. Found: C, 24.02; H, 1.23.

Catalytic Hydrogenation of Tetraiodothyroacrylic Acid (IIIi). A.—A solution of 368 mg. of IIIi and 400 mg. of anhydrous sodium acetate in 40 ml. of ethanol was hydrogenated in the presence of 200 mg. of 10% palladium–charcoal. After the absorption of hydrogen ceased, the catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in water and the solution was acidified with dilute hydrochloric acid. The resulting precipitate was collected, dried, and recrystallized from ethyl acetate–petroleum ether to give 107 mg. (85%) of colorless needles, m.p. 163–165°. This substance was identified as thyropropionic acid by mixture melting point determination and by comparison of its infrared spectrum with that of an authentic sample of thyropropionic acid, m.p. 162–163°, which was prepared by catalytic hydrogenation of 3,5,3′,5′-tetraiodothyropropionic acid,[8] lit. m.p. 161°[23] and 175°.[24]

B.—A solution of 200 mg. of IIIe and 200 mg. of anhydrous sodium acetate in 20 ml. of ethanol was hydrogenated in the presence of 100 mg. of 10% palladium–charcoal which had been stored over a year after its preparation. After the absorption of hydrogen ceased (80 min.), the mixture was treated as described in A. Recrystallization of the product from ethyl acetate gave 32 mg. of thyroacrylic acid as colorless needles, m.p. 227–228° dec.; infrared spectrum (Nujol): 3140, 1693, 1628, 1600, 1500, 980, and 837 cm.$^{-1}$; λ_{max}^{EtOH} 206.5 mμ (log ε 4.32), 224.5 (4.21), 297 (4.32), and inflexion at 308 (4.31).

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 69.97; H, 5.01.

Reaction with 2,4,6-Triiodophenol (IIj).—In this reaction an additional 30 ml. of 1-butanol was added in order to render triiodophenol soluble at pH 7.6. The precipitate A (2.31 g.) was recrystallized from methanol to give triiodophenol (1.44 g., 70% recovery), m.p. 159–160°. Paper chromatography of the mother liquor showed the presence of triiodophenol and 4-hydroxy-3,5-diiodobenzaldehyde (IV), but of no analog of thyroxine.

Reaction with 3-(3,5-Dibromo-4-hydroxyphenyl)propionic Acid (IIk).[25]—The precipitate A (0.84 g.) was recrystallized twice from benzene to give 0.22 g. of colorless needles, m.p. 172–175°. Concentration of the mother liquor yielded 0.25 g. of crystals, m.p. 160–165°, which infrared spectroscopy and paper chromatography showed to consist of a roughly equimolecular mixture of IIIk and IV. On this basis the yield of IIIk was calculated to be about 12%; λ_{max}^{EtOH} 211 mμ (log ε 4.77), 240 (3.58), 287 (3.58), and 302 (3.65).

Anal. Calcd. for $C_{15}H_{10}Br_2I_2O_4$: C, 27.01; H, 1.51. Found: C, 27.13; H, 1.71.

The infrared spectrum of this substance was identical with that of an authentic sample of 3,5-dibromo-3′,5′-diiodothyropropionic acid (IIIk).[7]

Reaction with 3-(3,5-Dichloro-4-hydroxyphenyl)propionic Acid (III).—The precipitate A (0.79 g.) was recrystallized twice from benzene to give 0.36 g. (16%) of colorless plates, m.p. 186–188°; λ_{max}^{EtOH} 213 mμ (log ε 4.65), 221 (4.63), 237 (4.24), 285 (3.59), and 303 (3.69).

Anal. Calcd. for $C_{15}H_{10}Cl_2I_2O_4$: C, 31.12; H, 1.74. Found: C, 31.12; H, 1.83.

The infrared spectrum was identical with that of an authentic sample of 3,5-dichloro-3′,5′-diiodothyropropionic acid (IIII).[7]

Reaction with 3-(4-Hydroxy-3-iodophenyl)propionic Acid (IIm).—Recrystallization of the precipitate A (0.59 g.) from ethyl acetate–petroleum ether gave 0.16 g. of 4-hydroxy-3,5-diiodobenzaldehyde (IV). Paper chromatography of the mother liquor showed the presence of IV and of 3,3′,5′-triiodothyropropionic acid (IIIm) which could not be isolated in pure form.

Reaction with 3-Methoxy-4-hydroxy-5-iodocinnamic Acid (IIn).—Recrystallization of the precipitate A (1.15 g.) from ethyl acetate gave 0.30 g. of 4-hydroxy-3,5-diiodobenzaldehyde (IV). Fractional recrystallization of crystals obtained from the mother liquor gave 76 mg. (2.2%) of 3-methoxy-5,3′,5′-triiodothyroacrylic acid (IIIn) as colorless needles, m.p. 226–228° (sintering at 220°); infrared spectrum (Nujol): 3520, 2700–2500, 1690, 1636, 1280, and 906 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{11}I_3O_5$: C, 28.94; H, 1.67. Found: C, 29.33; H, 2.19.

Reaction with 3-(4-Hydroxyphenyl)propionic Acid (IIo).[8]—Fractional recrystallization of the precipitate A (0.29 g.) from ethyl acetate gave 45 mg. of 4-hydroxy-3,5-diiodobenzaldehyde (IV) and 9 mg. of 3,5,3′,5′-tetraiodothyroformic acid (IIIb), m.p. 250–251° dec., which was identical with an authentic sample.

Reaction with 3-(4-Hydroxy-3,5-dinitrophenyl)propionic Acid (IIp).[26]—Fractional recrystallization of the precipitate A (0.23 g.) from ethyl acetate–benzene gave 43 mg. of 4-hydroxy-3,5-diiodobenzaldehyde and 7 mg. of 3,5,3′,5′-tetraiodothyroformic acid (IIIb), both identified by comparison of infrared spectra, but no analog (IIIp) of thyroxine.

Reaction with 3-(3,5-Di-*t*-butyl-4-hydroxyphenyl)propionic Acid (IIq).—The reaction was carried out with 0.80 g. (2.9 mmoles) of IIq. Recrystallization of the precipitate A (0.85 g.) from benzene gave 0.45 g. (53% recovery) of colorless needles, m.p. 173–175°, which were identical with IIq. Paper chromatography of the mother liquor showed the presence of IV, but not of the analog IIIq of thyroxine.

Reaction with 3-(2-Hydroxy-3,5-diiodophenyl)propionic Acid (VI).[7]—Recrystallization of the precipitate A from benzene gave

(19) N. Kharasch and S. H. Kalfayan, *J. Org. Chem.*, **21**, 929 (1956).

(20) Schering Corp., Bloomfield, N. J.

(21) S. Wawzonek, S. C. Wang, and R. Lyons, *J. Org. Chem.*, **15**, 593 1950.

(22) R. C. Cookson and G. F. H. Green, *J. Chem. Soc.*, 827 (1952).

(23) J. Walker, *ibid.*, 347 (1942).

(24) R. I. Meltzer, S. Farber, E. Merrill, and A. Caro, *J. Org. Chem.*, **26**, 1413 (1961).

(25) T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **82**, 2055 (1960).

(26) R. K. Callow, J. M. Gulland, and R. D. Haworth, *J. Chem. Soc.*, 1452 (1929).

0.38 g. of needles, m.p. 122–123°, which were identical with the starting material VI. The paper chromatogram of the mother liquor showed the presence of 4-hydroxy-3,5-diiodobenzaldehyde (IV), triiodophenol (IIj), VI, and the analog X[7] of thyroxine. R_f values of these substances were identical to those of authentic samples.

Reaction with 3-(3-Hydroxy-4,6-diiodophenyl)propionic Acid (VII).[7]—Recrystallization of the precipitate A (0.49 g.) from benzene gave 20 mg. (1%) of crystals, m.p. 219–220°; λ_{max}^{EtOH} 215 mμ (log ε 4.70), 228 (4.71), 238.5 (4.58), 293 (3.84), and inflexion at 300 (3.82).

Anal. Calcd. for $C_{15}H_{10}I_4O_4$: C, 23.65; H, 1.33. Found: C, 24.94; H, 1.64.

The microanalysis shows that the product XI was partly deiodinated.

Fractional recrystallization of crystals obtained from the mother liquor gave 172 mg. of the starting material VII and 55 mg. of 4-hydroxy-3,5-diiodobenzaldehyde (IV).

Reaction with 3-(3-Hydroxy-2,4,6-triiodophenyl)propionic Acid (VIII).[7]—The paper chromatogram of the precipitate A (1.02 g.) showed the presence of a considerable amount of the starting material VIII, in addition to 4-hydroxy-3,5-diiodobenzaldehyde (IV) and the analog XII[7] of thyroxine. Attempts to isolate XII were unsuccessful. The precipitate and A 1 g. of anhydrous sodium acetate were therefore dissolved in 100 ml. of ethanol and the solution was hydrogenated in the presence of 0.5 g. of 10% palladium–charcoal. After the absorption of hydrogen ceased, the catalyst was removed by filtration, the solvent was evaporated under reduced pressure, and the residue was taken up 50 ml. of water. Acidification of the mixture with dilute hydrochloric acid yielded 0.12 g. (10%) of 3-[3-(4-hydroxyphenoxyphenyl)]-propionic acid (XIII) as colorless plates, m.p. 145–149°. Recrystallization from water raised the melting point to 149–151°. The infrared spectrum was identical with that of an authentic sample of XIII.[7]

In a control run, catalytic hydrogenation of the precipitate A obtained from 3-(4-hydroxy-3,5-diiodophenyl)propionic acid (IId) yielded thyropropionic acid in 10% yield.

Reaction with Diiodo-L-histidine (IX).[27]—The precipitate A (0.31 g.) was treated with hot benzene. The insoluble material (25 mg.) was removed by filtration. This material was dissolved in a small volume of 7 *N* aqueous ammonia and the solution was then acidified. The infrared spectrum of the precipitate formed (19 mg.) was almost identical with that of tetraiodothyroformic acid (IIIb). The filtrate from the above mentioned insoluble material was evaporated and the residue was fractionally recrystallized from benzene to yield 105 mg. of 4-hydroxy-3,5-diiodobenzaldehyde (IV) and 9 mg. of IIIb. No coupling product (XIV) was detected.

Acknowledgment.—This work was supported by Grant A-3706 from the National Institutes of Health, U. S. Public Health Service. The authors are indebted to Dr. H. J. Cahnmann of the National Institutes of Health and to Dr. T. Shiba of Osaka University for helpful discussions and also to Professor T. Kubota for his interest in this work.

(27) K. J. Brunnings, *J. Am. Chem. Soc.*, **69**, 205 (1947).

Phosphorylating Agents by the Activation of Phosphates with Ethoxyacetylene[1,2]

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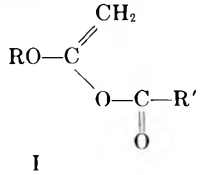
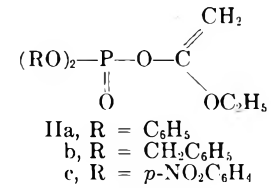
1-Alkoxy vinyl esters of phosphoric acids (IIa and b, R = C_6H_5 and $CH_2C_6H_5$) have been isolated from the reaction of the corresponding phosphoric acids with ethoxyacetylene and shown to be active phosphorylating agents for a variety of nucleophiles. Monoesters of phosphoric acid were activated and allowed to react *in situ* to form methyl adenylate, thymidine-3′ thymidine-5′ phosphate, and flavine adenine dinucleotide (FAD). Uridine-5′ diphosphate (UDP) was prepared by reaction of IIb (R = $CH_2C_6H_5$) with uridine-5′ monophosphate (UMP) followed by debenzylation.

Arens and his co-workers have, in the course of extensive studies,[3] shown that alkoxy acetylenes are effective agents for the conversion of carboxylic acids to anhydrides, and, in the case of acids containing strongly electronegative groups, intermediates of the type I have been isolated.[4]



I

In these laboratories, we have found that such 1-alkoxy vinyl esters of carboxylic acids can *generally* be prepared at moderate temperatures either with the aid of a mercuric ion catalyst or by the use of a large excess of alkoxy acetylene.[5,6] In this report, we describe the extension of this method to the activation of



IIa, R = C_6H_5
b, R = $CH_2C_6H_5$
c, R = p-$NO_2C_6H_4$

phosphoric acid esters. The utility of these enol phosphate intermediates in synthesis has been demonstrated by the formation of internucleotidic and coenzyme linkages. As described below, we have selected a number of applications, and although effects were not made to work out optimum yields for each case, we have shown the potential and versatility of the method.

The active intermediates (II)[7] were prepared by re-

(1) A preliminary report of these findings has already appeared: H. H. Wasserman and D. Cohen, *J. Am. Chem. Soc.*, **82**, 4435 (1960).

(2) Supported by Grant RG 7874, U. S. Public Health Service.

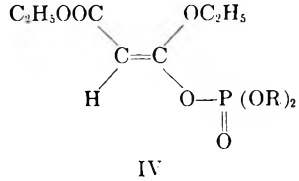
(3) See J. F. Arens and H. C. Volger, *Rec. trav. chim.*, **77**, 1170 (1958), and earlier papers in this series.

(4) R. Broekema, S. van der Werf, and J. F. Arens, *ibid.*, **77**, 258 (1958).

(5) H. H. Wasserman and P. S. Wharton, *Tetrahedron*, **3**, 321 (1958).

(6) H. H. Wasserman and P. S. Wharton, *J. Am. Chem. Soc.*, **82**, 661 (1960).

(7) F. Cramer [*Angew. Chem.*, **69**, 727 (1957); **72**, 246 (1960)] has reported the preparation of similar systems (IV) using the Perkow reaction between triesters of phosphorous acid and bromomalonic esters. Intermediates of this type have been shown to be useful phosphorylating agents of carboxylic,



IV

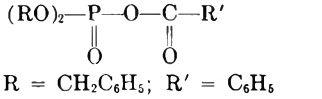
sulfonic, and phosphoric acids and also adenylic acid. However, the fact that symmetrical triesters of phosphorous acid are not readily available limits the applicability of this type of intermediate.

action of the phosphoric acid diesters either with an excess of ethoxyacetylene in chloroform, carbon tetrachloride, methylene chloride, or a mixture of methylene chloride–dimethylformamide (DMF) at 0°, or with the aid of mercuric ion (as mercuric acetate). In the latter cases roughly equimolar amounts of phosphate and ethoxyacetylene were employed and yielded intermediates virtually uncontaminated by pyrophosphate.[8]

These esters are stable oils at moderate temperatures (*ca.* 25°) but tend to polymerize on heating. In particular, the benzyl ester decomposes readily during attempts to purify it by distillation under high vacuum. An analytical sample of IIb could be prepared only by using a very large excess of ethoxyacetylene (5 *M* excess) and removal of excess acetylene and solvents without further handling. The diphenyl ester IIa was more tractable and could be stored for long periods at low temperature without significant decomposition.

As was observed in the case of the alkoxy vinyl carboxylates,[5,6] the alkoxy vinyl phosphates exhibit characteristic infrared absorption in the 5–6-μ region. For example, both the diphenyl and the dibenzyl esters show sharp peaks at 5.74 and at 5.95–5.96 μ. Although the di-*p*-nitrophenyl ester IIc (R = *p*-$NO_2C_6H_4$) was not isolated in a pure state, its presence in the reaction mixture was shown by the appearance of the typical infrared bands at 5.74 and 5.95 μ in methylene chloride–dimethylformamide (DMF) solution.

Phosphorylation reactions of these esters can be carried out *in situ* by following the disappearance of this pair of infrared bands. Thus we observed that treatment of solutions of both IIa and IIb with methanol, phenol, thymidine, diesters of phosphoric acid, cyclohexylamine, and benzoic acid produced a diminution in intensity of the 5.74- and 5.96-μ peaks corresponding to the amount of added nucleophile. The product of phosphorylation was isolated and identified in the reaction with cyclohexylamine whereby diphenyl N-cyclohexylphosphoroamidate was formed in nearly quantitative yield. The formation of the mixed anhydride III (R = $CH_2C_6H_5$; R′ = C_6H_5) by reaction



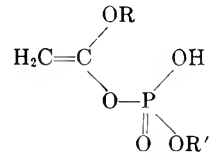
III, R = $CH_2C_6H_5$; R′ = C_6H_5

of IIb with benzoic acid was shown by the infrared, and by further reaction with cyclohexylamine to produce the expected products, N-cyclohexylbenzamide and cyclohexylammonium dibenzyl phosphate.[9]

The rate of formation of alkoxy vinyl phosphate appears to be roughly equal to the rate of reaction of the phosphoric acid with the active intermediate to form pyrophosphate (in the absence of mercuric ion). This was noted by an infrared study during an experiment utilizing excess ethoxyacetylene and dibenzylphosphoric acid. Gradual addition of diphenylphosphoric acid to the acetylene solution resulted in a steady diminution of the acetylenic peak in the 4–4.5-μ region, while the ester peaks remained approximately constant, indicating that the rate of formation of ester was about equal to its further reaction to give pyrophosphate.

The ease with which the activated intermediates II appeared to form mixed pyrophosphates offered promise of a convenient method of coenzyme synthesis. Accordingly, IIb was allowed to react with the pyridinium salt of uridine-5′ monophosphate at room temperature for 3 days, and the product was isolated after successive anionic and hydrogenolytic debenzylation. Comparison by paper chromatography with standard samples of UMP and UDP showed that the product (*ca.* 15% yield) contained UDP and UMP in the ratio 9:1, estimated by comparing the relative ultraviolet intensities of the eluted chromatographic spots.

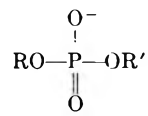
We next investigated the possibility of preparing active esters of type V in view of the obvious advantage



V, R = C_2H_5; R′ = adenosine-5′

of the direct activation of nucleotides. Although early experiments with monophenyl phosphate and ethoxyacetylene were not promising, in that a pure active ester could not be isolated, we were able to use this type of intermediate successfully in other cases. Thus, adenosine-5′ phosphate as either the pyridinium or the triethylammonium salt was allowed to react with ethoxyacetylene to produce V (R = C_2H_5; R′ = adenosine-5′, not isolated), which in methanol solution was slowly converted to the corresponding methyl ester. This product was identical with the monomethyl ester of AMP prepared by Khorana,[10] *et al.*, using the carbodiimide technique, as shown by both chromatography and paper electrophoresis.

To explore the usefulness of this simple esterification technique in the formation of internucleotidic linkages, we next attempted the synthesis of the well-characterized thymidine-3′ thymidine-5′ phosphate. Thymidine-5′ phosphoric acid was acetylated in the manner described by Khorana[11] to give 3′-acetylthymidine-5′ phosphoric acid, which, as the pyridinium salt, was allowed to react with 6 moles of ethoxyacetylene, followed by 1 mole of 5′-tritylthymidine.[11] After 48 hr. the product was detritylated and deacetylated and a compound corresponding to the previously described[11,12] dinucleoside phosphate (VI, R = thymidine-3′; R′ = thymidine-5′) was isolated



VI, R = thymidine-3′; R′ = thymidine-5′

in approximately 33% yield by elution of the bands (R_f, 0.41) from strips of Whatman 3 mm. seed test paper. This material had the correct ratio of nucleoside to phosphorus as shown by ultraviolet absorption and phosphorus analysis. Its behavior on electro-

(8) J. F. Arens and T. Doornbos [*Rec. trav. chim.*, **74**, 79 (1955)] showed that tetraethylpyrophosphate could be formed from diethyl phosphate and ethoxyacetylene. No intermediate enol phosphate was isolated.

(9) Compare peptide synthesis by F. Cramer and K. G. Gärtner, *Ber.*, **91**, 1562 (1958).

(10) M. Smith, J. G. Moffat, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6204 (1958).

(11) P. T. Gilham and H. G. Khorana, *ibid.*, **80**, 6212 (1958).

(12) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 2632 (1955).

phoresis also showed clearly that the product was the expected dithymidine phosphate.

Having demonstrated that an internucleotidic linkage could be formed from an ethoxyacetylene-activated nucleotide, we sought to prepare a nucleotide coenzyme by the reaction of V with riboflavine-5′ monophosphate to produce flavine adenine dinucleotide (FAD). This has previously been prepared by Todd and co-workers[13] in a many stage synthesis giving a 6% yield, while methods using carbodiimides gave even lower yields.[14] In both of these cases, separation of the reaction products was difficult. More recently, however, much better results have been obtained by conversion of adenosine-5′ phosphoric acid to the corresponding phosphoroamidate which was isolated and subsequently allowed to react with the riboflavine-5′ phosphate in a mixture of pyridine and *o*-chlorophenol. The product was obtained by elution from DEAE–cellulose with hydrochloric acid and lithium chloride solution.[15]

We found that dimethyl sulfoxide was an excellent medium for the reaction, being a good solvent for adenylic acid or its pyridinium salt and for riboflavine-5′ phosphate as its pyridinium salt. Here, the advantage of the ethoxyacetylene reagent over the carbodiimide stemmed from the fact that the adenylic acid could be activated and excess acetylene removed before the addition of the riboflavine phosphate. Thus formation of the cyclic 4′,5′-riboflavine phosphate (the major product in the carbodiimide route) was kept to a minimum.[16] Furthermore, this method retains the simplicity of the carbodiimide method in that the protecting groups used by earlier workers[13] need not be used, avoiding the losses experienced in debenzylation, deacetylation, etc.

The crude product was obtained by precipitation from dimethyl sulfoxide with a large excess of acetone, and the material thus obtained readily was separated into its components by a process of gradient elution on an ECTEOLA column with lithium chloride–lithium acetate buffer at 5°. Flavines present due to light-induced decomposition of the products were eluted first, followed by riboflavine-5′ phosphate and then the desired FAD. The products were obtained by concentration of the eluent fractions to a small volume and precipitation with acetone in which the buffer (lithium) salts are soluble. The FAD, obtained in yields varying from 10–15%, was identical in its chromatographic and electrophoretic behavior with an authentic sample.

It seems clear from the examples described above that ethoxyacetylene is a versatile reagent for activation of mono- and dialkyl phosphates, and undoubtedly this method is capable of extension in the field of nucleotides and nucleotide coenzymes.

Experimental

The ethoxyacetylene used in this work was prepared by a modification of the procedure of Nazarov and co-workers.[17] It was found to be more convenient and more rapid to carry out the bromination of ethyl vinyl ether at lower temperatures (*ca.* −20°). The final purification of the product was accomplished by distillation at atmospheric pressure.

Chromatography was carried out with Whatman No. 1 paper, by both ascending and descending techniques. The solvent systems employed were A, butanol–acetic acid–water, 4:1:5; B, isopropyl alcohol–NH_4OH–water, 7:1:2; C, *t*-butyl alcohol–water, 6:4. Paper electrophoresis was carried out using Whatman No. 1 and Whatman No. 3 paper, using 0.1 *M* K_2HPO_4 and 0.1 *M* KH_2PO_4 buffers in a water-cooled paper electrophoresis apparatus.

1-Ethoxyvinyl Diphenyl Phosphate.—Ethoxyacetylene (1.0 g., 14.3 mmoles) was added to a suspension of mercuric acetate (0.02 g., 0.06 mmole) in dry methylene chloride (50 ml.) at 0° and the solution was stirred magnetically. A solution of diphenylphosphoric acid (2.5 g., 10.3 mmoles) in methylene chloride (20 ml.) was added in the course of 30 min., after which the solution was allowed to warm to room temperature (1 hr.).

Solvents were removed by evaporation under reduced pressure and the pale brown oil was purified by molecular distillation at 2×10^{-4} mm. A small first fraction at 60° was discarded and then the major product (80%) distilled from 95–105°, leaving a small amount of residual tarry material.

Anal. Calcd. for $C_{16}H_{17}O_5P$: C, 60.00; H, 5.31; P, 9.68. Found: C, 59.90; H, 5.47; P, 9.67.

The infrared spectrum shows the characteristic strong bands of alkoxy vinyl esters at 5.74 and 5.95 μ.

Conversion of II (R = C_6H_5) to Diphenyl N-Cyclohexyl Phosphoroamidate.[18]—Cyclohexylamine (0.1 g.) in chloroform solution (5 ml.) was added to a solution of 1-ethoxyvinyl diphenyl phosphate (0.39 g.) in chloroform (5 ml.). After 30 min., solvents were removed and the white solid remaining was recrystallized from 80% ethyl alcohol to give a small quantity of cyclohexylammonium diphenylphosphate (m.p. 192°). The mother liquors yielded fine white needles of the phosphoroamidate, m.p. 105–106°, lit.[18] m.p. 104–105°.

Anal. Calcd. for $C_{18}H_{22}NO_3P$: C, 65.25; H, 6.69; N, 4.23. Found: C, 65.20; H, 6.71; N, 4.45.

1-Ethoxyvinyl Dibenzyl Phosphate.—Dibenzylphosphoric acid (1.74 g., 6.25 mmoles) prepared by the method of Clark and Todd[19] in dry methylene chloride (10 ml.) was added to a magnetically stirred solution of ethoxyacetylene (1.8 g., 25 mmoles) in methylene chloride (20 ml.) at 0°. After 36 hr. at room temperature, the solvents were removed at reduced pressure and the somewhat viscous oil was held at 90° (15 mm.) for 2 hr.

Anal. Calcd. for $C_{18}H_{21}O_6P$: C, 62.06; H, 6.03. Found: C, 61.85; H, 5.86.

The infrared spectrum of the analytical sample, $n^{25}D$ 1.5348, has characteristic bands at 5.74 and 5.96 μ.

Dibenzylphosphoric Benzoic Anhydride.—To a solution of 1-ethoxyvinyl dibenzyl phosphate (from 0.87 g. of dibenzylphosphoric acid) in methylene chloride was added a small excess of benzoic acid. After 30 min. the infrared spectrum showed complete absence of the characteristic enol ester peak at 5.96 and a new band at 5.59 μ corresponding to the anhydride. The presence of the anhydride was shown by reaction with N-cyclohexylamine. After 4 hr. the solution was poured into water and the methylene chloride was removed by heating on a steam bath. The aqueous solution was made acidic with concentrated hydrochloric acid and then carefully neutralized with potassium hydroxide solution. N-Cyclohexylbenzamide was precipitated, m.p. and m.m.p. 167°.

Methyl Adenosine-5′ Phosphate. A.—Adenosine-5′ phosphoric acid (0.10 g., 0.29 mmole, Schwarz Laboratories, Mt. Vernon, N. Y.) was dissolved in methanol (100 ml.) containing 0.07 ml. of pyridine. To this solution (at 0°) was added mercuric acetate (0.01 g.) followed by an excess of ethoxyacetylene (0.5 ml.).

After 36 hr. at room temperature, paper chromatography (isopropyl alcohol–ammonia–water, 7:1:2) showed the complete absence of the AMP spot and the appearance of a single, faster moving compound.

B.—An identical procedure was followed using triethylamine in place of pyridine. AMP proved more soluble in this system but the over-all reaction time was longer.

(13) S. M. H. Christie, *et al.*, *J. Chem. Soc.*, 46 (1954).

(14) F. M. Huennekens and G. L. Kilgour, *J. Am. Chem. Soc.*, **77**, 6716 (1955).

(15) J. F. Moffatt and H. G. Khorana, *ibid.*, **80**, 3756 (1958).

(16) All attempts to carry out the reaction by a one-stage coupling in which both nucleotides were mixed in the presence of ethoxyacetylene gave up to 80% of the riboflavine-4′,5′ cyclic phosphate, identified by chromatography and electrophoresis.

(17) I. N. Nazarov, Z. A. Krasnaia, and V. P. Vinogradov, *J. Gen. Chem. USSR*, **28**, 451 (1958).

(18) L. F. Andrieth and A. D. F. Toy, *J. Chem. Soc.*, 1337 (1942).

(19) V. M. Clark and A. R. Todd, *ibid.*, 2023 (1950).

The products from procedures A and B formed in nearly quantitative yield showed identical chromatographic and electrophoretic behavior with an authentic sample prepared by Khorana's method using DCC (Table I).

TABLE I

CHROMATOGRAPHIC AND ELECTROPHORETIC DATA

	R_f values in solvents		Electrophoretic mobility (cm. towards anode)[a]	
	System A	System B	0.1 *M* K_2HPO_4	0.1 *M* KH_2PO_4
Product	0.35	0.69	1.6	3.2
Authentic methyl adenosine-5′ phosphate[b]	0.35	0.69	1.6	3.2
Adenosine-5′ phosphate		0.65	3.5	3.2

[a] For 3.5 hr. at 300 v. [b] Prepared by the method of Smith, Moffatt, and Khorana (ref. 10). The triethylammonium salt of AMP was used in place of the tri-*n*-butylammonium salt.

Uridine-5′ Pyrophosphate (UDP).—Sodium uridine-5′ phosphate (100 mg., 0.27 mmole) was converted to the pyridinium salt (ion exchange on 1R 120 column) and the dried product was dissolved in a mixture of methylene chloride and dimethylformamide. Ethoxyvinyl dibenzyl phosphate (from 76 mg., 0.27 mmole, of dibenzylphosphoric acid) in methylene chloride was added and the reaction mixture was kept in a sealed flask at room temperature for 72 hr. Electrophoresis of the product in 0.1 *M* K_2HPO_4 showed the presence of two compounds (4.3 and 5.6 cm. towards the anode; UMP, 6.6 cm. towards the anode).

The solution was evacuated to give a resinous material which was partially debenzylated by treatment with freshly fused lithium chloride (0.2 g.) in Cellosolve (10 ml.) under reflux.[20] (Electrophoresis in 0.1 *M* KH_2PO_4 showed a product moving faster than UMP.) This solution was evacuated to dryness, dissolved in water (20 ml.), acidified with dilute hydrochloric acid to a normality of 5.0×10^{-3} *N*, and catalytically hydrogenated with a mixture of palladium oxide and 10% palladized charcoal. Hydrogen uptake was complete in 4 hr. The solution was filtered and brought to pH 7 (lithium hydroxide); barium chloride solution was added. After filtration, the solution was evaporated *in vacuo* to 15 ml., and ethanol (40 ml.) was added. On standing overnight, a gelatinous precipitate formed which was centrifuged, washed with acetone and ether, and dried over phosphorus pentoxide.

Paper chromatography [isopropyl alcohol–ammonium sulfate (1%), 60:40] against authentic UMP and UDP showed that the product contained 90% UDP and 10% UMP as the only ultraviolet-absorbing materials.

Thymidine-3′ Thymidine-5′ Phosphate.—Thymidine-5′ phosphoric acid (0.096 g., 0.3 mmole) was converted to the pyridinium salt (1R 120 column), and after drying overnight at 50° (0.3 mm.) the salt was dissolved in dry pyridine (2.5 ml.) and acetic anhydride (2.5 ml.) with shaking. On evacuation after 26 hr. at room temperature, the gum was dissolved in aqueous pyridine and left 3 hr. at room temperature, after which it was again evacuated, then freeze-dried. The product was dissolved in freshly distilled DMF and evacuated again at 50° (0.1 mm.), yielding a glassy material. This was dissolved in dry DMF and finally 5′-tritylthymidine (165 mg., 0.3 mmole) and ethoxyacetylene (0.1 ml., 2 mmoles) were added. The sealed flask was kept at room temperature for 48 hr. and the product was examined by paper chromatography (solvent system B) against markers of 5′-tritylthymidine, 3′-acetylthymidine-5′ phosphoric acid, and thymidine-5′ phosphoric acid. The product contained small amounts of all these materials and three new compounds showed R_f 0.56, 0.63, 0.35, the latter two being the most intense. All the spots (except 5′-tritylthymidine) gave positive phosphorus reactions with the Hanes and Isherwood reagent.

The solution was evacuated to dryness and the residue was heated under reflux in 80% acetic acid (10 ml.). After cooling and dilution with water to 20 ml., the triphenylmethanol was filtered off (60% of theoretical amount recovered). The aqueous filtrate was evacuated to dryness, then dissolved in water (3 ml.), and dilute sodium hydroxide solution was added dropwise to pH 13. After 30 min. the solution was diluted with water (5 ml.) and passed through a short ion-exchange column (1R 120, H form). (A small amount of triphenylmethanol which precipitated at this stage was left at the top of the column.) The eluate was concentrated *in vacuo* to a low bulk, and a portion was run as a chromatogram on Whatman 3 mm. seed test paper. There were four ultraviolet-absorbing products which were identified by comparison with known standards. The relative amounts were estimated by comparison of the optical densities of the eluted spots: thymidylic acid, 15%, R_f 0.13; dithymidine (3′-5′ phosphate), 30%, R_f 0.41; dithymidine-5′ pyrophosphate, 45%, R_f 0.28; unknown, 10%, R_f 0.75. Three spots of fluorescent material (R_f 0.38, 0.67, and 0.89) were also observed.

The product was then run as bands on four strips of seed test paper and the bands at R_f 0.41 were eluted with water.

The ratio of thymine to phosphorus was determined as 2.03:1 (calcd. for dithymidine phosphate, 2:1), and per cent phosphorus was 5.2 (calcd. for $C_{10}H_{31}N_5O_{13}P$, 5.36%).

Paper electrophoresis values using thymidine-5′ phosphate as a standard gave the results shown in Table II.

TABLE II[a]

ELECTROPHORETIC MOBILITY (cm. to anode)

	0.1 *M* K_2HPO_4	0.1 *M* KH_2PO_4
Product	2	0.2
Thymidine-5′ phosphate	4	1.2
	(3 hr. at 300 v.)	(1 hr. at 300 v.)

Flavine Adenine Dinucleotide.—Adenylic acid (0.5 g.), dried at 100° over P_2O_5 at 10^{-1} mm. for 25 hr., was dissolved in dimethyl sulfoxide (10 ml.). A large excess of ethoxyacetylene was added at the temperature of freezing dimethyl sulfoxide, and the solution was allowed to warm to room temperature. After 1–2 hr., the excess ethoxyacetylene was removed by distillation under vacuum and the remaining solution was added to the pyridinium salt of FMP previously dried over P_2O_5. The mixture was allowed to stand at room temperature for 36–48 hr. and then poured into a large excess of acetone. The products which precipitated were removed by filtration, and dissolved in water before application to an ECTEOLA column (chloride form). Gradient elution was carried out in the dark at 5° in the cold room (500 ml. of water in the first flask and 500 ml. of a mixture of 0.2 *M* LiCl and 0.02 *M* LiAc, 1:1, in the reservoir). Free flavines were eluted at once, followed by an unidentified fraction which appears to be identical with the impurity found in commercial FMP.[21a,b]

The next fraction was FMP, and finally the FAD was obtained. It was also observed that the commercial FAD[21b] contained a small amount of flavine-containing impurity which could be separated as a band running slightly slower than FAD. The eluant was monitored by an arrangement which permitted continuous observation of the ultraviolet absorption through a quartz cell. The variation in optical density *vs.* the fraction number was recorded automatically. The products were isolated by evaporation of the appropriate collection of fractions to a small volume and precipitation of the phosphates was effected by slowly pouring into a large excess of acetone. The identity of the FAD was established by comparison with an authentic sample,[21b] in both chromatographic and electrophoretic systems as outlined in Table III.

TABLE III

CHROMATOGRAPHIC AND ELECTROPHORETIC DATA

	R_f values in solvents		
	System C	System A (organic phase)	Cm. towards anode 0.1 *M* K_2HPO_4
FMP	0.60	0.13	7.8
FAD	0.50	0.05	4.2
Synthetic FAD	0.50	0.05	4.2
			(3 hr. at 300 v.)

From a number of experiments, the best yield was 15% conversion of FMP to FAD. Approximately 50% of FMP was recovered unchanged in all cases.

(20) J. Lecoq and A. R. Todd, *J. Chem. Soc.*, 2381 (1954).

(21) (a) The FMP was obtained from the California Foundation for Research, 3408 Fowler Street, Los Angeles 63, Calif.; (b) the FAD was obtained from the Sigma Chemical Co., 3500 Dekalb Street, St. Louis 18, Mo.

Some Observations of Ultraviolet Absorption Spectra Involving Partial Chromophores in Di- and Trisubstituted Benzenes

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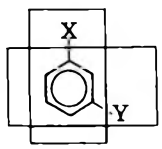
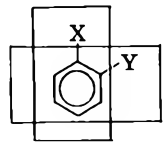
The ultraviolet absorption spectra of substituted benzenes in which absorption by more than one chromophore takes place are discussed. The term "hybrid spectra" is proposed for such cases. It is suggested that this type of absorption is a common feature of the spectra of those disubstituted benzenes in which mesomeric and other interactions are incomplete. The appearance of two high intensity bands at long wave lengths in the spectra of certain trisubstituted benzenes is explained.

It is generally accepted[2] that the mesomeric interactions of conjugated systems are largely responsible for the characteristics of their ultraviolet absorption spectra. If, therefore, a molecule contains two or more absorbing species or "partial chromophores" that are not conjugated with each other, its spectrum will be the sum of the separate absorptions of the partial chromophores. This has been shown for, *e.g.*, 1,4-diphenylbutane,[3] the spectrum of which resembles very closely that of ethylbenzene at twice the concentration.

In disubstituted benzenes, conjugation is at a maximum in the *para* isomer and the molecule generally absorbs as a single chromophore. Partial isolation of the chromophores, leading to local excitation, occurs in *meta*-disubstituted benzenes (I) because of the absence of classical conjugation, and in *ortho*-disubstituted benzenes (II) largely because of steric effects.[4] Although some features of the absorption of both chromophores in an *ortho*- or *meta*-disubstituted benzene will be retained, the spectrum of such a compound will not be a simple summation of the spectra of the two con-



I



II

stituent monosubstituted benzenes. This follows firstly because it has been generally shown[5] (*cf.*, however, ref. 6) that separation of two chromophores by a single carbon atom, which is analogous to the separation of groups X and Y in structure I, does not result in complete loss of interaction; secondly because short-range interactions, such as inductive effects and hydrogen bonding, may affect the spectrum of an *ortho*-disubstituted benzene (II). For example, the ultraviolet absorption spectrum of *m*-nitrophenol consists of three bands[7] ascribed to nitrobenzene absorption and one band ascribed to phenol absorption[8-10]; the spectrum is not the sum of the spectra of the two parent compounds, as can be seen from Table I.

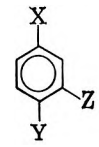
TABLE I

THE ABSORPTION MAXIMA OF NITROBENZENE, PHENOL, AND *m*-NITROPHENOL IN CYCLOHEXANE SOLUTION[a,b]

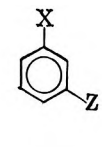
Bands in nitrobenzene spectrum		Bands in phenol spectrum		Corresponding bands in *m*-nitrophenol spectrum	
λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}
206.2	13000[c]			210	10500
253	9000			258.5	6100
ca. 287	*1500*			311	2810
		211	6060	221	10200[d]
		265	1400		
		271	2070	...	...
		276	1960		

[a] Values italicized represent inflections. [b] From ref. 8–10. [c] A. Burawoy and J. P. Critchley, *Tetrahedron*, **5**, 340 (1959). [d] Partially fused band.

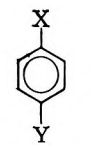
In the case of trisubstituted benzenes, Doub and Vandenbelt[11] have suggested that the absorption spectrum of a compound of type III (in which only one of the substituents is electron attracting) can be interpreted on the assumption that it is a composite of the absorption spectra of the three "constituent compounds," IV, V, and VI. They also stated that each of the bands appearing in the spectrum of the trisubstituted compound corresponded to that band which



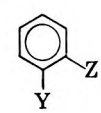
III



IV



V



VI

was at longest wave length among the corresponding bands of the "constituent compounds." This statement will be referred to as "Doub and Vandenbelt's rule."

(1) "Shell" Research Limited, Thornton Research Centre, Chester, England.

(2) See, for example, W. F. Forbes and A. S. Ralph, *Can. J. Chem.*, **34**, 1447 (1956), and other papers in that series; B. M. Webster, "Steric Effects in Conjugated Systems," G. W. Gray, Ed., Butterworths Scientific Publications, London, 1958, p. 82; C. N. R. Rao, "Ultraviolet and Visible Spectroscopy," Butterworths Scientific Publications, London, 1961, Chapter 5; A. R. Katritzky and P. Simmons, *J. Chem. Soc.*, 490 (1960).

(3) P. Ramart-Lucas and P. Amagat, *Bull. soc. chim. France*, **51**, 965 (1932).

(4) W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **34**, 1340 (1956).

(5) P. Ramart-Lucas, *Bull. soc. chim. France*, **10**, 13 (1943); H. P. Koch, *J. Chem. Soc.*, 1111 (1948); E. A. Braude, *ibid.*, 1902 (1949).

(6) F. Yamada, *Kogyo Kagaku Zasshi*, **62**, 1389 (1959).

(7) The band nomenclature used in this paper is that proposed by A. Burawoy [*J. Chem. Soc.*, 1177 (1939) and references cited there] and E. A. Braude [*Ann. Rept. Progr. Chem.*, **42**, 105 (1945)] with the modification that a K band attributed to a chromophore containing an electron-attracting substituent is called a K_X band and one attributed to a chromophore containing only an electron-donating substituent is called a K_D band.

(8) W. F. Forbes, *Can. J. Chem.*, **36**, 1350 (1958).

(9) J. C. Dearden and W. F. Forbes, *ibid.*, **37**, 1294 (1959).

(10) J. C. Dearden and W. F. Forbes, *ibid.*, **38**, 896 (1960).

(11) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **77**, 4535 (1955).

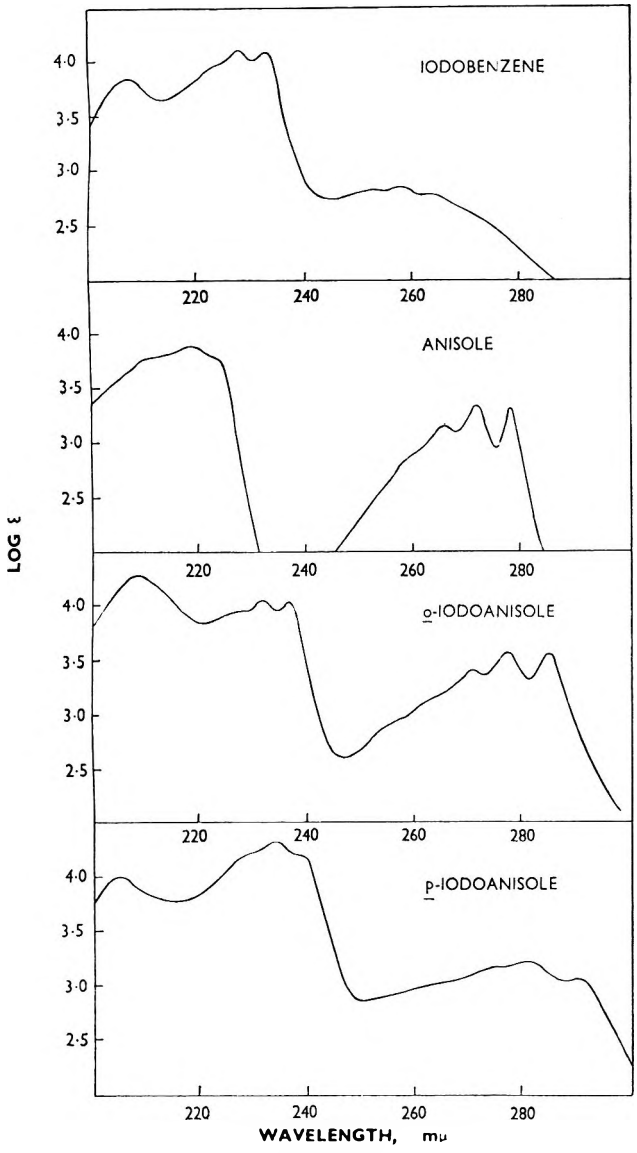


Fig. 1.—The spectra of iodobenzene, anisole, *o*-iodoanisole, and *p*-iodoanisole in cyclohexane solution.

The term "hybrid spectra" is proposed to describe spectra where absorption by more than one chromophore occurs.

The Spectra of Disubstituted Benzenes

The spectrum of a disubstituted benzene generally resembles the spectrum of the parent monosubstituted compound that absorbs at the longer wave length. For example, the spectrum of *p*-nitroanisole resembles that of nitrobenzene[8] rather than that of anisole, and the spectrum of *o*-aminophenol is similar to that of aniline.[12] In these examples, as with most disubstituted benzenes, all the bands in the spectrum of one of the parent monosubstituted compounds are at longer wave length than the corresponding bands in the spectrum of the other. However, some compounds, notably the halobenzenes, are anomalous. For example, the K band of iodobenzene is at longer wave length than that of anisole, but the B band is at shorter wave length (Table II). It would therefore be expected that the spectrum of *o*- or *m*-iodoanisole would exhibit an iodobenzene-type K band and an anisole-type B band.

TABLE II

THE ABSORPTION MAXIMA OF SOME PHENOLS, ANISOLES, AND HALOBENZENES IN CYCLOHEXANE SOLUTION[a]

	K band		B band	
Compound	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}
Phenol[b]	211	6060	265	1400
			271	2070
			276	1960
Anisole[c]	220	7700	265	1400
	ca. 224	*6050*	271.5	2100
			277.5	2050
Iodobenzene[d]	*ca. 224*	*9500*	*ca. 248*	*590*
	228	12700	253	670
	233	12000	257.5	710
			263	620
Chlorobenzene[e]	211	7500	245	70
	215	7500	251	120
	ca. 219	*6000*	257	180
			261	170
			264	250
			270	190
o-Iodophenol[b]	218.5[f]	9250	*ca. 263*	*1350*
	225	8300	270.5	2220
	230	6550	276.5	3010
			284	2800
p-Iodophenol[b]	231.5	15050	276	1280
	ca. 236	*12400*	282	1430
			290.5	1090
o-Iodoanisole[c]	*ca. 213*[f]	*13000*	*ca. 257*[g]	*880*
	ca. 228	*8700*	*ca. 265*	*1540*
	232	10200	271.5	2390
	236.5	10050	278	3380
			285.5	3230
m-Iodoanisole[c]	213[f,h]	25600	*ca. 256*[g]	*860*
	ca. 225	*9200*	*ca. 264*	*1310*
	229.5	9550	270	1970
	ca. 235	*6900*	277	2720
			284.5	2550
p-Iodoanisole[c]	234	19000	276	1450
	ca. 238	*15800*	281.5	1600
			290.5	1200
o-Chlorophenol[b]	212.5	6450	*ca. 257*	*670*
			ca. 267	*1540*
			273.5	2350
			280.5	2440
o-Chloroanisole[c]	*ca. 213*	*7100*	*ca. 261*	*760*
	218.5	7500	*ca. 269*	*1600*
	222.5	7350	275	2400
			282.5	2440

[a] Values italicized represent inflections. [b] Ref. 9. [c] Ref. 13. [d] Ref. 10. [e] Ref. 15a. [f] Ascribed to residual phenol or anisole absorption. [g] Ascribed to residual iodobenzene absorption. [h] Partially fused with Rydberg band.

Table II and Fig. 1 show that this phenomenon is in fact observed. The possibility that steric interactions are responsible for this behavior can be discounted, since it has been shown[13] that even an *o*-*t*-butyl substituent does not cause a steric effect on the spectrum of anisole.

Close inspection of Fig. 1 shows that inflections at *ca.* 213 mμ (ε 13,000) and *ca* 257 mμ (ε 800) are present in the spectrum of *o*-iodoanisole but that these are not evident in the spectra of iodobenzene and anisole respectively. Since the inflection at 213 mμ is close to the K band of anisole [λ_{max} 220 mμ (ε 7700)] and that at 257 mμ is close to the B band of iodobenzene [λ_{max} 257.5 mμ (ε 710)], it is suggested that these inflections

(12) W. F. Forbes and I. R. Leckie, *Can. J. Chem.*, **36**, 1371 (1958).

(13) J. C. Dearden and W. F. Forbes, *ibid.*, **37**, 1305 (1959).

TABLE III

THE ABSORPTION MAXIMA OF *o*-NITROPHENOL AND ITS 3-METHYL DERIVATIVE IN VARIOUS SOLVENTS[a,b]

	o-Nitrophenol				2-Nitro-3-methylphenol			
	K band		B band		K band		B band	
Solvent	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}
Cyclohexane	*ca. 230*[c]	*4000*	346	3700	*ca. 234*[c]	*3350*	351	2900
	271	7400			278	6550		
Ether	*ca. 234*[c]	*3000*	346	3550	*ca. 236*[c]	*2640*	348	1410
	271	6900			278	3300		
Ethanol	*ca. 230*[c]	*3550*	347	3240	*ca. 241*[c]	*1730*	*ca. 277*[c]	*1640*
	272.5	6050			269.5	1730	*ca. 290*[c]	*1130*
							ca. 340	*740*

[a] Values italicized represent inflections. [b] From ref. 19. [c] Ascribed to residual phenol absorption.

represent residual anisole K-band absorption and residual iodobenzene B-band absorption, respectively.[14]

Figure 1 shows that the entire spectrum of *p*-iodoanisole is very similar to that of iodobenzene, that is, the relative positions of the K bands, rather than the relative positions of the B bands, of the parent compounds govern the spectral behavior of the *para*-disubstituted compound. This statement has been found to hold generally for *para*-disubstituted benzenes.

The data of Forbes,[15] and Ferguson and Iredale[16] indicate that other substituted iodobenzenes behave similarly to the iodoanisoles and iodophenols listed in Table II.

As the spectrum of iodobenzene is very different from that of any other monosubstituted benzene, substituted iodobenzenes are excellent model compounds for the study of hybrid spectra. For many other disubstituted benzenes, however, no unambiguous assignment of the absorption bands is possible. For example, Fig. 2 shows that the K band of *o*-chloroanisole resembles that of chlorobenzene and that of anisole. The K band of *o*-chlorophenol resembles that of phenol, in its lack of structure, rather than that of chlorobenzene, although the latter is at longer wave length than that of phenol. The K band of phenol is, however, at an anomalously shorter wave length than would be expected from mesomeric and other considerations[13]; the K band of *o*-chlorophenol is, therefore, probably of phenol type. By analogy, the K band of *o*-chloroanisole can probably be attributed to absorption by an anisole-type chromophore. Table II shows that the B band of *o*-chloroanisole is undoubtedly an anisole-type band.

The occurrence of hybrid spectra in *meta*-disubstituted compounds containing an electron-attacting group has already been mentioned in connection with *m*-nitrophenol (*cf.* also ref. 8,9,12). Evidence that hybridization can occur in the spectra of the corresponding *ortho*-disubstituted benzenes is provided by the spectrum of *o*-nitrophenol, data for which are given in Table III. The inflection at *ca.* 230 mμ in the spectrum of this compound is ascribed to phenol K_D-band absorption, by analogy with the spectrum of *m*-nitrophenol. Since *p*-nitrophenol absorbs as a single chromophore, there is no K_D band in its spectrum.

It is to be expected that, in *ortho*- and *meta*-disubstituted benzenes, strong absorption by the chromophore containing the electron-attracting substituent will often completely submerge the residual absorption of the other chromophore. If absorption by the former chromophore could in some way be prevented, or greatly reduced, this residual absorption should become apparent. This can be shown to be so by a comparison of the spectra of 2-nitro-3-methylphenol[17] in different solvents, which are shown in Fig. 3 (taken from ref. 19). In cyclohexane solution the spectrum is very similar to that of *o*-nitrophenol (Table II) except for a slight decrease of molar absorptivity due to steric hindrance (*cf.* also ref. 18).

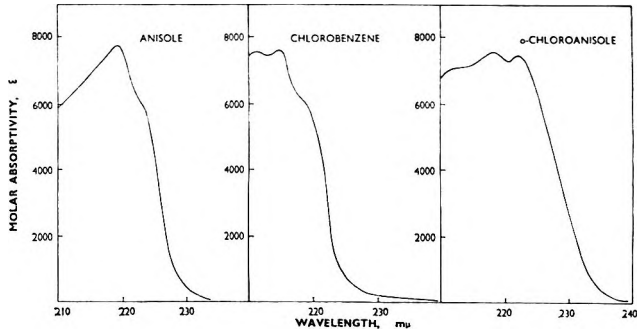
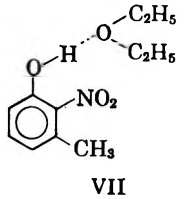
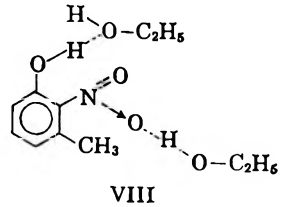


Fig. 2.—The K bands of anisole, chlorobenzene, and *o*-chloroanisole in cyclohexane solution.

In ether solution a marked decrease in molar absorptivity occurs, which is attributed to an increase in the effective size of the hydroxy group due to competitive intermolecular hydrogen bonding (VII). In ethanol



VII



VIII

solution, at least two intermolecular hydrogen bonds can be formed (VIII) and the resulting steric interactions force the nitro group to be far from coplanar with the benzene ring. Absorption by the nitrobenzene chromophore is thus reduced to such an extent that the residual phenol B-band absorption becomes evident as fine structure. This phenomenon has been noted for several other substituted 2-nitro-3-methylphenols.[19]

(14) Forbes[15c] has pointed out that the B band of *m*-chloroiodobenzene is approximately a summation of the B bands of chlorobenzene and iodobenzene.

(15) (a) W. F. Forbes, *Can. J. Chem.*, **38**, 1104 (1960); (b) W. F. Forbes, *ibid.*, **39**, 1131 (1961); (c) W. F. Forbes, *ibid.*, **39**, 2295 (1961).

(16) J. Ferguson and T. Iredale, *J. Chem. Soc.*, 2959 (1953).

(17) Since the methyl group is only weakly electron donating, its electronic effect on the spectrum may be neglected here, and 2-nitro-3-methylphenol can therefore be regarded as a disubstituted benzene, for the purpose of this argument.

(18) B. M. Wepster, *Rec. trav. chim.* **76**, 335, 357 (1957).

(19) J. C. Dearden and W. F. Forbes, *Can. J. Chem.*, **38**, 1837, 1852 (1960).

TABLE IV

THE ABSORPTION MAXIMA OF SOME DERIVATIVES OF *o*-NITROPHENOL IN CYCLOHEXANE SOLUTION[a]

Compound	K_D band		K_A band		B band	
	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}
4-Nitroresorcinol	231.5	9000	298	12800	...	...
			337	10700		
2-Nitro-5-methoxyphenol[b]	233	5250	307	8500	...	...
	237	5150	340	9000		
3-Methoxy-4-nitrophenol[c,d]	238	6400	*ca. 285*	*4840*	...	...
			328	6900		
2,4-Dimethoxynitrobenzene[b]	231	8700	272	6000	...	...
			308	5450		
2-Nitro-5-phenoxyphenol[c,e]	238	8900	*ca. 315*[f]	*10700*[f]	...	...
			350	14100		
2-Nitro-4-methoxyphenol[b]	244	5900	276.5	6500	388	3900
2,5-Dimethoxynitrobenzene[b]	*ca. 237*	*6300*	*ca. 256*	*2100*	339	2660
2-Nitro-5-chlorophenol[b]	*ca. 228*	*4700*	*281*	9750	340	5170
2-Nitro-5-methylphenol[b]	*ca. 233*	*3000*	281	9000	347	4550
2-Nitroresorcinol[b]	*ca. 230*	*6440*	314	10750	405	1620

[a] Values italicized represent inflections. [b] Ref. 19. [c] In ethanol solution. [d] This compound is almost completely insoluble in cyclohexane; a saturated solution showed very low absorbance bands at *ca.* 270 mμ and *ca.* 310 mμ. [e] Ref. 22. [f] Estimated from graph.

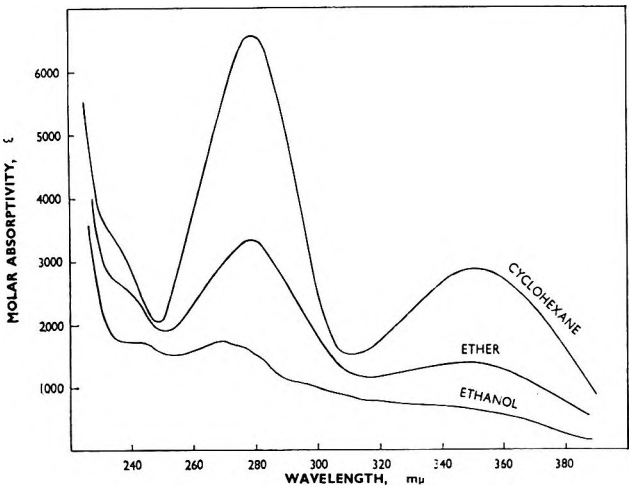


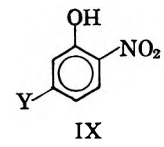
Fig. 3.—The spectra of 2-nitro-3-methylphenol in cyclohexane, ether, and ethanol solutions.

The existence of two absorbing species has thus been demonstrated in a number of *ortho-* and *meta*-disubstituted benzenes where both substituents are electron donating, and also where one of the substituents is electron attracting. There seems no reason why hybridization should not occur when both substituents are electron attracting. However, no conclusive evidence has been found for this. For example, the spectrum of *m*-nitroacetophenone in cyclohexane solution[8] shows an inflection at *ca.* 254 mμ (ε 7000) attributed to nitrobenzene-type absorption, and a peak at 224 mμ (ε 23000) which may be due to acetophenone-type absorption, but which may alternatively be a Rydberg band (possibly with acetophenone-type absorption submerged in it).

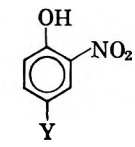
The above evidence suggests that hybrid spectra are by no means uncommon in disubstituted benzenes. It is unfortunate that the number of cases in which hybridization can be detected with certainty is very limited.

The Spectra of Trisubstituted Benzenes

The spectra discussed in this section are those of compounds containing one electron-attracting substituent,[20] since the observations made here arose initially from a previously reported study of the spectra of substituted *o*-nitrophenols.[19] It was noticed that the spectra of certain of these *o*-nitrophenols exhibited two K_A bands (Table IV and Fig. 4). Specifically, this phenomenon occurred when two conditions were satisfied: the third substituent was (i) in the *para* position relative to the nitro group (IX) and was (ii) quite strongly electron donating (*e.g.*, –OH, $-OCH_3$).



IX



X

The phenomenon can be rationalized in terms of the present hypothesis of hybridization if it is assumed that (i) in compounds of type IX, interaction between the hydroxy group and the substituent Y is not complete, and (ii) only if Y is a strongly electron-donating group will it affect the electronic state of the molecule sufficiently for two K_A bands to appear. The occurrence of two K_A bands is therefore ascribed to absorption by two partial chromophores, a *para*-substituted nitrobenzene and an *ortho*-substituted nitrobenzene. In the spectra of compounds of type X, however, only one K_A band is found (Table IV), because the two electron-donating substituents interact to the greatest extent, and act essentially as a single substituent.

In view of these considerations, the first condition for the spectrum of a trisubstituted benzene to display two K_A bands can be generalized as follows: the two electron-donating substituents must not be *para* to each other. From this, it follows that the spectra of compounds of types XI to XV (in which X is electron-attracting and Y and Z are electron-donating substituents) can exhibit two K_A bands, while those of type XVI cannot. Substituents Y and Z may be identical except in compounds of types XIII and XV, in which identical

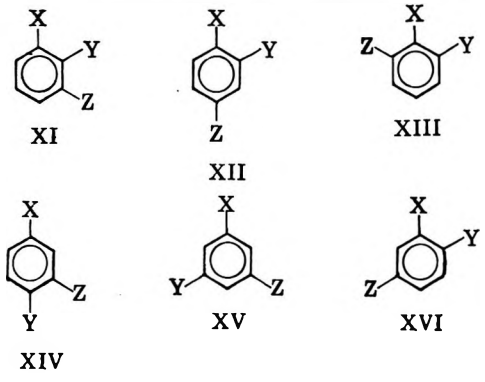
(20) After the completion of the present work, hybridization in the spectrum of 2,4-dinitroaniline, which contains two electron-attracting groups, was reported by E. E. Milliaresi and V. A. Izmail'skii [*Dokl. Akad. Nauk SSSR*, **146**, 1094 (1962)].

TABLE V

THE ABSORPTION MAXIMA OF SOME BENZENE DERIVATIVES WHICH EXHIBIT TWO K_A BANDS, AND OF THEIR REFERENCE COMPOUNDS[a]

Compound	Solvent or pH	K_A band λ_{max} (mμ)	K_A band ϵ_{max}	B band λ_{max} (mμ)	B band ϵ_{max}
2-Chloro-4-nitrophenol[b]	0.1 *N* HCl	317	8500	...	...
	0.1 *N* NaOH	265	4000	301	1400
		400	17400	...	...
m-Chloronitrobenzene[c]	Water	264	7100	313	1300
p-Nitrophenol[c]	pH 3	317.5	10000	...	...
	1 *N* NaOH	402.5	19200	...	...
β-Resorcylic acid[b]	pH 7	248	10800	292	4900
	pH 11	248	15400	...	...
		298	13000		
Salicylic acid[c]	pH 9	230.5	7200	296	3500
	pH 11	242	6900	306	3400
p-Hydroxybenzoic acid[c]	pH 8	245	11900	...	...
	1 *N* NaOH	280	16300	...	...
γ-Resorcylic acid[d]	Cyclohexane	263	8330	334	2300
3,4-Dimethyl-γ-resorcylic acid[d]	Cyclohexane	259[e]	14150[e]	356	5000
		272	10250		
3,5-Dimethyl-γ-resorcylic acid[d]	Cyclohexane	268	11250	353	1150
2,6-Dimethyl-4-nitro-N,N-dimethylaniline[f]	96% ethanol	267	5950	...	...
		380	5450		
4-Nitro-N,N-dimethylaniline[f]	96% ethanol	392	20000	314[g]	1870
2-*t*-Butyl-4-nitro-N,N-dimethylaniline[f]	96% ethanol	272	8650	...	...
		ca. 340[g]	*1630*		

[a] Values italicized represent inflections. [b] Ref. 11. [c] L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, 69, 2714 (1947); 71, 2414 (1949). [d] Ref. 21. [e] Estimated from graph. [f] Ref. 18. [g] Band assignment doubtful.



substituents would each exert exactly the same effect on the electron-attracting substituent. For example, the spectrum of 2-nitroresorcinol has only one K_A band (Table IV), while those of 4-nitrocatechol and 4-nitroresorcinol have two (Tables IV and VI). In addition, the data of Cram and Cranz,[21] which are given in Table V, show that while the spectra of γ-resorcylic acid and its 3,5-dimethyl derivative display only one K_A band, the spectrum of the 3,4-dimethyl derivative (in which the effects of the two hydroxy groups are no longer identical) exhibits two K_A bands.

The data of many workers[11,21-26] entirely bear out these findings. An examination of their results has shown that the spectra of compounds of type XVI never exhibit more than one K_A band. In compounds of types XI to XV, on the other hand, the data include numerous spectra that exhibit two K_A bands; some examples are listed in Table V. However, the phenomenon is not evident in every case. This may be because one of the K_A bands is so much weaker than the other that it is submerged or is mistaken for a B band. An interesting example of this is provided by the spectrum of 2-chloro-4-nitrophenol, the data for which are reproduced in Table V, together with the spectra of its "constituent compounds." In acid solution, this compound apparently exhibits only one K_A band, attributed to *p*-nitrophenol-type absorption. (A band at 231 mμ is ascribed to K_D-band absorption by the chlorobenzene or *o*-chlorophenol chromophore.) In alkaline solution, however, two more bands are evident in the spectrum; the band at 265 mμ can only be attributed to K_A-band absorption by a *meta*-substituted nitrobenzene chromophore, while the peak at 301 mμ is attributed to B-band absorption by the same chromophore. Clearly in acid solution these bands are submerged by *p*-nitro-

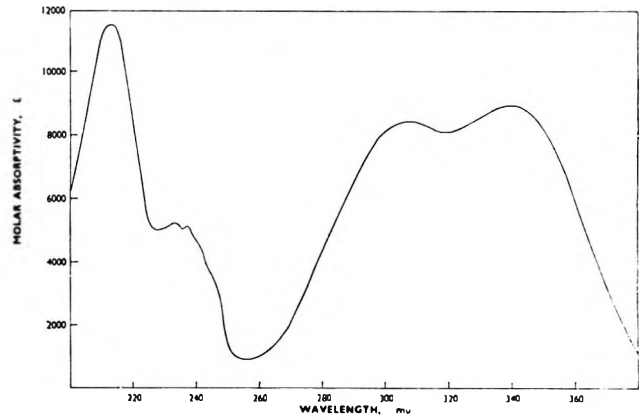


Fig. 4.—The spectrum of 2-nitro-5-methoxyphenol in cyclohexane solution.

(21) D. J. Cram and F. W. Cranz, *J. Am. Chem. Soc.*, 72, 595 (1950).
(22) H. E. Ungnade and I. Ortega, *J. Org. Chem.*, 17, 1475 (1952).
(23) A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.*, 2310, 3734 (1952).
(24) L. Andersen, *Suomen Kemistilehti*, B29, 94 (1956).
(25) H. W. Lemon, *J. Am. Chem. Soc.*, 69, 2998 (1947).
(26) G. Favini, *Rend. ist. lombardo sci. Letters A*, 92, 23 (1957); A. E. Lutskii, *Zh. Fiz. Khim.*, 19, 286 (1945); R. A. Morton and A. McGookin, *J. Chem. Soc.*, 901 (1934); H. H. Hodgson, *ibid.*, 520 (1937); F. M. Rowe, D. A. W. Adams, A. T. Peters, and A. E. Gillam, *ibid.*, 90 (1937); W. A. Schroeder, P. E. Wilcox, K. N. Trueblood, and A. O. Dekker, *Anal. Chem.*, 23, 1740 (1951); D. J. Cram, *J. Am. Chem. Soc.*, 70, 4240 (1948); R. F. Patterson and H. Hibbert, *ibid.*, 65, 1862 (1943); A. Butenandt, E. Biekert, M. Dauble, and K. H. Kohrmann, *Ber.*, 92, 2172 (1959); N. Kaneniwa, *J. Pharm. Soc. Japan*, 76, 253 (1956).

TABLE VI

THE EFFECT OF ALKALI ON THE K_A BANDS OF SOME PHENOLS WHICH EXHIBIT HYBRID SPECTRA[a]

Compound	Solvent or pH	1st K_A band		2nd K_A band[b]	
		λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}
2-Methoxy-4-nitrophenol[c]	0.1 *N* HCl	*310*	*5500*	345	7100
	0.1 *N* NaOH	*320*	*1450*	433	17400
3-Methoxy-4-nitrophenol	Ethanol	*ca. 285*	*4840*	328	6900
	0.1 *N* alcoholic NaOH	263	4100	393.5	21300
2-Nitro-5-methoxyphenol	Cyclohexane	340	9000	307	8500
	0.25 *N* NaOH	317	6350	403	7570
3-Methoxy-4-hydroxybenzaldehyde[d]	Ethanol	277[e]	10800[e]	310	10900
	Alkaline ethanol	294[e]	2800[e]	353	30200
3-Methoxy-4-hydroxyacetophenone[e]	Ethanol	276[e]	10100[e]	303	8500
	Alkaline ethanol	*ca. 295*[e]	*3360*[e]	348	24000
2-Amino-4-nitrophenol[f]	pH 5	256	9800	315	5100
	pH 11	275	6900	446	13400

[a] Values italicized represent inflections. [b] Corresponding to chromophore containing the hydroxy group. [c] Ref. 24. [d] Ref. 25. [e] Estimated from graph. [f] Ref. 11.

phenol-type absorption, and appear only when this strong absorption is displaced by the action of alkali. The ability of phenols to ionize in alkaline solution can thus be put to advantage in the identification of bands in hybrid spectra. Table VI gives a number of examples of band identification by this method.

Incomplete conjugation caused by steric hindrance can also lead to the appearance of hybrid spectra, as is shown by the data of Wepster[18] (*cf.* also ref. 23 and 27) on a series of *ortho*-substituted 4-nitro-N,N-dimethylanilines (Table V). The spectrum of 4-nitro-N,N-dimethylaniline itself exhibits only one K_A band; that of the *o-t*-butyl-substituted compound also exhibits only one K_A band (corresponding to nitrobenzene-type absorption, because the N,N-dimethylamino group is no longer conjugated). However, the spectrum of 4-nitro-2,6-dimethyl-N,N-dimethylaniline, which compound is only partially sterically hindered, exhibits two K_A bands, which are ascribed separately to 4-nitro-N,N-dimethylaniline- and nitrobenzene-type absorption.

(27) (a) R. T. Arnold and P. N. Craig, *J. Am. Chem. Soc.*, **72**, 2728 (1950); (b) W. R. Remington, *ibid.*, **67**, 1838 (1945).

Experimental

Spectra were determined in duplicate on a Unicam SP 500 spectrophotometer. The wave-length accuracy is estimated to be ±0.5 mμ at 270 mμ, and ±1 mμ at 350 mμ. The precision of ϵ_{max} values is ±5% or better. Values were generally reproducible to ±2%.

The compounds used in this work were mostly commercial materials. Others were prepared by standard methods. All compounds were purified until their melting points or refractive indices showed them to be pure.

Acknowledgment.—The author thanks Professor W. F. Forbes of the University of Waterloo, Ontario, and Mr. F. R. Heather and Dr. E. G. Vaal of Thornton Research Centre, for their valuable help and advice.

Isomerization and Decomposition Products of Methicillin[1]

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In weakly acidic media, methicillin (1) isomerizes to 2,6-dimethoxyphenylpenicillenic acid (2) which then decomposes spontaneously to 2,6-dimethoxyphenylpenicilloic acid (3), 2,6-dimethoxyphenylpenilloic acid (4), 2,6-dimethoxyhippuric acid (5), N-formyl-D-penicillamine (6), and 3,10-bis(2,6-dimethoxybenzamido)-6,6,13,13-tetramethyl-2,9-dioxo-5,12-dithia-1,8-diazatricyclo[9.3.0.0^{4,8}]tetradecane-7,14-dicarboxylic acid (7, see Scheme I). No penillic acid, penilloaldehyde, or penicillamine was detected as a product of this decomposition.

Methicillin (sodium 2,6-dimethoxyphenylpenicillinate, 1) is a semisynthetic penicillin which has gained clinical importance because of its resistance to destruction by the enzyme penicillinase.[2] Although highly effective when given by injection, it is ineffective when administered orally, probably because of its extreme lability toward acid. We wish to report on the course of the acid decomposition reactions.

The chemistry of the natural penicillins has been exhaustively investigated.[3] Under various acidic conditions, benzyl- and 2-pentenylpenicillins were reported to isomerize to their respective penillic acids or to decompose to D-penicillamine and the appropriate penilloaldehyde. In a more recent study of the decomposition of natural and semisynthetic penicillins in acidic solutions, Dennen and Davis indicated that the penillic and penicilloic acids were the main products formed.[4] An excellent and comprehensive study of spontaneous benzylpenicillin decomposition under mild conditions was recently reported by Hitomi, who identified ten products.[5]

(1) The trademark of Bristol Laboratories, a Division of Bristol-Myers Company, for methicillin is Staphcillin®.

(2) H. G. Steinman, *Proc. Soc. Exptl. Biol. Med.*, **106**, 227 (1961).

(3) "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949.

(4) D. W. Dennen and W. W. Davis, *Antimicrobial Agents Chemotherapy*, 531 (1961).

(5) H. Hitomi, *Yakugaku Zasshi*, **79**, 1600 (1959); *Chem. Abstr.*, **54**, 10,996g (1960).

We have studied the decomposition of methicillin in weakly acidic aqueous or solvent solutions. The progress of the reaction was followed by thin-layer chromatography. Silica gel coated plates were spotted periodically, starting with zero time. Within a 48-hr. period, six zones were observed besides that of the starting material. Figure 1 shows their relative order on a typical plate.

Zone C was the first foreign zone to appear and could only be observed if the reaction mixture had not aged more than 2 days. This labile behavior corresponded with that of a yellow substance, produced in the degradation, which absorbed in the 333-mμ region (methicillin absorbs only at 283 mμ owing to the 2,6-dimethoxybenzoyl chromophore). The absorptivity at 333 mμ reached a peak and then decreased asymptotically with time. The yellow color and ultraviolet absorption were indicative of a penicillenic acid structure.[5,6] Using a known procedure for the preparation of penicillenic acids,[7] a yellow crystalline compound, which had strong absorption at 333 mμ, was obtained from methicillin. This compound gave a spot in the same position as that of zone C. It gave a deep blue transient color with ferric chloride reagent, which would indicate that a free thiol group was present. Additional chemical and physical tests, spectral evidence, elemental analysis, and the manner in which it was prepared indicated that the compound which produced zone C was 2,6-dimethoxyphenylpenicillenic acid (**2**).

The degradation of methicillin probably involves the penicillenic acid as a primary intermediate. This was indicated by the fact that when pure 2,6-dimethoxyphenylpenicillenic acid was subjected to decomposition conditions, similar to those used on methicillin, all of the same zones were observed on silica gel plates after about 2 days.

The penicilloic and penilloic acids (**3** and **4**, respectively) are normal penicillin degradation products, and their identification in the methicillin acid decomposition mixture was expected. The latter compound was most easily prepared and isolated by the treatment of methicillin with aqueous base, followed by decarboxylation. It gave a spot on a silica gel plate which corresponded with zone E. It was characterized by chemical and physical data and elemental analysis. The presence of a penilloic acid in a penicillin decomposition mixture usually presupposes the presence of the penicilloic acid as its precursor. The solid, which was decarboxylated to the penilloic acid **4**, showed the presence of a second zone on silica gel plates, which had the same R_f value as zone D. This solid gave a positive test with arsenomolybdic acid–mercuric chloride reagent which is reputed to be specific for penicilloic acids.[8] Owing to its labile nature, however, it could not be purified sufficiently for elemental analysis. 2,6-Dimethoxyphenylpenicilloic acid (**3**) was assigned to zone D.

A white solid was obtained, after aqueous acid degradation of methicillin, which was found to be homogeneous by thin-layer chromatography (zone F). It did not contain sulfur and its empirical formula $C_{11}H_{13}NO_5$, neutralization equivalent, and molecular weight determinations indicated that it was a fragment of the methicillin molecule. This compound contained no aldehyde or ketone group, but did contain an acidic group. Its ultraviolet and infrared spectra showed that it still contained the 2,6-dimethoxybenzamido group.

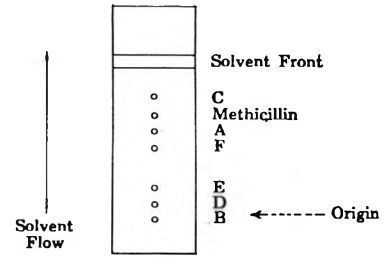


Figure 1.

The proof that zone F resulted from 2,6-dimethoxyhippuric acid (**5**), was attained by synthesis of this hippuric acid from known materials. 2,6-Dimethoxybenzoyl chloride was treated with benzyl glycinate to form benzyl 2,6-dimethoxyhippurate. Catalytic hydrogenolysis of the latter compound offered 2,6-dimethoxyhippuric acid (**5**) which was identical with compound F in every respect (melting point, R_f values, ultraviolet and infrared absorption properties, and solubilities).

The filtrates, resulting from the isolation of 2,6-dimethoxyhippuric acid from methicillin decomposition mixtures, were usually enriched in another compound which produced zone A on silica gel plates. This compound contained a free thiol group, and, even though it was never obtained completely pure, sulfur analyses indicated that this compound (A) was also only a part of the original penicillin. It was therefore assumed to be the remaining fragment after the 2,6-dimethoxyhippuric acid separates. The normal sulfur-containing fragment isolated from the degradation of benzyl or 2-pentenylpenicillin is D-penicillamine. However, compound A was not D-penicillamine; because it was not so soluble in water as the latter compound, it did not condense with carbonyl compounds (typical of D-penicillamine), nor did it give a zone in the same position as that of authentic D-penicillamine on a silica gel plate. Its neutralization equivalent, specific rotation, and solubilities agreed fairly well with N-formyl-D-penicillamine (**6**).

Authentic N-formyl-D-penicillamine was prepared by the formylation of D-penicillamine according to a known procedure.[9] Its melting point, behavior with ferric chloride and 2,4-dinitrophenylhydrazine reagents, and R_f value on a thin-layer plate were essentially identical. The final and conclusive proof that compound A was N-formyl-D-penicillamine (**6**) was supplied by infrared analysis. The spectrum of A was exactly the same as that of authentic N-formyl-D-penicillamine, except for a band at 1110 cm.$^{-1}$ in the former spectrum, which was due to the methoxyl group of the contaminating 2,6-dimethoxyhippuric acid (**5**).

N-Formyl-D-penicillamine, which has also been isolated as a degradation product of procaine benzylpenicillin,[5] and 2,6-dimethoxyhippuric acid were probably formed from 2,6-dimethoxyphenylpenicillenic acid (**2**), by hydration of the latter followed by a reverse aldol condensation.

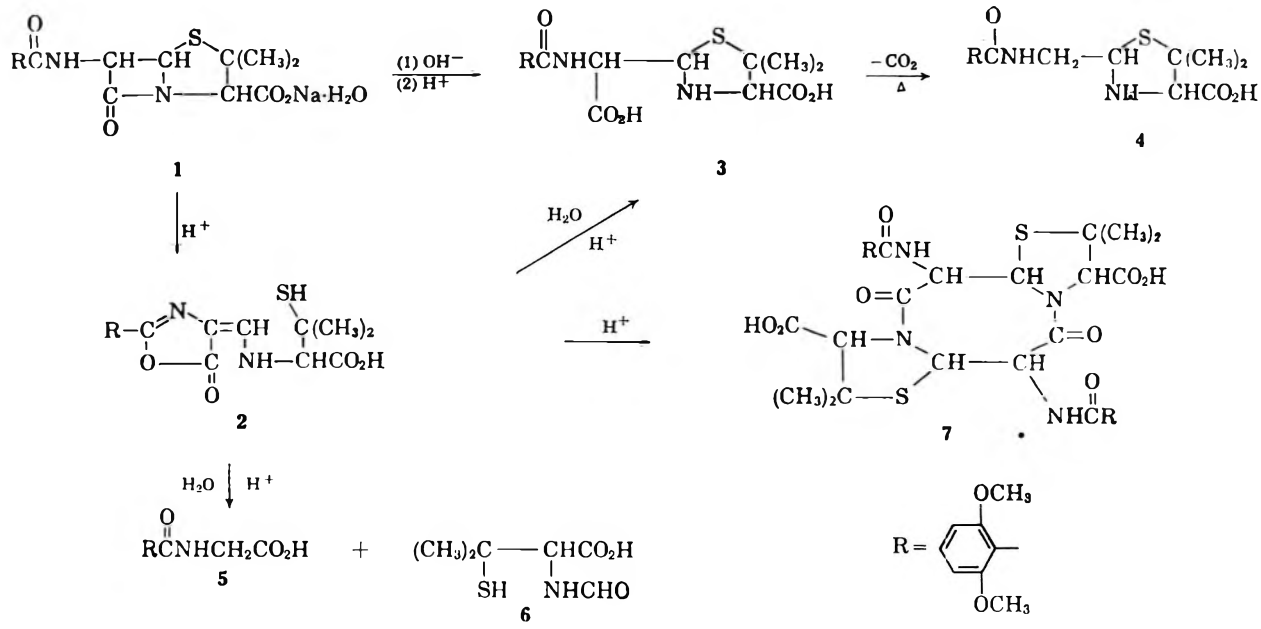
(6) N. Narasimhachari and G. Ramana Rao, *Hindustan Antibiot. Bull.*, **4**, 163 (1962); *Chem. Abstr.*, **57**, 16,758*b* (1962).

(7) B. B. Levine, *Arch. Biochem. Biophys.*, **93**, 50 (1961).

(8) S. C. Pan, *Anal. Chem.*, 26, 1438 (1954).

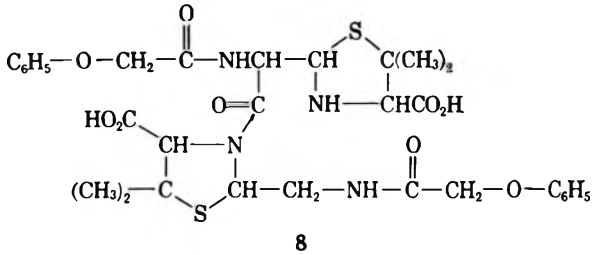
(9) Ref. 3, p. 467.

SCHEME I



Another crystalline reaction product separated during storage of a methyl isobutyl ketone solution of methicillin (pH 2.0) for several days. It did not move on a silica gel plate using the normal solvent system. This unknown, compound B, contained no free thiol group, and its infrared spectrum indicated a free carboxyl group. Its ultraviolet spectra contained only the 2,6-dimethoxybenzoyl peak. The fact that a molecular weight determination gave a value slightly larger than twice the neutralization equivalent intimated that compound B was a dimer of methicillin. Elemental analysis supported this fact. When the methyl ester of compound B was prepared, its molecular weight was found to be twice that of methicillin methyl ester, and this value, together with the elemental analysis, gave a molecular formula of $C_{36}H_{44}N_4O_{12}S_2$. Compound B was therefore assigned the structure of 3,10-bis-(2,6-dimethoxybenzamido)-6,6,13,13-tetramethyl-2,9-dioxo-5,12-dithia-1,8-diazatricyclo[9.3.0.0.^{4,8}]tetradecane-7,14-dicarboxylic acid (**7**) which was consistent with the infrared and nuclear magnetic resonance spectra.

The open-chain counterpart of this structure in the phenoxymethylpenicillin series had already been described in the literature,[10] and is called a penilloinamide **8**. The possibility that compound B was the methicillin analog of **8** was abandoned when it was found that both the free acid and the methyl ester of B gave negative tests with iodine–sodium azide reagent. This reagent is specific for thiazolidines with unacylated nitrogen atoms.[11] The basic character expected in the methicillin analog of **8** was not apparent when either the free acid or the methyl ester of compound B was titrated under nonaqueous conditions with perchloric acid.



8

The formation of the tricyclic penicillenic acid dimer **7** from methicillin is unique in the chemistry of penicillins. It appears that no similar compound has been reported as the result of penicillin degradation.

Experimental[12]

The thin-layer chromatograms used in this work were prepared using Camag silica gel D5. Spotting was performed using 3 μl. of a 1% methanolic or aqueous solution. The solvent system[13] which gave best separations was 60% benzene–35% acetone–5% acetic acid, and the zones were spotted with a 0.5% aqueous potassium permanganate solution.

2,6-Dimethoxyphenylpenicillenic Acid (2).—The following procedure was adapted from that of Levine for the preparation of benzylpenicillenic acid.[7] Mercuric chloride, 16.3 g. (0.06 mole), was dissolved in 1 l. of water and this was added to a solution of 21.0 g. (0.05 mole) of methicillin in 1 l. of water. The turbid mixture was stirred at 37° for 3.0 hr. The yellow mercuric mercaptide, which separated, was collected and washed with 1 l. of cold water and 0.5 l. of ether. It was immediately suspended in 400 ml. of chloroform and 100 ml. of water, cooled to 8°, and treated with hydrogen sulfide gas for 15 min. The resulting black, thick slurry was filtered through a Sil-Flo-precoated funnel and the yellow organic layer was washed with water and dried over sodium sulfate. The chloroform solution was added to 2 l. of Skellysolve B (b.p. 60–70°). The yellow penicillenic acid which separated was stirred cold for about 10 min., filtered, washed with Skellysolve B, and dried in a vacuum desiccator over Drierite. It melted at 124.3–129.2° dec. and weighed 10.9 g. Attempts to purify further this solid were unsuccessful and usually led to degradation. It was stored in a nitrogen atmosphere. It gave a deep blue transient color with 5% aqueous ferric chlo-

(10) A. S. Khokhlov and E. V. Kachalina, *Antibiotiki*, **5**, No. 5, 41 (1960).

(11) Ref. 3, p. 927.

(12) All melting points are corrected. Microanalyses were performed by Mr. R. M. Downing, and the infrared, ultraviolet, nuclear magnetic resonance, and molecular weight measurements were made by Mr. D. F. Whitehead. The molecular weight determinations were run using a Mechrolab vapor pressure osmometer, Model 301.

(13) Dr. E. J. Richardson developed the solvent system for methicillin degradation products and prepared and ran all the plates used in this investigation.

ride reagent and essentially one spot (zone C) on a silica gel plate, λ_{max}^{MeOH} 333 mμ (ε 23,350). The infrared spectrum was consistent with the proposed structure.

Anal. Calcd. for $C_{17}H_{20}N_2O_6S \cdot 0.5H_2O$: C, 52.50; H, 5.42; N, 7.20; S, 8.23; H_2O, 2.31; mol. wt., 389.39. Found: C, 52.75; H, 5.12; N, 7.10; S, 7.82; Karl Fischer, 3.0; neut. equiv., 368; mol. wt. (in pyridine), 364.

2,6-Dimethoxyphenylpenilloic Acid (4).—Methicillin, 42 g. (0.1 mole), was dissolved in 100 ml. of water and treated with a cold solution of 4.0 g. (0.1 mole) of sodium hydroxide in 100 ml. of water. The yellow solution was stored at 5° for 16 hr. It was filtered through a Sil-Flo-precoated funnel and combined with 200 ml. of cold methyl isobutyl ketone. The pH was adjusted from 11.0 to 2.0 with 6 *N* hydrochloric acid while the temperature was maintained below 4°. An amorphous white solid separated which slowly crystallized. It was collected and dried. It weighed 24.9 g., melted at 131.3–132.2° dec., and gave a neutralization equivalent of 220, a blue color with arsenomolybdic acid–mercuric chloride reagent,[8] and zones E and D on a silica gel plate. These facts were used to calculate that the solid was approximately 85% penicilloic acid (3) and 15% penilloic acid (4). This solid, 10 g., was refluxed in 50 ml. of water and 40 ml. of 95% ethanol for 2.25 hr. (the ethanol was omitted in later runs). Gas evolution ceased after about 10 min. The solvent was removed by distillation at reduced pressure and was replaced with 50 ml. of methyl isobutyl ketone. A white solid, 3.1 g., separated from the cooled mixture, which was collected and recrystallized from hot water to yield white rods, m.p. 194.9–195.0° dec. It gave no color change with aqueous ferric chloride reagent or with arsenomolybdic acid–mercuric chloride reagent,[8] and gave a spot on a silica gel plate which was in the same position as zone E. It reacted instantaneously with iodine–sodium azide reagent[11] causing decolorization and gas evolution. The ultraviolet, infrared, and nuclear magnetic resonance spectra were consistent with the structure of 2,6-dimethoxyphenylpenilloic acid (4).

Anal. Calcd. for $C_{16}H_{22}N_2O_5S$: C, 54.23; H, 6.26; N, 7.91; S, 9.02; mol. wt., 354.35. Found: C, 53.90; H, 6.10; N, 7.98; S, 8.78; neut. equiv., 354; mol. wt. (in 95% ethanol), 354.

2,6-Dimethoxyhippuric Acid (5). A. From Methicillin.—A solution of 21.0 g. (0.05 mole) of methicillin and 1 l. of water was stored at 37° for 8 days. It was filtered to separate a small amount of insoluble material and the pH of the filtrate was adjusted from 3.7 to 2.0. The filtrate was concentrated under reduced pressure to a volume of 200 ml. and this was cooled for 16 hr. in a refrigerator. Crystalline material separated which weighed 7.0 g. and contained several spots on a thin layer chromatogram. After two recrystallizations from hot methanol, a nicely crystalline white solid was obtained which was homogeneous (zone F), melted at 222.0–223.0° dec., weighed about 1.0 g., gave no color change with 5% aqueous ferric chloride solution, and gave no precipitate with aqueous, alcoholic 2,4-dinitrophenylhydrazine reagent. It was soluble in 5% aqueous sodium bicarbonate and gave a negative test for sulfur after decomposition with sodium.[14] It gave a neutralization equivalent of 248 and molecular weight determinations (in 95% ethanol) of 237 and 242; λ_{max}^{MeOH} 282 mμ (ε 1530) and 240 (1220); the infrared spectrum was consistent with the assignment of the structure of 2,6-dimethoxyhippuric acid (5) to this solid.

B. From Benzyl Glycinate.—Glycine benzyl ester *p*-toluenesulfonate,[15] 33.7 g. (0.1 mole), was added to 300 ml. of methylene chloride, 200 ml. of water, and 14.0 ml. (10.1 g., 0.1 mole) of triethylamine, and the resulting mixture was stirred for 10 min. The organic layer was washed with water, dried over sodium sulfate, and treated with 15.4 ml. (11.2 g., 0.11 mole) of triethylamine.

In another flask, 2,6-dimethoxybenzoyl chloride was prepared. 2,6-Dimethoxybenzoic acid (18.2 g., 0.1 mole), 100 ml. of methylene chloride, 0.4 ml. of dimethylformamide, and 8.0 ml. (13.1 g., 0.11 mole) of thionyl chloride were combined and stirred at room temperature for 20 min. The excess thionyl chloride and solvent were removed *in vacuo* and replaced with 100 ml. of fresh methylene chloride. This solution was then added dropwise to the solution of benzyl glycinate held at 1–7°. The mixture was allowed to come to room temperature and was washed twice with 5% aqueous sodium bicarbonate solution, twice with 15% aqueous sulfuric acid, once with water, and dried. The methylene chloride solution was diluted with 2.5 l. of Skellysolve B (b.p. 60–70°) and white needles of (23.1 g.) benzyl 2,6-dimethoxyhippurate separated, and were collected and dried, m.p. 134.2–134.6°. The ultraviolet, infrared, and n.m.r. spectra were consistent with the proposed structure.

Benzyl 2,6-dimethoxyhippurate, 6.6 g. (0.02 mole), was dissolved in 130 ml. of methanol and 1.5 g. of 30% palladium on Celite and 4 drops of glacial acetic acid were added. The mixture was shaken under 51 p.s.i.g. of hydrogen. The theoretical amount of hydrogen was consumed within the first 5 min. The mixture was filtered hot through a Sil-Flo-precoated funnel. When cooled, white crystals (4.0 g.) separated from the filtrate, and were collected, and dried, m.p. 220.1–222.4° dec. This solid was identical with 2,6-dimethoxyhippuric acid (5) obtained from methicillin, with respect to thin-layer R_f values, ultraviolet and infrared absorption properties, and solubilities.

N-Formyl-D-penicillamine (6). A. From Methicillin.—The procedure for the preparation of 2,6-dimethoxyhippuric acid (5) from methicillin (*vide supra*) was followed, but the aqueous filtrate was concentrated further to separate 4.3 g. of a ferric chloride-positive solid, which melted at 143.0–151.4° dec. A 0.6-g. portion of this solid was recrystallized from 20 ml. of hot water using 0.3 g. of Darco KB. The white product, 0.4 g., m.p. 152.6–153.5° (with gas evolution), gave a very deep blue transient color with 5% aqueous ferric chloride reagent, but no precipitate with 2,4-dinitrophenylhydrazine reagent. Its silica gel chromatogram showed essentially two spots, the slowest one being that from 2,6-dimethoxyhippuric acid. Its neutralization equivalent was 190 (theory is 177), $[\alpha]^{25}D$ +50.0° (*c* 0.3, pyridine).

Anal. Found: S, 15.45.

B. From D-Penicillamine.—N-Formyl-D-penicillamine was prepared from D-penicillamine *via* a known procedure.[9] The recrystallized product gave $[\alpha]^{25}D$ +63.97° (*c* 1, pyridine) and melted at 154.1–154.5° (with gas evolution). The melting point was not depressed after being admixed with similar material from methicillin. It was identical with N-formyl-D-penicillamine from methicillin in its behavior with ferric chloride and 2,4-dinitrophenylhydrazine reagents, in R_f value on silica gel plates, and in infrared spectrum (except for the 1110-cm.$^{-1}$ band in the material prepared from methicillin, which was due to the contamination of 2,6-dimethoxyhippuric acid, 5).

3,10-Bis(2,6-dimethoxybenzamido)-6,6,13,13-tetramethyl-2,9-dioxo-5,12-dithia-1,8-diazatricyclo[9.3.0.0^{4,8}]tetradecane-7,14-dicarboxylic Acid (7).—Methicillin (105 g., 0.25 mole) was taken up in 700 ml. of methyl isobutyl ketone at pH 2.0. The solution was dried and stored at room temperature for 7 days. A yellow solid separated, which was collected and dried. It weighed about 42 g. It was dissolved in 500 ml. of methanol and reprecipitated as a cream-colored semicrystalline solid by addition of two volumes of water. When dry, it melted at 176.7–178.3° dec. This procedure was repeated three more times, the last time using Darco KB. A white semicrystalline solid was obtained, m.p. 188.8–189.6° dec.; λ_{max}^{MeOH} 337 and 283 mμ; no color change with 5% aqueous ferric chloride solution. The 337-mμ peak became less intense with each successive crystallization. When the filtrate from this solid was concentrated *in vacuo*, a small amount (about 1.2 g.) of a white crystalline solid was obtained, m.p. 191.0–192.1° dec.; λ_{max}^{MeOH} 284 (ε 6700); ν_{max}^{KBr} 3400 (NH), 2900–3100 (CH), 1740 (C=O), 1660 (C=O), 1515 (NH), 1250 (Ph–O), and 1115 cm.$^{-1}$ (CH_3O). It gave no color change with the ferric chloride reagent and did not decolorize iodine–sodium azide reagent.[11] This solid gave one slightly elongated spot at the origin (zone B) on a silica gel plate. It also gave but one zone when run in a 95% methanol and 5% acetic acid solvent system in which its R_f value was much larger. No inflection of the titration curve was observed when this solid was titrated with perchloric acid in glacial acetic acid.

Anal. Calcd. for $C_{34}H_{40}N_4O_{12}S_2 \cdot 2H_2O$: C, 51.26; H, 5.56; N, 7.03; mol. wt., 796.7; H_2O, 4.5. Found: C, 51.25; H, 5.52; N, 6.57; neut. equiv., 383; mol. wt. (in 95% ethanol), 868; H_2O (Karl Fischer), 5.9.

Methyl Ester of 7.—N-Methyl-N-nitrosourea[16] (4.5 g. 0.044 mole) was slurried in 60 ml. of ether and cooled to 10° while 9.0

(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 57–58.

(15) L. Zervas, M. Winitz, and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

(16) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 461.

ml. of 50% aqueous potassium hydroxide solution was added. The yellow ether layer was slowly decanted into a solution of 5.6 g. (0.007 mole) of the tricyclotetradecane dicarboxylic acid **7** in 50 ml. of methanol. After 15 min., the cooling bath was removed and 1.7 ml. of glacial acetic acid was added to the yellow solution. After another 15 min., the solution was concentrated under reduced pressure to a thick orange-yellow oil, 5.5 g. This was taken up in carbon tetrachloride, and a semicrystalline solid separated when the solution was diluted with Skellysolve B. This solid was then recrystallized once from 200 ml. of chloroform and 800 ml. of Skellysolve B, and once from 70 ml. of chloroform and 100 ml. of ether. When the filtrate from the second recrystallization was diluted with Skellysolve B, a small amount (0.5 g.) of a white crystalline solid was obtained, m.p. 136.7–138.6° dec.; λ_{max}^{MeOH} 283 mμ (ε 8650); ν_{max}^{KBr} 3400 (NH), 2900–3100 (CH), 1745 (C=O), 1665 (C=O), 1525 (NH) 1255 (Ph-O), and 1115 cm.$^{-1}$ (CH_3O). No color change with 5% aqueous ferric chloride reagent was produced and iodine–sodium azide reagent was not decolored. N.m.r. data shows δ 1.5 (CH_3) 12H; 3.8 (OCH_3) 18H, (N-CH) 6H; 6.6 (NH) 2H, (=CH-) 4H; 7.3 (=CH-) 3H (theory requires 2H). No inflection of the titration curve was observed when this solid was titrated with perchloric acid in glacial acetic acid.

Anal. Calcd. for $C_{36}H_{44}N_4O_{12}S_2$: C, 54.82; H, 5.62; N, 7.10; mol. wt., 788.9. Found: C, 55.30; H, 5.78; N, 7.28; mol. wt. (in 95% ethanol), 798.

Synthesis of Thioethers. Amide Solvent-Promoted Nucleophilic Displacement of Halide by Thiolate Ion

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A new general procedure for synthesizing aryl thioethers *via* nucleophilic displacement of aryl halide by thiolate ion is reported. The reaction is shown to be dependent upon amide solvents exclusively with more than simple catalysis involved. Many different thioethers, both old and new, have been prepared in very good yield by this method.

Methods for the preparation of aryl thioethers have generally suffered from limited applicability in that activated reactants, severe reaction conditions, complicated procedures, or a combination of these requirements were involved.[1-5] Parker[6] has stated that unsymmetrical aryl sulfides can be prepared in high yields providing the halogen substrate is activated by at least one powerful electron-withdrawing substituent.

A recent method[7] developed in these laboratories involving reaction of disulfides with copper in the presence of halides has provided a means of synthesizing many different thioethers in a convenient way. An even more convenient and general sulfide preparation is described in the present paper. The method involves simply heating an alkali metal thiolate (either aliphatic or aromatic) and a halide together in an amide solvent. Results are summarized in Tables I and II.

$$\underset{(R)}{ArSK} + Ar'X \xrightarrow[\text{solvent}]{\text{amide}} \underset{(R)}{ArSAr'} + KX$$

An indication of the generality of the method is evident from the variety of sulfides reported. Not only is the method valuable for the preparation of polyaryl sulfides, but it also provides a convenient way to alkyl aryl sulfides from alkane thiols and aryl halides.

Examination of the data in Table I covering experiments on the preparation of bis(phenylmercapto)benzenes in certain solvents illustrates this method's amide solvent dependency. First attempts at aryl thioether synthesis involved Ullmann-like conditions found in aryl ether preparations where aryl halide and potassium aryl thiolate were heated in excess thiol at temperatures above 200° in the presence of copper salts. No reaction occurred, presumably because of the extreme insolubility of the potassium thiolate even under drastic conditions. Various high boiling solvents then were employed to attempt solution of the salt, but without avail until dimethylformamide was employed. The effectiveness of this solvent in solubilizing all reactants and in promoting formation of aryl thioethers from aryl thiolates and activated aryl halides has been described previously,[5,8] but was thought to be limited to activated halides. As shown in Table I, dimethylformamide serves in unactivated cases also, giving poorer yields of product.

Higher amide solvents, *i.e.*, N,N-dimethylacetamide, N,N-dimethylbutyramide, N,N-dibutylacetamide, and N-methyl-2-pyrrolidone, proved even more effective presumably because of their higher boiling points, thus higher reaction temperatures. For reasons of availability and ease of removal, dimethylacetamide was considered to be the solvent of choice and then was used most frequently. The utility of these amides apparently stems from two properties: (1) their ability to solubilize potassium aryl thiolates, and (2) their evident participation in the reaction. The first property has already been mentioned, but the second requires elaboration.

Prior to discussion of solvent participation it should be pointed out that the reaction appears to be a bimolecular nucleophilic substitution. Examination of data in Table I shows that it differs from an Ullmann-type reaction since no copper catalyst is really necessary. Preliminary kinetic and spectral data indicate the reaction is second order and that no other mechanisms are operating. Detailed kinetics and a suggested

(1) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. II, Chemical Publishing Co., Inc., New York, N. Y., 1960, p. 28.

(2) E. Müller, *et al.*, "Methoden der Organischen Chemie" (Houben-Weyl), Vol. IX, Georg Thieme Verlag, Stuttgart, 1955, pp. 97–118.

(3) J. F. Bunnett and W. D. Merritt, Jr., *J. Am. Chem. Soc.*, **79**, 5967 (1957).

(4) R. Adams, W. Reifschneider, and M. D. Nair, *Croat. Chem. Acta*, **29**, 277 (1957); R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, **81**, 4927 (1959).

(5) J. H. Uhlenbrock, *Rec. trav. chim.*, **80**, 1057 (1961).

(6) N. Kharasch, "Organic Sulfur Compounds," Vol. I, Pergamon Press, Inc., New York, N. Y., 1961, p. 107.

(7) J. R. Campbell, *J. Org. Chem.*, **27**, 2207 (1962).

(8) J. R. Campbell and R. E. Hatton, *ibid.*, **26**, 2480 (1961).

TABLE I

m- OR *p*-BIS(PHENYLMERCAPTO)BENZENES

m- or *p*-$XC_6H_4Y + C_6H_5SK \longrightarrow$ *m*- or *p*-$C_6H_5SC_6H_4SC_6H_5$ (A) + *m*- or *p*-$XC_6H_4SC_6H_5$ (B)

Isomer	Halide X	Halide Y	Halide mole	Thiol, mole	Solvent	Catalyst, ml.	Time, hr.	Yield A, %	Yield B, g.	Starting halide recovered, %
p	Cl	C_6H_5S	0.16	0.2	DMF[a]	None	24	25.7		40.3
m	Br	Br	0.11	0.21	DEA[b]	$CuCl_2$	10	57[c]	11.2	
m	Cl	C_6H_5S	0.32	0.6	DEA	$CuCl_2$	20	15		66.5
m	Cl	Cl	0.20	0.5	DEA	None	15	Trace		
m	Cl	Cl	0.50	1.1	DMA[d]	CuCl–KI	24	40.7	57.9	
m	Br	Br	0.11	0.3	DMA	$CuCl_2$	24	97	2.8	0
m	Br	Br	0.11	0.3	DMA	$CuCl_2$	13	98	0	0
m	Br	Br	0.65	1.8	DMA	$CuCl_2$	13	95	13.2	0
m	Cl	Cl	0.65	1.8	DMA	$CuCl_2$	14	79.3	31.4	
m	Br	Br	0.11	0.3	DMA	None	20	Quant.	0	0
m	Cl	Cl	0.2	0.5	DMA	None	15	92.7	18.8	
p	Cl	Gl	0.2	0.5	DMB[e]	None	15	81	0	0
p	Cl	Cl	0.2	0.5	NMP[f]	None	15	94.5	0	0
m	Cl	Cl	0.2	0.5	EG[g]	None	15	0	0	74.8
m	Cl	Cl	0.2	0.5	EG	$CuCl_2$	15	0	0	86.1
m	Cl	Cl	0.2	0.5	EG	DMA (25)	15	0	*h*	77.6
m	Cl	Cl	0.2	0.5	EG	DMA (50)	15	0	*h*	85.8
m	Cl	Cl	0.2	0.5	DG[i]	None	15	0	2.3	88.5
m	Cl	Cl	0.2	0.5	DG	DMA (50)	15	11.2	32	
m	Cl	Cl	0.2	0.5	DG	NMP (15)	15	0	12	72.2
m	Cl	Cl	0.2	0.5	DG	NMP (50)	15	14.8	31.5	34.7

[a] Dimethylformamide, reaction temp. *ca.* 160°. [b] Diethylaniline, reaction temp. 210–216°. [c] Product contained many amine impurities. [d] N,N-Dimethylacetamide, reaction temp. 170–175°. [e] N,N-Dimethylbutyramide, reaction temp. *ca.* 180°. [f] N-Methyl-2-pyrrolidone, reaction temp. 185–190°. [g] Ethylene glycol, reaction temp. 180–190°. [h] Only product was $C_6H_5SCH_2CH_2OH$, b.p. 85–88° (0.25 mm.), $n^{22}D$ 1.5915; W. R. Kirner and G. H. Richter [*J. Am. Chem. Soc.*, **51**, 3409 (1929)] report b.p. 115–116° (2 mm.), $n^{20}D$ 1.5917. [i] Diglyme, reaction temp. 155–160°.

reaction mechanism consistent with results will be the subject of the second paper of this series.

The last eight examples of Table I illustrate very well the peculiar ability of amide solvents in this thioether synthesis. Solvents employed in these examples were ethylene glycol and diglyme both of which differed from most solvents in that they dissolved potassium benzenethiolate when employed in optimum quantities. It is noteworthy that no reaction occurred in the neat solvents with or without cupric chloride! When dimethylacetamide was added to the reaction in ethylene glycol (25–50 ml. to 200 ml.), a most unusual product, 2-phenylmercaptoethanol, was the only material isolated. Evidently displacement of one of ethylene glycol's hydroxy groups by the thiophenoxide ion is promoted by dimethylacetamide. This may constitute the first example of hydroxyl displacement by thiol, especially among aliphatic alcohols.

More important is the effect that added amide solvents had on the nucleophilic substitution in diglyme. Some intermediate monosubstituted product, B, was produced at low concentrations of amide (15 ml. to 200 ml. diglyme), but as the quantity of added amide was increased, the yield of B almost trebled and 11–15% yield of bissulfide, A, was realized. Although the exact function of amide solvent is not known, it is definitely not one of catalysis here. Zaugg and co-workers[9] have found that less than 5% concentrations of amides exert profound catalytic effects in alkylations of certain enolate anions.

The unique solvent characteristics of dimethylformamide have been known for many years, but only recently has it achieved distinction as a solvent for aromatic nucleophilic substitution reactions. Friedman and Schechter[10] found it was very efficient in the preparation of aryl nitriles from aryl halides and cuprous cyanide. Similar results have also been reported by Newman and Boden[11] for N-methyl-2-pyrrolidone. An investigation by Bacon and Hill[12] on copper-catalyzed aromatic displacements in polar solvents placed dimethylformamide better than dimethylsulfoxide but not so good as pyridines. Finally, Uhlenbrock[5] has shown dimethylformamide to be the preferred solvent in the preparation of halo aryl sulfides from aryl thiolates and aryl halides. This latter procedure is similar to that reported here and deserves some comment: (1) the scope is generally limited to sulfides which could be formed from activated halides, (2) a very large excess of thiolate was employed, and (3) yields were usually only fair.

Dimethylacetamide did not prove so beneficial in typical Ullmann reactions as it did in our thioether synthesis. For instance, a very poor yield of a five-membered ring polyphenyl ether was obtained from potassium *m*-phenoxyphenate and *m*-dihalo benzenes in dimethylacetamide according to usual Ullmann procedures. Without solvent except for excess phenol this preparation proceeded in good yield. Such results again point out the unique function of amide solvents in thioether formation. This can probably be ascribed in part to specific solvation of the cation by solvent in accord with the work and suggestions of others.[9,13,14] Part of the success could also be due to the efficacy of the benzenethiolate ion which is cer-

(9) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Am. Chem. Soc.*, **82**, 2895 (1960); H. E. Zaugg, *et al.*, *J. Org. Chem.*, **26**, 644 (1961).

(10) L. Friedman and H. Shechter, *ibid.*, **26**, 2522 (1961).

(11) M. S. Newman and H. Boden, *ibid.*, **26**, 2525 (1961).

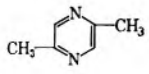
(12) R. G. R. Bacon and H. A. O. Hill, *Proc. Chem. Soc.*, 113 (1962).

(13) H. E. Zaugg, *J. Am. Chem. Soc.*, **83**, 837 (1961).

(14) T. J. Wallace and A. Schriesheim, *J. Org. Chem.* **27**, 1514 (1962).

TABLE II

YIELDS, PHYSICAL PROPERTIES, AND ANALYSES OF THIOETHERS

R	X	Ar	Yield, %	M.p. and b.p. (mm.), °C.	Formula	Sulfur, % Calcd.	Sulfur, % Found
			Monosulfides				
			$RBr(Cl) + C_6H_5SH \longrightarrow R—S—C_6H_5$				
3,4-$(CH_3)_2C_6H_3$			30.4	117–120 (0.45)[a]			
C_6H_5			64.8	173–183 (30)[b]			
2-C_5H_4N			97.8	107–110 (0.3)[c]			
2-CH_3-5-$(CH_3)_2CH—C_6H_3$			78.2	115–120 (0.3)[c]	$C_{16}H_{18}S$	13.23	13.60
			89.0	190–192 (26)	$C_{12}H_{12}N_2S$	14.82	14.70
			Bissulfides				
			$RC_6H_4SH + ArX_2 \longrightarrow Ar(SC_6H_4R)_2$				
p-$(CH_3)C$	*m*-Cl	C_6H_4	67.1	210–237 (0.55)[d]	$C_{26}H_{30}S_2$	15.77	15.60
H	*o*-Cl[e]	C_6H_4	92.0	180–187 (0.25)	$C_{18}H_{14}S_2$	21.79	22.00
H	*m*-Cl	C_6H_4	92.7	180–185 (0.35)[f]			
H	*p*-Cl	C_6H_4	94.5	82–83 [f,g]			
H	*p*-Br	$—C_6H_4OC_6H_4—$	81.6	82–84 [h]	$C_{24}H_{18}OS_2$	16.59	16.90
H	*p*-Br	$—C_6H_4C_6H_4—$	98.7	119–120 [h]	$C_{24}H_{18}S_2$	17.37	17.21
H	Br		74.3	189–195 (0.5)	$C_{16}H_{12}S_3$	32.02	31.79
H	Cl		89.0	51–52[h]	$C_{17}H_{13}NS_2$	21.71	21.27
			Trissulfide				
			$3C_6H_5SH + 1,2,4\text{-}C_6H_3Cl_3 \longrightarrow 1,2,4\text{-}C_6H_3(SC_6H_5)_3$				
			94	243–248 (0.2)	$C_{24}H_{18}S_3$	23.89	23.64

[a] E. Bourgeois [*Ber.*, **28**, 2312 (1895)] reports b.p. 182° (11 mm.). [b] D. R. Stull [*Ind. Eng. Chem.*, **39**, 517 (1947)] gives b.p. 162° (20 mm.) and 195° (40 mm.). [c] L. G. S. Brooker, *et al.* [*J. Am. Chem. Soc.*, **73**, 5326 (1951)], report b.p. 160–162° (8 mm.), 95% yield. [d] Solidified on standing. [e] Orthene. [f] Reported previously in ref. 7. [g] Reported previously in ref. 4. [h] From isopropyl alcohol.

tainly one of the most effective nucleophiles known,[6] especially in dimethylformamide.[15]

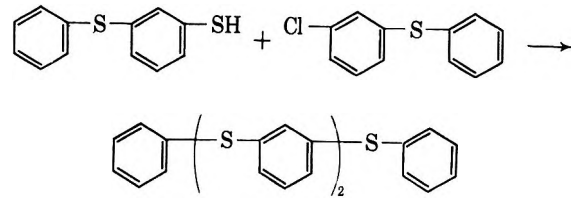
As expected, aryl bromides were more reactive than the chlorides. Thus, a 57% yield of bissulfide was obtained from dibromobenzene in diethylaniline whereas dichlorobenzene under identical circumstances gave none. Diethylaniline did not prove satisfactory as a reaction medium however; products were always contaminated with amine which could not be removed.

Reaction time in hours includes both the period of reflux and the time to distil excess solvent. Preliminary rate data suggest that this can be reduced significantly to a matter of a few hours.

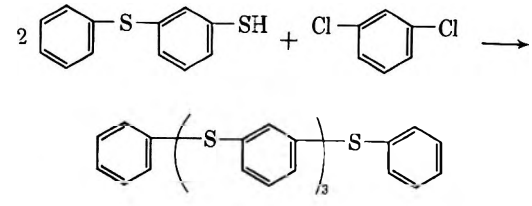
Both expected and wholly unexpected by-products formed in many of the reactions between potassium thiolates and aryl halides. The intermediate monosubstituted material, halo phenyl aryl or alkyl sulfide (*cf.* Table I and Experimental), was often produced when a dihalo benzene was involved in the synthesis of bissulfides. Of course the largest quantities formed in cases where reaction conditions were below optimal or reactants were sluggish. Aryl disulfides were sometimes isolated, usually in small quantities only, *via* oxidation of starting thiols. Completely unexpected was the formation of diphenyl sulfide as the only product from the attempted reaction of potassium benzenethiolate and 2,5-dimethoxychlorobenzene. No reasonable interpretation of this result has been forthcoming.

The generality of this thioether synthesis is exemplified in the variety of compounds reported: various aryl mono-, bis-, tris-, and polysulfides; mono- and bis-phenylmercapto heterocyclics; alkyl aryl sulfides; and phenylmercaptobiphenyl mixtures. It would appear that the only retarding influences to facile reaction and good yields might be (1) a weak thiolate nucleophile made impotent through electron-withdrawing groups, or (2) an unreactive halide containing strong electron donors which cause nucleophile repulsion.

The preparation of the four- and five-membered ring polyphenyl thioethers, bis(*m*-phenylmercaptophenyl) sulfide and *m*-bis(*m*-phenylmercaptophenylmercapto)-benzene, respectively, involved application of the amide procedure as the last step in both. The four-membered ring compound was obtained from potassium *m*-phenylmercaptobenzenethiolate and *m*-chlorophenyl phenyl sulfide in dimethylacetamide and the five-membered



ring thioether from *m*-dichlorobenzene and potassium *m*-phenylmercaptobenzenethiolate in the same solvent.



(15) A. J. Parker, *J. Chem. Soc.*, 4398 (1961).

Previous attempts to prepare these two polysulfides by other methods failed. Thus, no reaction occurred between *m*-chlorophenyl phenyl sulfide and sodium sulfide in trying to synthesize the four-membered ring compound, and only unidentifiable material resulted from an Ullmann reaction with *m*-dithioresorcinol and *m*-chlorophenyl phenyl sulfide for the five-membered ring compound.

Experimental[16]

General Procedure for Synthesis of Sulfides in Tables I and II.—Water of reaction and that from the starting alkali was distilled from a mixture of 0.5 mole of thiol, 0.5 mole of potassium hydroxide, and 200 ml. of dimethylacetamide until the vapor temperature reached 150°. Complete solution occurred from this point until the terminal part of the preparation when salts precipitated.

Very few solvents will dissolve an alkali metal thiolate and only the amides appear to be generally applicable. It can be seen from Table I that the only useful solvents are the carboxamides which include dimethylformamide, N,N-dimethylacetamide, N,N-dimethylbutyramide, N,N-dibutylacetamide, and N-methyl-2-pyrrolidone, whereas such solvents as ethylene glycol, diglyme, etc., are wholly unsatisfactory. With its lower boiling point, dimethylformamide is not so effective as the other high boiling amides.

After the water was removed, the solution of aryl thiolate was cooled to 120–130° and 0.2 mole of aryl dihalide (0.4 mole of aryl monohalide and approximately 0.14 mole of aryl trihalide) were added in one portion. Cooling was employed in this step only in cases where vigorous exothermic reactions occurred with highly reactive halides, *e.g.*, N-heterocyclic halides. The solution was heated immediately to reflux (170–175°) which was maintained for 5–10 hr. Solvent was distilled to a thick slurry to which was added water and benzene.

The benzene layer was separated, washed with water, and evaporated to a residue. Distillation or recrystallization of the latter isolated the pure thioethers. The mono-, bis-, and trisulfides prepared in this way together with physical properties and analytical data are presented in Table II.

In a few of the preparations of bissulfides, some monosubstituted intermediates were obtained along with desired products. These are listed in Table III.

TABLE III

Intermediate	B.p. (mm.), °C.	$n^{25}D$
m-Chlorophenyl phenyl sulfide	108–117 (0.4)[a]	1.6363
p-Chlorophenyl phenyl sulfide	160–170 (10)[b]	1.6387
m-Chlorophenyl *p*-*t*-butylphenyl sulfide	150–170 (0.6)[c]	
3-Chloro-5-phenylmercaptopyridine	125–128 (0.5)[c]	

[a] M. Rolla, M. Sanesi, and G. Leandri [*Ann. Chim.*, **42**, 644 (1952)] report b.p. 173–174° (13 mm.). [b] The previous reference gives b.p. 167–168° (10 mm.). [c] No further identification was made.

Another by-product encountered in some of the syntheses was the disulfide corresponding to starting thiol, but it never amounted to very much.

***m*-Bis(*n*-dodecylmercapto)benzene and *m*-Chlorophenyl *n*-Dodecyl Sulfide.**—Using the above procedure, 163.5 g. (0.8 mole) of 1-dodecanethiol, 52.7 g. (0.8 mole) of 86% potassium hydroxide, and 71.2 g. (0.3 mole) of *m*-dibromobenzene in 300 ml. of dimethylacetamide yielded about 50 ml. of starting materials, b.p. 81–170° (0.4 mm.); 49.4 g. of intermediate *m*-chlorophenyl *n*-dodecyl sulfide, b.p. 175–200° (0.55 mm.); and a residue which solidified. This was recrystallized from isopropyl alcohol giving 85 g. (59%) of *m*-bis(*n*-dodecylmercapto)benzene as off-white crystals, m.p. 34–35°.

Anal. Calcd. for $C_{30}H_{54}S_2$: S, 13.39. Found: S, 13.2.

Mixed Isomer, Bis(phenylmercaptobiphenyl).—A mixture of 0.5 mole of potassium benzenethiolate (from 55 g. of benzenethiol and 32.6 g. of 85% potassium hydroxide) and 57.6 g. (0.26 mole) of a dichlorinated biphenyl mixture in 200 ml. of dimethylacetamide was heated at reflux for 24 hr. Otherwise the method above was followed to give 26.3 g. of intermediate *x*-chloro-*x'*-phenylmercaptobiphenyl, b.p. 170–195° (0.25 mm.); and 46.3 g. (approx. 50%) of bis(phenylmercapto)biphenyl, a light yellow viscous oil with b.p. 205–250° (0.25 mm.).

Bis(*m*-phenylmercaptophenyl) Sulfide.—The Grignard of *m*-chlorophenyl phenyl sulfide was prepared in the usual manner from 63.4 g. (0.29 mole) of the halide and 7.8 g. (0.32 g.-atom) of magnesium ribbon in tetrahydrofuran with ethyl bromide as the initiator. It was cooled in an ice bath and treated with 9.2 g. (0.29 g.-atom) of sulfur, added at such a rate that the reaction temperature never exceeded 35°. The mixture was stirred for 5 min., solvent was evaporated *in vacuo*, and ether followed by 30 ml. of water and 80 ml. of 6 *N* hydrochloric acid was added. The organic layer and ether extract of the aqueous layer were combined and washed thoroughly with 200 ml. of 2 *N* sodium hydroxide. Acidification of the latter released the mercaptan which was separated with the aid of ether, washed with salt water, dried, and distilled. *m*-Phenylmercaptobenzenethiol was obtained in a yield of 30.1 g. (48%) as a colorless oil, b.p. 127–138° (0.35 mm.), $n^{25}D$ 1.6705.

Anal. Calcd. for $C_{12}H_{10}S_2$: C, 66.1; H, 4.6; S, 29.3. Found: C, 65.5; H, 4.5; S, 29.5.

Utilizing the method described previously, 0.28 mole of potassium *m*-phenylmercaptobenzenethiolate (from 62.2 g. of the above thiol and 18.3 g. of 87% potassium hydroxide) in 250 ml. of dimethylacetamide was treated with 50 g. (0.23 mole) of *m*-chlorophenyl phenyl sulfide for 36 hr. at 150 ± 5°. Isolation procedures provided an oil which was distilled giving 22.4 g. of unchanged halide and 38.8 g. (42%) of the four-membered ring thioether, b.p. 252–265° (0.25 mm.).

Anal. Calcd. for $C_{24}H_{18}S_3$: C, 71.8; H, 4.5; S, 23.8. Found: C, 71.3; H, 4.4; S, 23.9.

***m*-Bis(*m*-phenylmercaptophenylmercapto)benzene.**—The same procedure was employed to synthesize this orange viscous five-membered ring thioether from 0.23 mole of potassium *m*-phenylmercaptobenzenethiolate and 15.3 g. (0.104 mole) of *m*-dichlorobenzene in 200 ml. of dimethylacetamide. It was obtained in a yield of 9 g. (17%) with b.p. 300–308° (0.18 mm.).

Anal. Calcd. for $C_{30}H_{22}S_4$: C, 70.6; H, 4.35; S, 25.1. Found: C, 70.0; H, 4.28; S, 25.4.

Polymer from Pentachlorobenzenethiol.—In an attempt to synthesize *m*-bis(pentachlorophenylmercapto)benzene from 0.11 mole of *m*-dibromobenzene and 0.3 mole of potassium pentachlorobenzenethiolate, 73 g. of a yellow amorphous polymer was obtained. It melted above 300° and was insoluble in every solvent tried including water, alcohols, hydrocarbons, ethers, diglyme, amides, pyridine, chlorobenzene, ethyl acetate, etc. No solvent has yet been found to dissolve even a part of it.

Acknowledgment.—The author wishes to express his gratitude to Dr. F. S. Clark for some of the preparations and to our Analytical Group for all of the analytical determinations.

(16) All melting and boiling points are uncorrected.

The Preparation of Decahydro- and Dodecahydro-4a-azachrysenes Related to Azasteroids[1a]

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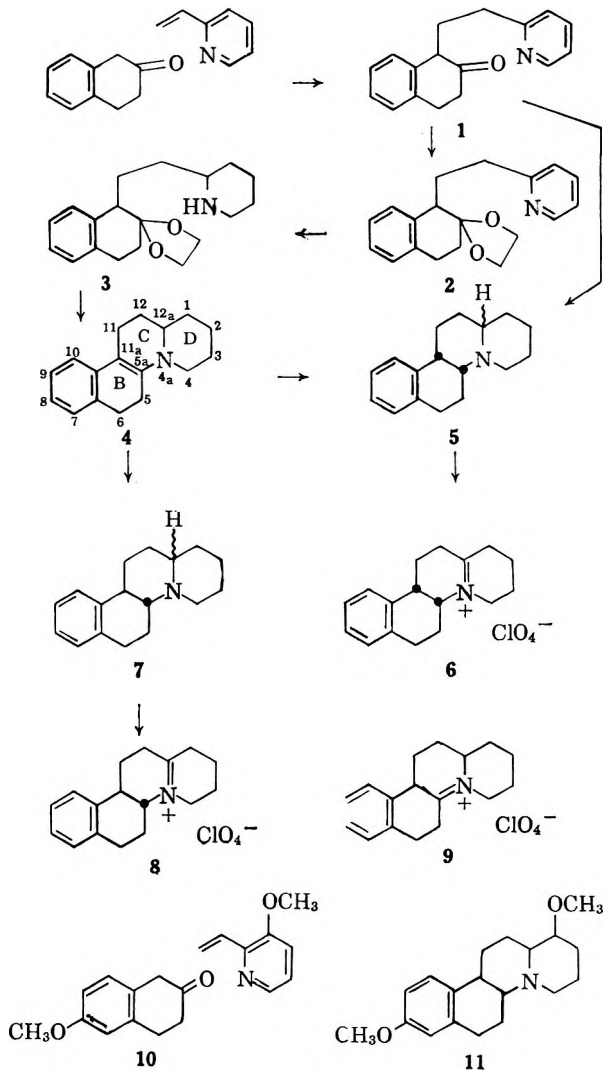
In a study designed to obtain azasteroids, the Michael addition of 2-tetralone to 2-vinylpyridine gave 1-(β-2-pyridylethyl)-2-tetralone (1) which on reduction of the pyridine ring gave the decahydro-4a-azachrysene **4**. Catalytic reduction of **4** gave a dodecahydro-4a-azachrysene formulated as **5** while sodium borohydride reduction of the perchlorate of **4** gave the isomeric dodecahydro-4a-azachrysene **7**. Mercuric acetate oxidation of **5** and **7** gave different enamine perchlorates (**6** and **8**, respectively), thus demonstrating a difference in the stereochemistry of the B–C ring fusion of **5** and **7** as well as the perchlorates. The synthesis of 3-methoxy-2-vinylpyridine is reported.

Because of the interest in the preparation of 4a-aza-D-homosteroids[2] we first concerned ourselves with the synthesis of 1,2,3,4,5,6,11,12,12a,4a-decahydro-4a-azachrysene (**4**) and then studied methods by which *trans* reduction of the Δ^{5a}-double bond could be accomplished. If such a reduction could be demonstrated, the remaining asymmetric center at position 12a should present no problem in the synthesis of a 17α-keto-14-aza-D-homosteroid (corresponds to a carbonyl group at position 1 of structure **4**). Such a steroid should be capable of equilibration to a product having the *trans-anti-trans* backbone configuration of naturally occurring steroids.

The Michael condensation of 2-tetralone with 2-vinylpyridine in dioxane in the presence of sodium hydride gave 1-(β-2-pyridylethyl)-2-tetralone (**1**) in 49% yield (55–64% based on recovered starting materials). A sample of this compound was reduced with lithium aluminum hydride giving one of the isomers of (β-2-pyridylethyl)-2-hydroxytetralin in 42% yield. The possibility of converting this substituted hydroxytetraline *via* its tosylate to a 5,6,11,11a,5a-hexahydro-4a-azaoniachrysene salt which, in turn, could be reduced selectively to other polyhydro-4a-azachrysenes was being considered. However, the early success of the method described below precluded further experimentation along these lines.

1-(β-2-Pyridylethyl)-2-ethylenedioxytetralone (**2**) was prepared in 66% yield from the sulfate salt of **1** by exchange with 2-methyl-2-ethyl-1,3-dioxolane. Hydrogenation of **2** in acetic acid–ethanol using Adams catalyst proceeded selectively and gave 77% of 1-(β-2-piperidylethyl)-2-ethylenedioxytetralone (**3**). Hydrolysis of the cyclic ethylene ketal grouping of **3** with hydrochloric acid followed by the addition of base resulted in the formation of the cyclic enamine **4** in 49–75% yields. The structure of the crystalline 1,2,3,4,-5,6,11,12,12a,4a-decahydro-4a-azachrysene (**4**) was substantiated by its ultraviolet absorption spectrum which is essentially the same as for 1-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline.[3] As in the case of this latter compound, treatment of the decahydro-4a-azachrysene **4** with methyl iodide resulted in a methiodide in which alkylation had occurred on nitrogen.[4,5] The infrared and ultraviolet spectra of the perchlorate of **4** indicate proton attachment chiefly on nitrogen.[6] (See Scheme I.)

SCHEME I



(1) (a) This investigation was supported in part by a research grant, CY-2999 (C5), from the National Cancer Institute, U. S. Public Health Service; (b) address correspondence to Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Del.

(2) The synthesis of 8-azaestrone has appeared in a recent communication: R. I. Meltzer, D. M. Lustgarten, R. I. Stanaback, and R. E. Brown, *Tetrahedron Letters*, **23**, 1581 (1963).

(3) N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958).

(4) For other examples of carbon and/or nitrogen alkylation of enamines, see G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(5) The literature of enamines is reviewed in a chapter by J. Szmuszkovicz, "Advances in Organic Chemistry: Methods and Results," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 1.

(6) Attachment of the proton to the β-carbon which might be expected in an enamine system[4,5] would, in this case, shift the double bond out of conjugation with the benzene ring.

1,2,3,4,5,6,11,12,12a,4a-Decahydro-4a-azachrysene (**4**) was reduced catalytically using Adams catalyst in ethanolic hydrochloric acid and also with palladium on charcoal in ethanol to 1,2,3,4,5,6,11,12,12a,4a,11a,5a-dodecahydro-4a-azachrysene (**5**). This same product was prepared by reductive cyclization of 1-(β-2-pyridylethyl)-2-tetralone (**1**) using Adams catalyst in ethanolic hydrochloric acid.

The stereochemistry of the B–C ring fusion of **5** is provisionally assigned as *cis* on the basis that catalytic hydrogenations of imines have given the *cis* isomer.[7] The relationship of the hydrogens at the *cis* B–C juncture with the C-12a hydrogen can either be *syn* or *anti*, more likely an equal mixture of the two. From the melting point spread of the perchlorate (m.p. 177–205°) it appears that indeed one deals with such a mixture. Mercuric acetate oxidation[5] of **5** gave a single product in the form of a new enamine[8] which was isolated as its perchlorate **6**. Such oxidations of amines occur by abstraction of a tertiary in preference to a secondary or primary hydrogen, α to the nitrogen.[5,9] Of the two possible tertiary perchlorates **6** and **9**, the latter is rejected because it would be expected to rearrange to the perchlorate of **4**. Since by destroying the asymmetry at C-12a oxidatively one gets a single isomer, it is concluded that the mixture of isomers in **5** is due to the relationship of the *cis*-hydrogens at C-11a and C-5a to the one at C-12a.

Attention was next turned to chemical reductions of the decahydro-4a-azachrysene **4** in an effort to produce compounds in which the hydrogens at C-11a and C-5a would have a *trans* relationship. Formic acid did not reduce **4**, starting material being isolated. However, the sodium borohydride reduction of the perchlorate of **4** gave a new amine (or a mixture of amines), **7** as a product, which had a different infrared spectrum from **5** as well as different derivatives. The derivatives (picrate m.p. 228–232°, perchlorate m.p. 231.5–233.5°) are not very sharp melting, indicating that small amounts of other isomers could be present. Mercuric acetate oxidation[5] of **7** gave a new enamine[8] as a single product isolated as its perchlorate, and assigned structure **8** on the basis of reasoning similar to that applied for structure **6**. Thus the elimination of the C-12a asymmetric center makes the enamine perchlorates **6** and **8** different only in the nature of the B-C ring juncture, and, since **6** has been provisionally assigned as the *cis* isomer, **8** is assigned as the *trans* isomer.

The Michael addition of 6-methoxy-2-tetralone to 3-methoxy-2-vinylpyridine followed by other chemical transformations of the product as described above in the model series would be expected to yield one or more 1,8-dimethoxydodecahydro-14-azachrysenes (**11**). Cleavage of the ether groups would be expected to give the corresponding dihydroxy compound which by appropriate chemical manipulations, should lead to 18-nor-D-homo-14-azaestrone and related steroids.

6-Methoxy-2-tetralone is readily prepared[10]; however, a convenient synthesis of the unknown 3-methoxy-2-vinylpyridine had to be worked out. Methylation of 3-hydroxy-2-picoline with trimethylphenylammonium chloride[11] gave a mixture of 3-methoxy-2-picoline and dimethylaniline which was difficult to separate, and for this reason, methylation with diazomethane was used to obtain the desired product. Ethyl 3-methoxy-2-pyridylacetate was prepared by metalation of 3-methoxy-2-picoline with phenyllithium followed by carbonation and esterification.[12] Reduction of the ester with lithium aluminum hydride and dehydration of the resulting 2-hydroxyethyl-3-methoxypyridine with concentrated sodium hydroxide gave 3-methoxy-2-vinylpyridine. This latter material is fairly stable at room temperature, but tends to polymerize if distilled at temperatures much above 100°.

The condensation of 6-methoxy-2-tetralone and 3-methoxy-2-vinylpyridine appeared to proceed normally; however, this and other reactions leading to a functionalized 14-azasteroid have not been studied further.

Experimental[13]

1-(β-2-Pyridylethyl)-2-tetralone (**1**).—To a solution of 100 g. of 2-tetralone,[14] 200 ml. of dry dioxane, and 66.0 g. of redistilled 2-vinylpyridine was added 3 g. of sodium hydride. The mixture was stirred and refluxed for 16 hr. under a nitrogen atmosphere. Most of the dioxane was removed *in vacuo* and the residue was dissolved in excess dilute hydrochloric acid. Extraction of the aqueous solution with ether and distillation of the ether extract gave 13.0 g. of unchanged 2-tetralone, b.p. 90–92° (0.4 mm.). The acidic solution was rendered alkaline with sodium carbonate and extracted with ether. The dried ether extract was concentrated *in vacuo* and distilled giving 13 g. of unchanged 2-vinylpyridine, b.p. 40–45° (12 mm.), followed by 83.0 g. of 1-(β-2-pyridylethyl)-2-tetralone, b.p. 175–178° (0.02 mm.), and infrared absorption at 1710 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.25; H, 6.82; N, 5.57. Found: C, 81.20; H, 6.76; N, 5.67.

1-(β-2-Pyridylethyl)-2-tetralone picrate was obtained from ethanol quantitatively, m.p. 130–138°, and recrystallized from ethanol–acetonitrile, m.p. 132–140° (capillary m.p. 135–137°).

Anal. Calcd. for $C_{23}H_{20}N_4O_8$: C, 57.50; H, 4.19; N, 11.66. Found: C, 57.21; H, 4.21; N, 11.70.

1-(β-2-Pyridylethyl)-2-hydroxytetralin.—To a stirred solution of 0.76 g. of lithium aluminum hydride in 30 ml. of ether was added with stirring over a 30-min. period, 10.1 g. of 1-(β-2-pyridylethyl)-2-tetralone in 20 ml. of ether. The mixture was stirred for 1 hr., when the excess hydride was decomposed by the cautious addition of water followed by sodium bicarbonate. The product was extracted with ether and the dried ether extract was concentrated to give an oil which was crystallized from ethyl acetate–hexane yielding 4.2 g. of 1-(β-2-pyridylethyl)-2-hydroxytetralin, m.p. 78–81°, and infrared absorption at 3300 cm.$^{-1}$ (associated O–H).

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.78; H, 7.56; N, 5.32.

1-(β-2-Pyridylethyl)-2-ethylenedioxytetralone (**2**).—To a flask containing 24.0 g. (0.096 mole) of 1-(β-2-pyridylethyl)-2-tetralone was added slowly with stirring at 0°, 9.4 g. (0.096 mole) of con-

(7) The catalytic reduction of a mixture of 1-methyloctahydroquinolines has been reported to give *cis*-1-methyldecahydroquinoline; see N. J. Leonard, L. A. Millller, and P. D. Thomas, *J. Am. Chem. Soc.*, **78**, 3463 (1956).

(8) There are two possible enamines, one where the double bond is in the C and the other in the D ring.

(9) N. J. Leonard, W. J. Middleton, P. D. Thomas, and D. Croudhury, *J. Org. Chem.*, **21**, 344 (1956); N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955); N. J. Leonard, R. W. Fulmer, and A. S. Hay, *ibid.*, **78**, 3457 (1956).

(10) N. A. Nelson, R. S. P. Hsi, J. M. Schuck, and L. D. Kahn, *ibid.*, **82**, 2573 (1960).

(11) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 136 (1955).

(12) *Cf.* R. B. Woodward and E. C. Kornfeld, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 413.

(13) Melting points were determined using a hot-stage microscope and are corrected. Boiling points are uncorrected. The infrared spectra were determined in carbon tetrachloride unless otherwise stated with a Baird, Model B, or a Perkin-Elmer, Model 21 or 137, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, Model 11 MS. The microanalyses were performed by Dr. S. M. Nagy and his associates.

(14) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

centrated sulfuric acid followed by 75 ml. of redistilled 2-methyl-2-ethyl-1,3-dioxolane and 1 g. of *p*-toluenesulfonic acid. The flask, equipped with a short Vigreux column, was immersed in an oil bath at 125–130° while 2-butanone was collected by distillation. When the ketone ceased to distill, the excess 2-methyl-2-ethyl-1,3-dioxolane was distilled and the solid residue was treated with excess 10% methanolic potassium hydroxide solution. The product was extracted with benzene and the extract was washed with water and concentrated *in vacuo*. Distillation of the residue gave 18.7 g. of a light yellow liquid, b.p. 165–185° (0.005 mm.), and no carbonyl infrared absorption. The analytical sample of 1-(β-2-pyridylethyl)-2-ethylenedioxytetralone had b.p. 161–162° (0.002 mm.).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74. Found: C, 77.32; H, 7.27; N, 4.98.

The **oxalate** derivative was prepared in ethanol and precipitated with hexane, m.p. 107.5–109.5°.

Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.01; N, 3.63. Found: C, 65.32; H, 6.32; N, 3.46.

1-(β-2-Piperidylethyl)-2-ethylenedioxytetralone (3).—A solution of 18.6 g. of 1-(β-2-pyridylethyl)-2-ethylenedioxytetralone in 100 ml. of absolute ethanol and 30 ml. of glacial acetic acid was hydrogenated at an initial pressure of 30 p.s.i. in the presence of 0.3 g. of platinum oxide. After 18 hr. the theoretical amount of hydrogen had been absorbed. The mixture was filtered and the filtrate was rendered alkaline with a 10% methanolic potassium hydroxide solution. The mixture was concentrated *in vacuo* and the residue was diluted with benzene. The benzene solution was washed with water and distilled giving 14.6 g. of product, b.p. 164° (0.005 mm.). As expected, the product showed no carbonyl or substituted pyridine absorption near 1710 and 1600 cm.$^{-1}$, respectively.

The **oxalate** of 1-(β-2-piperidylethyl)-2-ethylenedioxytetralone was formed in ethanol, precipitated with hexane, and recrystallized from ethanol–hexane, m.p. 158–160°.

Anal. Calcd. for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.47; H, 7.62; N, 3.80.

1,2,3,4,5,6,11,12,12a,4a-Decahydro-4a-azachrysene (4).—A solution of 40.0 g. of 1-(β-2-piperidylethyl)-2-ethylenedioxytetralone (**3**) in 180 ml. of 6 *N* hydrochloric acid was stirred for 10 hr. at room temperature under a nitrogen atmosphere. The solution was made basic with sodium hydroxide and extracted with benzene. The benzene extract was concentrated *in vacuo* and the residue distilled giving 24.9 g. of material, b.p. 152–168° (0.02 mm.), which on trituration with ethanol gave crystalline material. The product was recrystallized from ethanol–water giving 16.0 g. of **4**, m.p. 57–58.5°; infrared absorption at 1615, 1698, and 1565 cm.$^{-1}$ (conjugated C=C and aromatic ring), and ultraviolet maxima at 236 mμ (ε 8600) and 313 (10,030).

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.85; N, 5.85. Found: C, 85.30; H, 8.99; N, 5.97.

A **perchlorate of 4** was formed in ether and recrystallized from ethanol, m.p. 184–185°, infrared maximum at 1642 cm.$^{-1}$ (KBr disk), and an ultraviolet maximum at 251 mμ (ε 8150).

Anal. Calcd. for $C_{17}H_{22}ClNO_4$: C, 60.08; H, 6.53; N, 4.12. Found: C, 60.01; H, 6.58; N, 3.98.

A **methiodide of 4** was prepared in methyl iodide and recrystallized from ethyl acetate–ethanol, m.p. 184–185°, ultraviolet maxima 215 mμ (ε 39,000), 221 (32,600), and 259 (11,850).

Anal. Calcd. for $C_{18}H_{24}IN$: C, 56.70; H, 6.34; N, 3.74. Found: C, 56.82; H, 6.08; N, 3.90.

1,2,3,4,5,6,11,12,12a,4a,11a,5a-Dodecahydro-4a-azachrysene (5). A. From 1-(β-2-Pyridylethyl)-2-tetralone (1).—Platinum oxide catalyst (0.25 g.) was added to a solution of 10.3 g. of 1-(β-2-pyridylethyl)-2-tetralone, 35 ml. of ethanol, and 12 ml. of concentrated hydrochloric acid. The mixture was hydrogenated at an initial pressure of 30 p.s.i. After 12 hr. the theoretical amount of hydrogen had been absorbed and the mixture was filtered. The filtrate was concentrated somewhat, rendered alkaline with sodium hydroxide, and extracted with benzene. Concentration of the benzene extract and distillation of the residue gave 8.02 g. of product, b.p. 106–108° (0.001 mm.), ultraviolet maxima at 267 mμ (ε 500) and 274 (500) with a shoulder at 260 (400). The infrared spectrum of the product showed the absence of hydroxyl, carbonyl, and substituted pyridine chromophores.

Anal. Calcd. for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 83.72; H, 9.81; N, 5.62.

A **picrate of 5** was formed essentially in quantitative yield in absolute ethanol, m.p. 257–259°, and on recrystallization from ethanol–acetonitrile melted at 260–262° dec.

Anal. Calcd. for $C_{23}H_{26}N_4O_7$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.96; H, 5.82; N, 11.68.

A **methiodide of 5** was formed in methyl iodide and recrystallized from ethanol–hexane, m.p. 270–271°.

Anal. Calcd. for $C_{18}H_{26}IN$: C, 56.54; H, 6.85; N, 3.66. Found: C, 56.39; H, 6.76; N, 3.72.

A **perchlorate of 5** was formed in ether essentially quantitatively, m.p. 177–205°, and, after repeated recrystallizations from ethanol–hexane, it melted at 178–208°.

Anal. Calcd. for $C_{17}H_{24}ClNO_4$: C, 59.73; H, 7.18; N, 4.10. Found: C, 59.83; H, 7.26; N, 4.04.

B. From 1,2,3,4,5,6,11,12,12a,4a-Decahydro-4a-azachrysene (4).—A mixture of 0.60 g. of **4**, 8 ml. of ethanol, 2 ml. of concentrated hydrochloric acid, and 0.04 g. of platinum oxide was hydrogenated at atmospheric pressure. The theoretical amount of hydrogen was absorbed in 90 min. The catalyst was removed, the filtrate was rendered alkaline and shaken with benzene and water, and the benzene layer was concentrated. The residue was converted essentially quantitatively to the picrate, m.p. 262–263° dec. A mixture melting point with the picrate prepared in part A was undepressed.

Hydrogenation of 1.5 g. of **4** in 15 ml. of absolute ethanol with 0.10 g. of 10% palladium on charcoal was complete in 7 hr. The catalyst was removed and the filtrate was concentrated, then distilled giving material identical with the spectrum of the dodecahydro-4a-azachrysene **5** prepared as described in part A. The picrate formed in ethanol had m.p. 262–263° dec. (undepressed with the samples of this material described above).

1,2,3,4,5,6,11,12,11a,5a-Decahydro-4a-azachrysene Perchlorate (6).—A solution of 2.61 g. of 1,2,3,4,5,6,11,12,12a,4a,11a,-5a-dodecahydro-4a-azachrysene (**5**), 14.0 g. of mercuric acetate, and 70 ml. of 5% aqueous acetic acid was heated on the steam bath for 2 hr. The precipitated mercurous acetate (5.0 g., 89%) was removed and the filtrate was saturated with hydrogen sulfide. The mixture was filtered, the filtrate was rendered alkaline with sodium hydroxide, and the product was extracted with ether. The ether extract was concentrated to about 20 ml. and treated with 1 ml. of 72% perchloric acid to give 2.5 g. of a perchlorate which on recrystallization from ethanol afforded 1.7 g. of product, m.p. 217.5–218.5°, ultraviolet maxima at 265 mμ (ε 680) and 272 (715), and infrared maximum at 1670 cm.$^{-1}$ (C=N$^+$) (KBr pellet).

Anal. Calcd. for $C_{17}H_{22}ClNO_4$: C, 60.08; H, 6.53; N, 4.12. Found: C, 60.16; H, 6.58; N, 4.33.

The free base corresponding to **6** was obtained by treating the perchlorate **6** with 10% aqueous sodium hydroxide. The crude product was extracted with benzene and distilled through a Hickmann apparatus to give the enamine, m.p. 50.5–54.5° with previous softening, and infrared maximum at 1650 cm.$^{-1}$ (C=C) (in $CHCl_3$).

1,2,3,4,5,6,11,12,12a,4a,11a,5a-Dodecahydro-4a-azachrysene (7).—A stirred solution of the perchlorate salt of 1,2,3,4,5,6,11,-12,12a,4a-decahydro-4a-azachrysene (**4**) in 45 ml. of methanol was treated cautiously with 4.0 g. of sodium borohydride. When the addition was complete, the mixture was stirred under reflux for 1 hr. The mixture was concentrated, rendered alkaline with sodium hydroxide solution, and extracted with benzene. The benzene extract was concentrated and the residue was distilled through a semimicro column giving 0.90 g. of product, b.p. 106–109° (0.001 mm.). The infrared spectrum of this material is similar to but not identical with the isomer **5**.

The **picrate of 7** was obtained in the usual way and recrystallized from ethanol, m.p. 228–232° dec. (softening at 225°).

Anal. Calcd. for $C_{23}H_{26}N_4O_7$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.70; H, 5.77; N, 12.02.

A **methiodide of 7** was prepared in methyl iodide and recrystallized from ethanol–hexane, m.p. 276.5–277.5°.

Anal. Calcd. for $C_{18}H_{26}IN$: C, 56.54; H, 6.85; N, 3.66. Found: C, 56.59; H, 6.92; N, 3.68.

The **perchlorate of 7** was formed in ether and recrystallized from ethanol, m.p. 231.5–233.5°.

Anal. Calcd. for $C_{17}H_{24}ClNO_4$: C, 59.73; H, 7.08; N, 4.10. Found: C, 59.80; H, 7.22; N, 4.09.

1,2,3,4,5,6,11,12,11a,5a-Decahydro-4a-azachrysene Perchlorate (8).—Following the procedure described above for the preparation of the isomer **6**, 2.45 g. of 1,2,3,4,5,6,11,12,12a,4a,-11a,5a-dodecahydro-4a-azachrysene (**5**) in a solution of 13.0 g. of

mercuric acetate and 60 ml. of 5% aqueous acetic acid was converted to 1.75 g. of perchlorate **8**, m.p. 233.5–235.5°, infrared maximum 1670 cm.$^{-1}$ (C=N$^+$) (in KBr pellet) and ultraviolet maxima at 264 mμ (ε 1200) and 272 (1200). A mixture melting point of this material with the perchlorate **6** was depressed (m.p. 202–205°).

Anal. Calcd. for $C_{17}H_{22}ClNO_4$: C, 60.08; H, 6.53; N, 4.12. Found: C, 59.78; H, 6.28; N, 4.36.

A portion of the perchlorate **9** was converted to the corresponding enamine using sodium hydroxide. Distillation of the product through a Hickmann apparatus and trituration of the distillate with a drop of ethanol gave material with m.p. 74.5–76.5° and infrared maximum at 1650 cm.$^{-1}$ (C=C) (in chloroform).

3-Methoxy-2-picoline.—To a stirred solution of 26 g. of diazomethane in 2 l. of ether cooled to 5° was added dropwise over a 30-min. period 60 g. of 3-hydroxy-2-picoline in 500 ml. of butanol. With continued stirring overnight, the temperature of the solution was allowed to rise to room temperature. The solution was distilled through a short Vigreux column and gave 31 g. of 3-methoxy-2-picoline, b.p. 84.5–85.5° (17 mm.), n^{28}D 1.5128, ultraviolet maxima at 221 mμ (ε 7150) and 279 (5400), and picrate derivative m.p. 166–168° (lit.[13] m.p. 167–168°). The residue from the distillation was crystallized from an acetonitrile–hexane mixture and gave 13.0 g. of unchanged 3-hydroxy-2-picoline, m.p. 167–169° (lit.[15] m.p. 170–171°).

Ethyl 3-Methoxy-2-pyridylacetate.—To a solution of phenyllithium prepared from 5.0 g. of lithium wire, 400 ml. of ether, and 56.3 g. of bromobenzene was added with stirring 44.0 g. of 3-methoxy-2-picoline over a 45-min. period. The red solution was treated with excess Dry Ice. The mixture was allowed to stand overnight and the ether was then removed *in vacuo*. Absolute ethanol (300 ml.) was added to the solid and, while the mixture was cooled in an ice bath, a saturated solution of ethanolic hydrogen chloride was added dropwise with stirring until the mixture was strongly acidic. The mixture was allowed to stand for 10 hr. at room temperature when most of the ethanol was removed *in vacuo* and 400 ml. of chloroform was added. The chloroform solution was stirred with a paste of 110 g. of potassium carbonate and 65 ml. of water for 30 min., then filtered. The filtrate was washed with water, concentrated, and distilled to give 17.7 g. of 3-methoxy-2-picoline, b.p. 85–87° (18 mm.), and 20.8 g. of ethyl 3-methoxy-2-pyridylacetate, b.p. 94.0–94.5° (0.5 mm.), n^{21}D 1.5038, and infrared maximum at 1730 cm.$^{-1}$ (ester C=O).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.40; H, 6.77; N, 7.34.

The **picrate** derivative was obtained from ethanol and melted at 156–158°.

Anal. Calcd. for $C_{16}H_{16}N_4O_{10}$: C, 45.29; H, 3.80; N, 13.21. Found: C, 45.32; H, 4.01; N, 13.24.

2-Hydroxyethyl-3-methoxypyridine.—To a stirred solution of 800 ml. of ether and 8.3 g. of lithium aluminum hydride was added dropwise 37.0 g. of ethyl 3-methoxy-2-pyridylacetate. After 1 hr., 8.3 ml. of water was added cautiously followed by 8.3 ml. of 15% sodium hydroxide solution and 25 ml. of water. The ether solution was filtered, dried, and concentrated giving 27.5 g. of product with m.p. 76–80° and infrared maximum at 3340 cm.$^{-1}$ (associated O–H). The analytical sample was recrystallized from hexane–ethyl acetate, m.p. 79–80°.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.96; H, 7.37; N, 9.28.

The **picrate** derivative was prepared in ethanol and had m.p. 146–149°.

Anal. Calcd. for $C_{14}H_{14}N_4O_9$: C, 43.98; H, 3.69; N, 14.66. Found: C, 44.03; H, 3.61; N, 14.90.

3-Methoxy-2-vinylpyridine (12).—To 150 ml. of 50% sodium hydroxide solution heated to reflux was added dropwise a solution of 6.5 g. of 2-hydroxyethyl-3-methoxypyridine in 25 ml. of water. The product steam distilled from the reaction mixture. The distillate was extracted with ether and the ether extract was dried over sodium hydroxide. Distillation of the solution gave 3.5 g. of 3-methoxy-2-vinylpyridine, b.p. 60–62° (0.5 mm.), n^{23}D 1.5600, and ultraviolet maxima at 237 mμ (ε 9850) and 308 (7000).

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.30; H, 6.96; N, 10.58.

The **picrate** derivative was obtained from ethanol, m.p. 139–141° (softened at 132°).

Anal. Calcd. for $C_{14}H_{12}N_4O_8$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.25; H, 3.30; N, 15.34.

Acknowledgment.—The author is indebted to Dr. N. A. Nelson for his helpful suggestions and constant interest and encouragement.

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Studies on the Base Strengths of N,N-Disubstituted Amides

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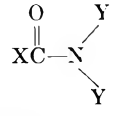
The carbonyl stretching vibration frequencies were determined for a series of N,N-disubstituted alkanoic acid amides and closely related compounds in dilute solution in isooctane ($\gamma_{C=O(iso)}$) and in chloroform ($\gamma_{C=O(HCCl_3)}$). pK_a values were determined by potentiometric titration in dilute nitromethane solution using perchloric acid as titrant. A linear relationship was found between $\gamma_{C=O(iso)}$ and $\Sigma\sigma^*$, where σ^*-values for X were the Taft polar factors, and σ^*-values for NY_2 were empirically estimated. A linear relation was also observed between pK_a and σ^* for the N,N-disubstituted formamides and acetamides but not for the N,N-disubstituted propionamides. With chloroform as the electron acceptor, relative base strengths were measured by $\Delta\gamma_{C=O}/\gamma_{C=O(iso)}$, where $\Delta\gamma_{C=O}$ was $\gamma_{C=O(iso)} - \gamma_{C=O(HCCl_3)}$. In this case, an increase in $\Delta\gamma_{C=O}/\gamma_{C=O(iso)}$ with increase in $\Sigma\sigma^*$ was observed only for the formamides. Using published data for log K_{assn} with phenol as the acid, $\Sigma\sigma^*$–log K_{assn} relationships were obtained which were intermediate to those using perchloric acid and chloroform. These results permitted an analysis of the variable steric effects in the free base and in the associated complexes. The order of steric requirements was found to be perchloric acid < phenol < chloroform. Evidence is presented that relief of steric strains in these complexes occurs through twisting about the C–N bond.

We have been concerned with various Lewis bases in nonaqueous systems and how the base strength relates to structure. Toward this end, spectroscopic and potentiometric titration measurements were made on



N,N-Disubstituted alkanoic acid amides

a series of N,N-disubstituted alkanoic acid amides and closely related compounds in dilute solution, using perchloric acid and chloroform as electron acceptors. The relative base strengths were compared with literature values using phenol and also iodine as electron acceptors.

The general approach and results are presented in the next section and in Tables I–III. This is followed by a discussion of the base strength parameters and an

TABLE I

PHYSICAL CONSTANTS OF N,N-DISUBSTITUTED AMIDES

	N,N-Disubstituted amides	B.p. (mm.), °C.	Density at 25°	Refractive index, $n^{25}D$	$\Sigma\sigma^*$ [a]	Log K_{assn} (phenol, 20°)
(1)	N,N-Dimethylformamide	55 (20)[b]	0.94	1.4279[c]	+0.49	1.90[d]
(2)	N,N-Diethylformamide	79 (20), 67 (14)[e]	0.90	1.4321[f]	+0.41[g]	1.87[h]
(3)	N,N-Dimethylacetamide	65 (20)	0.94	1.4351	0	2.21[h]
(4)	N,N-Diethylacetamide	86 (24)[i]	0.90	1.4369[j]	−0.20	2.20[d]
(5)	N,N-Di-*n*-propylacetamide	101 (16)[k]	0.88	1.4410[l]	−0.23	
(6)	N,N-Diisopropylacetamide	87–88 (17)[m]	0.88	1.4378	−0.38	
(7)	N,N-Dimethylpropionamide	77 (22)	0.92	1.4376	−0.10	2.11[h]
(8)	N,N-Diethylpropionamide	91.5–92 (22)[n]	0.89	1.4390	−0.30	2.13[d]
(9)	N,N-Di-*n*-butylpropionamide	125 (13)[o]	0.87	1.4450	−0.36	
(10)	N,N-Diisobutylpropionamide	110 (12)[p]	0.87	1.4436	−0.35	
(11)	N-Acetylpiperidine	109 (18)[q]	1.00	1.4790	−0.18	2.13[d]
(12)	N-Formylpyrrolidine	96 (14)	1.02	1.4770	+0.39[r]	
(13)	N,N-Diethylbutyramide	52 (0.5)[d]			−0.32	2.09[d]
(14)	N-Propionylpiperidine	50 (4)[d]			−0.28	2.09[d]
(15)	N-Butyrylpiperidine	70 (1)[d]			−0.30	2.11[d]

[a] Where $\Sigma\sigma^* = \Sigma$ Taft σ^*-values for X and 2Y in all cases except 1, 2, and 12, where $\Sigma\sigma^* = \sigma_X{}^* + 0.4\Sigma(2\sigma_Y{}^*)$. $\sigma_Y{}^*$-values for 11 and 12 from ref. 17. [b] 153° (760), product information bulletin on dimethylformamide, Du Pont Industrial and Biochemicals Department. [c] 1.4269, footnote *b*. [d] Ref. 1. [e] 39° (15), Eastman Chemical Catalog; 59° (6), ref. 1. [f] 1.4296, J. H. Robson and J. Reinhard, *J. Am. Chem. Soc.*, **77**, 498 (1955). [g] $\Sigma\sigma^*$ uncorrected +0.29. [h] Calculated from K_{assn}, ΔH data at 25°, ref. 13. [i] 88.5–91° (31), footnote *f*. [j] 1.4333, footnote *f*. [k] 94.5° (12), footnote *f*. [l] 1.4411, footnote *f*. [m] 71–73° (6), footnote *e*. [n] 55° (2), ref. 1. [o] 115–116° (6), footnote *e*. [p] 99–100° (4), footnote *e*. [q] 60° (0.4), ref. 1. [r] $\Sigma\sigma^*$ uncorrected +0.23.

TABLE II

SPECTROSCOPIC DATA ON N,N-DISUBSTITUTED AMIDES

	N,N-Disubstituted amides	$\gamma_{C=O(iso)}$, cm.$^{-1}$	$\gamma_{C=O(HCCl_3)}$, cm.$^{-1}$	$10^3\Delta\gamma/\gamma$[a]	Relative frequency shifts— Acetophenone reference[b]	Relative frequency shifts— Dimethylformamide reference[c]
(1)	N,N-Dimethylformamide	1697[d,e]	1673[f]	14.2[g]	0.58[h]	1.00
(2)	N,N-Diethylformamide	1693	1663	17.7	0.46	0.80
(3)	N,N-Dimethylacetamide	1674	1633	24.4	0.34	0.58
(4)	N,N-Diethylacetamide	1665[i,j]	1627[k]	22.8	0.36[l]	0.62
(5)	N,N-Di-*n*-propylacetamide	1663	1627	21.6	0.38	0.66
(6)	N,N-Diisopropylacetamide	1660	1625	21.1	0.39	0.67
(7)	N,N-Dimethylpropionamide	1675	1633	25.1	0.33	0.58
(8)	N,N-Diethylpropionamide	1664[m]	1625	23.4	0.35	0.61
(9)	N,N-Di-*n*-butylpropionamide	1662	1624	22.8	0.36	0.62
(10)	N,N-Diisobutylpropionamide	1661	1624	22.3	0.37	0.64
(11)	N-Acetylpiperidine	1666[n]	1625	24.6	0.33	0.58
(12)	N-Formylpyrrolidine	1693	1660	19.5	0.42	0.73
(13)	N,N-Diethylbutyramide	1657[o]				
(14)	N-Propionylpiperidine	1659[o]				
(15)	N-Butyrylpiperidine	1658[o]				

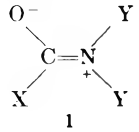
[a] $\gamma_{C=O(iso)} - \gamma_{C=O(HCCl_3)}/\gamma_{C=O(iso)}$. [b] $[\Delta\gamma/\gamma_{(acetophenone)}]/[\Delta\gamma/\gamma_{(amide)}]$. [c] $[\Delta\gamma/\gamma_{(DMF)}]/[\Delta\gamma/\gamma_{(amide)}]$. [d] 1696 cm.$^{-1}$, L. J. Bellamy and R. L. Williams, *Trans. Faraday Soc.*, **55**, 14 (1959). Hexane was solvent. [e] 1699 cm.$^{-1}$ as estimated by addition of 7 cm.$^{-1}$ to $\gamma_{C=O(CCl_4)}$-value, as reported in ref. 1. [f] 1673 cm.$^{-1}$, footnote *d*. [g] 13.6 as calculated from footnotes *d* and *f*. [h] 0.60 as calculated from footnotes *d* and *f*. [i] 1667, ref. 14. [j] 1664, estimated as in footnote *e*. [k] 1628, ref. 14. [l] 0.35, calculated from footnotes *i* and *k*. [m] 1664, as estimated in footnote *e*. [n] 1664, estimated as in footnote *e*. [o] Estimated as in footnote *e*.

analysis of the variable steric effects present in these systems.

Results

I. Polarity Measurements on the Free Base.—For an analysis of structural effects in the associated complexes, it was of value to examine initially the free base, to demonstrate a polarity parameter, and to determine the effects of structural variations on polarity.

It is generally recognized that (1) the N,N-disubstituted amides exist essentially in a planar configuration, (2) that the polar resonance structure makes an important contribution to the ground state (structure 1), and (3) that the acid–base interactions occur through the nonbonding electrons on the oxygen atom.[1-6]



1

The electron density on the oxygen atom is directly related to the polar effects of the substituents on the carbonyl group. Therefore, two parameters related to the polar contributions of the substituents were compared: (1) the carbonyl stretching vibration frequency

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TABLE III

POTENTIOMETRIC TITRATION DATA ON VARIOUS AMIDES, UREAS, AND AMINES WITH PERCHLORIC ACID AS TITRANT IN DILUTE NITROMETHANE

	Base	E.m.f. at half neutralization, v.	ΔHNP (Δe.m.f. at half neutralization), v.[a]	$pK_{a(H_2O)}$ Calcd.	$pK_{a(H_2O)}$ Lit.	K_b[b]
(0)	N,N′-Diphenylguanidine	+0.010	0.00	+10.0	+10.0[c]	1×10^{-10}
(1)	N,N-Dimethylformamide	0.930	+0.917	−0.70	−0.01[d]	5.02
(2)	N,N-Diethylformamide	0.925	0.909	−0.50		3.17
(3)	N,N-Dimethylacetamide	0.870	0.851	+0.10		0.80
(4)	N,N-Diethylacetamide	0.865	0.843	+0.20		0.63
(5)	N,N-Di-*n*-propylacetamide	0.885	0.854	+0.10		0.80
(6)	N,N-Diisopropylacetamide	0.860	0.826	+0.50		0.32
(7)	N,N-Dimethylpropionamide	0.895	0.870	−0.10		1.26
(8)	N,N-Diethylpropionamide	0.890	0.862	0		1.00
(9)	N,N-Di-*n*-butylpropionamide	0.890	0.853	+0.10		0.80
(10)	N,N-Diisobutylpropionamide	0.905	0.870	−0.10		1.26
(11)	N-Acetylpiperidine	0.875	0.829	+0.40		0.40
(12)	N-Formylpyrrolidine	0.920	0.868	−0.10		1.26
(13)	Tetramethylurea	0.875	0.83	+0.40		0.40
(14)	N-Methyl-2-pyrrolidone	0.895	0.846	+0.20	−0.2[e]	0.63
(15)	Repeat of N,N′-diphenylguanidine (0)	0.050	0.00	+10.0	+10.0[c]	1×10^{-10}
(17)	Pyridine	0.455	0.461	+4.70	+5.30[c]	2×10^{-9}
(18)	Triethylamine			+10.70	+10.75[f]	2×10^{-11}
(19)	New sample of N,N′-diphenylguanidine	0.010	0.00	+10.0	+10.0[c]	1×10^{-10}
(20)	Acetamide	0.865	0.855	+0.10	−0.48[c] +0.11[d]	3.02
(21)	Urea	0.830	0.820	+0.50	+0.50[g]	0.32

[a] HNP = half-neutralization potential. Corrected for change in e.m.f. of reference solution (N,N′-diphenylguanidine in nitromethane), *i.e.*, 15 *vs.* 0. [b] The inverse of the base strength of the amide, expressed as the ionization constant of the conjugate acid BH^+ in the equilibrium $BH^+ \rightleftarrows B + H^+$; that is, $K_a = [B][H^+]/[BH^+]$. [c] W. F. Hall, *J. Am. Chem. Soc.*, **52**, 5115 (1930). [d] R. Huisgen and H. Brade, *Ber.*, **90**, 1432 (1957). [e] Ref. 12. [f] Lange's "Handbook of Chemistry," 7th Ed., Handbook Publishers, Inc., Sandusky, Ohio, 1949, p. 1410. [g] H. Le Marie and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 5193 (1951).

in dilute isooctane solution ($\gamma_{C=O(iso)}$) and (2) Taft's polar factors (σ^*)[7] for the substituents X and Y. The $\gamma_{C=O(iso)}$ is generally a complex vibration, in which the frequency depends, even within a given class of compounds and in the absence of H-bonding effects (in dilute isooctane), on inductive effects, resonance effects, and bond angle strain.[4,8-10]

Taft has shown that σ^*-values are quantitative measures of the contribution of substituent groups, directly attached to the reaction center, to the polarity of the molecule.[7] Thus, if σ^*-values for X and for the $-NY_2$ group in $X-C(O)-NY_2$ were available, then $\Sigma\sigma^*$-values could be used to estimate the total polar contribution of the substituents to the electron density on the oxygen atom.

The relative polarity contributions to the carbonyl group of NY_2, as compared to X, may be empirically estimated, by plotting published σ^*-values for X and Y *vs.* $\gamma_{C=O(iso)}$ for the two lowest members of the series (to minimize steric differences), holding X constant and varying Y, and also holding Y constant and varying X.

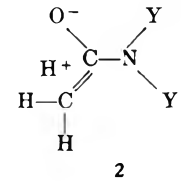
The results are summarized in Table IV. Changes in the N,N-disubstituted acetamide series (X = CH_3, Y = variable) are essentially equivalent to changes in the N,N-dimethylalkanoic acid amide series (Y = CH_3, X = variable).

TABLE IV

EFFECTS OF CHANGES IN THE INDUCTIVE CONTRIBUTIONS OF SUBSTITUENTS ON THE POLARITY OF THE CARBONYL GROUP OF N,N-DISUBSTITUTED AMIDES

$X-C(O)-NY_2$	Variable	$\Delta\gamma_{C=O(iso)}/\Delta\sigma^*$
Acetamides	Y	43
N,N-Dimethylamides	X	42
Formamides	Y	16

That is, the sum of inductive and resonance contributions for $-NY_2$ fortuitously equals the effect of published σ^*-values for X. This permits the simple summation of published σ^*-values for X and 2Y to obtain the total polar contribution of the substituents. In the formamide series, however, the polar effect of Y is only about 0.4 as great as in the acetamide series (Table IV), which suggests a reduced resonance contribution for NY_2. This qualitatively agrees with the somewhat reduced barrier for the rotation for the formamides as compared to the acetamides.[3] Perhaps the hyperconjugative structures in the acetamides and higher acid amides of the type shown below (structure 2) help stabilize the planar configuration of the molecule, and increase the contribution of the resonance structures to the polarity of the carbonyl group.



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(7) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 586–675.
(8) J. C. Evans and J. Overend, *Spectrochim. Acta*, **19**, 701 (1963).
(9) R. C. Lord and F. A. Miller, *Appl. Spectry.*, **10**, 115 (1956).
(10) (a) R. E. Kagarise, *J. Am. Chem. Soc.*, **77**, 1377 (1955); (b) E. M. Arnett and C. Y. Wu, *ibid.*, **84**, 1684 (1962).

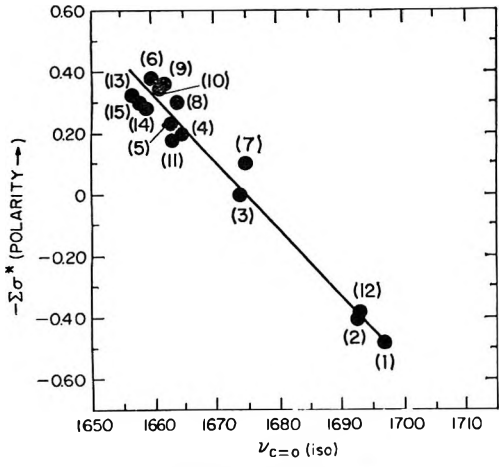


Fig. 1.—$\Sigma\sigma^*$ *vs.* $\nu_{C=O(iso)}$ for N,N-disubstituted amides and related compounds.

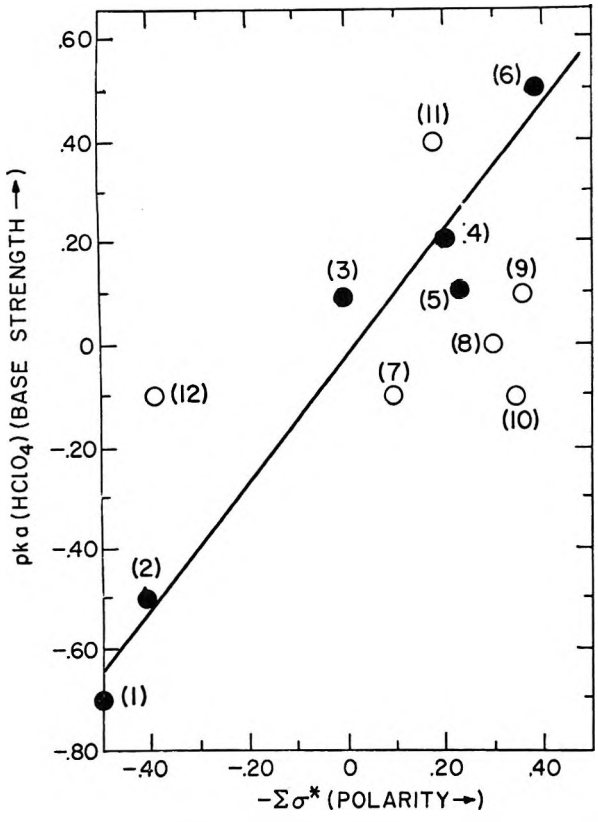


Fig. 2.—$\Sigma\sigma^*$ *vs.* $pK_{a(H_2O)}$ with perchloric acid as acid in nitromethane.

The $\Sigma\sigma^*$-values (with the formamide values corrected) were plotted against $\gamma_{C=O(iso)}$, as shown in Fig. 1. Quite a good linear relationship was obtained for the simple alkanoic acid amides, fitting the equation $+\Sigma\sigma^* = -0.0275\gamma_{C=O(iso)} + 46.1$ with standard deviation for $\gamma_{C=O(iso)}$ of 2.5 cm.$^{-1}$, just slightly higher than experimental error.

The straight line relationship for $\Sigma\sigma^*$ *vs.* $\gamma_{C=O(iso)}$ for the alkanoic acid amides lends confidence to the view that these parameters are accurate measures of carbonyl group polarity through this series. It further indicates that steric effects (B-strain, electron correlation repulsions[10b]) on the polarity of the free bases are negligible. Thus variable steric effects in the associated complexes would be essentially a result of complex formation.

II. Steric Effects in Forming the Associated Species.—The $\Sigma\sigma^*$(or $\gamma_{C=O(iso)}$)-values were plotted against published base strength parameters and against new data obtained in the present study. Deviations from the Taft linear polar energy relationship indicated the onset of variable steric effects in the associated complexes.[11]

Support for use of these parameters and an analysis of the steric factors involved is presented in the Discussion section.

A. Perchloric Acid as Electron Acceptor.—The potentiometric titration technique in nitromethane solvent followed essentially the method of Streuli,[12] and is described in the Experimental section. The collected pK_a data (for the conjugate acids) are given in Table III.

A plot of the base strengths (pK_a) *vs.* polarity of the free bases ($\Sigma\sigma^*$) is given in Fig. 2. A reasonably linear relationship is evidenced for the formamides and acetamides (darkened circles, points (1–6)), with $pK_{a(H_2O)} = -0.0315 - 1.235\Sigma\sigma^*$, and with a standard deviation for $\Sigma\sigma^*$ of 0.07. Deviations from linearity however, were marked for the larger propionamides, with base strengths lower than expected. Deviation was also significant for the cyclically substituted amide, N-formylpyrrolidine, and in the opposite direction. However, ease of hydrolysis make the pK_a data on this compound suspect. With the propionamides, the base strength reached a maximum with N,N-di-*n*-butyl-, and dropped for the N,N-diisobutylpropionamide.

B. With Phenol as Electron Acceptor.—A log K_{assn}–$\Sigma\sigma^*$ plot for nine N,N-disubstituted alkanoic acid amides as bases, with phenol as electron acceptor, was made from literature data. Joesten and Drago[13] determined the association constant in carbon tetrachloride using ultraviolet absorption techniques. Gramstad and Fuglevick[1] used infrared techniques, also in carbon tetrachloride, based on the shift of the hydroxyl stretching frequency of the free and complexed phenol. These were placed on the same temperature basis by the thermodynamic data of Joesten and Drago.[13] The results of both research groups for dimethylformamide agreed closely.

The plot of $\Sigma\sigma^*$ *vs.* log $K_{assn(phenol)}$ is shown in Fig. 3. For the simple alkanoic acid amides, it is evident that deviation from a linear relationship (and the onset of steric effects) occurs at least with N,N-diethylacetamide (entry 4 in Fig. 3). With the larger homologs, or with the cyclic derivatives, the log K_{assn} values are insensitive to increases in polarity of the substituents. Thus steric effects set in more quickly with phenol (in carbon tetrachloride) than with perchloric acid in nitromethane.

C. With Chloroform as Electron Acceptor.—To observe the effects of change of base strength with change in structure using chloroform as electron acceptor, a spectral parameter was used. This parameter was the relative frequency shift of the carbonyl stretching vibration frequency in dilute solution in isooctane and in chloroform $[(\gamma_{C=O(iso)} - \gamma_{C=O(HCCl_3)})/\gamma_{C=O(iso)}]$.

(11) Ref. 7, pp. 620–623.
(12) C. A. Streuli, *Anal. Chem.*, **31**, 1652 (1959); **32**, 985 (1960).
(13) R. L. Joesten and R. S. Drago, *J. Am. Chem. Soc.*, **84**, 2696 (1962).

Bellamy and Williams showed that plots of $\Delta\gamma_{C=O}/\gamma_{C=O}$ for several N-cyclically disubstituted amides in a set of solvents *vs.* $\Delta\gamma_{C=O}/\gamma_{C=O}$ for a reference solute (acetophenone) in the same solvents are linear.[14] Further, their data show that for the amides of the same range of base strength as those in our study, the slopes of such plots are linearly related to the polarity contribution of the substituents to the carbonyl group.[15]

In this work, instead of using a set of solvents, relative slopes were obtained by frequency measurements for the base in only two solvents: isooctane (in which the base is essentially nonassociated) and chloroform, the acid under investigation. The error in making this approximation for the relative slope is small; for dimethylacetamide, the approximate slope (relative to acetophenone as reference base) is 0.36 rather than 0.38 from the literature.[15]

The spectroscopic data are tabulated in Table II, and the relative slopes (relative frequency shifts $\Delta\gamma_{C=O}/\gamma_{C=O}$ divided into the relative frequency shift of the lowest member of the series, dimethylformamide); are plotted against $\Sigma\sigma^*$ in Fig. 4.

A straight line is indeed obtained for dimethylformamide, diethylformamide, and formylpyrrolidine, but curvature is exhibited at least as early as dimethylacetamide (point 3, Fig. 4), and with almost immediate development at this level of substitution of insensitivity of the base strength to the polarity of the substituents. Thus steric effects set in even more quickly with chloroform than with phenol as reference acid.

D. With Iodine as Electron Acceptor.—A few data for the N,N-disubstituted amides with iodine as electron acceptor are available from the literature,[16] which suggest that the steric interference for iodine complexes is somewhat greater than for phenol complexes. Thus, the deviation of σ^*, taken from the published log K_{assn}–$\Sigma\sigma^*$ plot for dimethylpropionamide,[16] is 0.4 for iodine, and 0.25 for phenol as acid.

To sum up, the order of increasing steric requirements of the acids in the associated species with N,N-disubstituted amides is perchloric acid < phenol < iodine, chloroform. This order should be independent of changes in solvent, as will be indicated in the Discussion, part III.

Discussion

I. Determination of pK_a.—It is recognized that measuring pK_a by titration of weak bases in nonaqueous solvents is a semiempirical technique, yet good estimates of basicity are often obtained, in which the e.m.f. at half neutralization is linearly related to the pK_a values determined in water.[17,18] Particularly good correlations have been obtained for amides titrated with perchloric or sulfuric acids in glacial acetic acid solution.[19]

It has also been shown that thermodynamic pK_a values for amides cannot at present be determined in concentrated aqueous acids using the Hammett acidity function H_0 and the log (protonated amide)/(amide). This is, presumably, a result of decreased hydration of the protonated species with increasing acidity.[20]

This difficulty would not be encountered in the nonaqueous titration method using nitromethane as the solvent, for the latter has practically no associative tendencies with cationic species.[21,22]

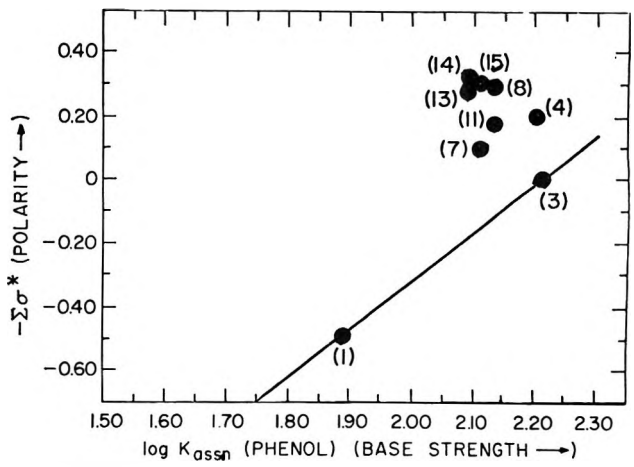


Fig. 3.—$\Sigma\sigma^*$ *vs.* log $K_{assn(phenol)}$ in carbon tetrachloride.

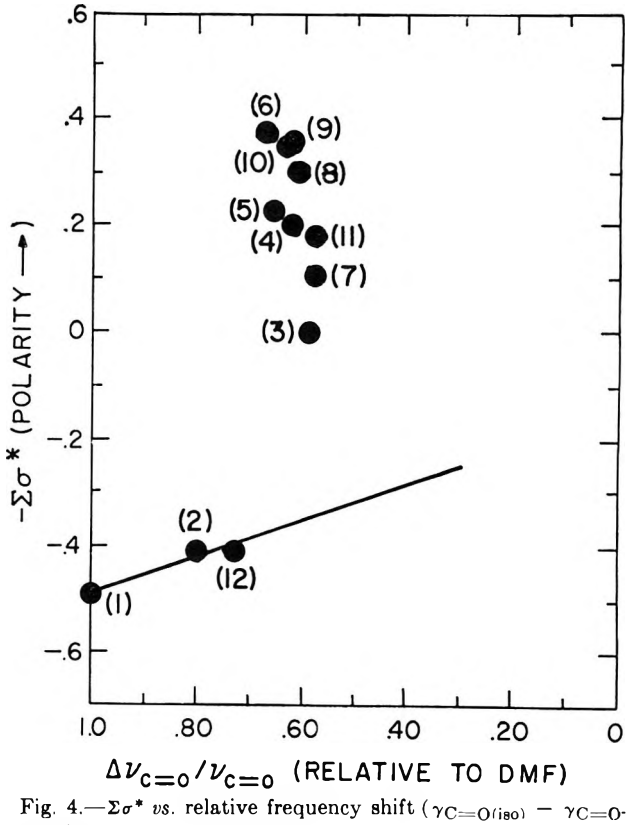


Fig. 4.—$\Sigma\sigma^*$ *vs.* relative frequency shift $(\gamma_{C=O(iso)} - \gamma_{C=O\cdot(HCCl_3)})/\gamma_{C=O(iso)}$. Expressed as $\Sigma\sigma^*$ *vs.* ratio of $\Delta\gamma/\gamma_{(dimethylformamide)}$:$\Delta\gamma/\gamma_{(amide)}$.

(14) L. J. Bellamy and R. L. Williams, *Proc. Roy. Soc.* (London), **255**, 22 (1960), and earlier references.

(15) Specifically note Fig. 16 in ref. 14, the first six points of the plot. These include diethylacetamide, N-acetylpyrrolidine, N-acetylindole, N-acetylpyrrole, N-acetyliminazole, N-acetyl-1,2,4-triazole. The polarity of the carbonyl group was taken to be inversely proportional to the resonance energy of the heterocyclic ring.

(16) R. S. Drago, D. A. Wenz, and R. L. Carlson, *J. Am. Chem. Soc.*, **84**, 1106 (1962).

(17) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 62 (1956).

(18) E. M. Arnett, "Progress in Physical Organic Chemistry," Vol. I, S. G. Cohen, *et al.*, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp. 248–250, 270–274, and reference cited.

(19) N. F. Hall, *J. Am. Chem. Soc.*, **52**, 5115 (1930).

(20) R. B. Homer and R. B. Moodie, *J. Chem. Soc.*, 4377 (1963), and references cited.

(21) L. C. Smith and L. P. Hammett, *J. Am. Chem. Soc.*, **67**, 23 (1945).

(22) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 34 (1957).

In addition, Van Looy and Hammett have shown that strong acids in nitromethane solvent at concentrations less than 0.1 *M* probably undergo acid–base equilibria of the following type.[23]

$$\text{Base} + \text{HA} \rightleftharpoons \text{BH}^+\cdot\text{A}^- \quad (1)$$

$$\text{Base} + 3\text{HA} \rightleftharpoons [\text{BH}^+]\cdot[\text{A}(\text{HA})_2^-] \quad (2)$$

At the concentration of our titrations (<0.005 *M* acid), equilibrium 1 could be highly favored. This gives us an opportunity to compare the steric requirements of three acids, differing widely in the degree of proton transfer in forming the complex, yet uncomplicated by variations in solvation. (See also Discussion, part IV.)

It was recognized that nitromethane is very difficult to purify,[23] and so nitromethane practical grade was used, as it was by Streuli.[12] The linear $pK_{a(H_2O)}$–e.m.f.$_{(1/2)}$ relationship for amides and amines was corroborated. Hall has also shown that linear polar energy relationships exist for tertiary amine–perchloric acid complexes in a variety of solvents, including nitromethane, and that the relative orders of base strengths were equivalent in these solvents.[17,24]

II. Order of Steric Requirements.—The observation that the variable steric effects with amides as bases are smaller with perchloric acid nonsolvated ion pairs than with phenol associates is in line with previous studies using tertiary aliphatic amines as bases. Thus, negligible variable steric effects were observed for tertiary amines with perchloric acid,[24] but were indeed found with phenol as electron acceptor.[25]

Gramstad has shown that N,N-disubstituted amides may be considered to have lower steric requirements (with phenol as acid) than the tertiary amines or aliphatic ethers (the former gave linear log K–$\Delta\gamma_{OH}$ plots, while the amines or ethers did not).[25]

The low steric requirements for the perchloric acid–amide complexes may be due to loose association of the perchlorate anion with the oxonium cations, characteristic of perchlorate ion pairs with large planar cations.[26]

III. Base Strength–Potential Energy Relationships for the Various Electron Acceptors.—With phenol as acid, and for N,N-disubstituted amides at least up to N,N-diethylbutyramide as bases, Gramstad has shown that the enthalpy change on association, $\Delta\Delta H_{assn}°$, is proportional to the entropy change, $\Delta\Delta S_{assn}°$.[27] Thus the standard free energy change, $\Delta\Delta F_{assn}°$, is also proportional to $\Delta\Delta S_{assn}°$. Therefore, $\Delta\Delta F_{assn}°$ or log K_{assn}, the base strength parameters,[28] as well as $\Delta\Delta H_{assn}°$ are proportional to the potential energy change, $\Delta\Delta E_p°$—the quantity related to structural factors such as dipole fields, resonance energies, bond energies, and electronic displacements.[30]

With perchloric acid as electron acceptor, log K ($\Delta\Delta F°$) values were determined. Since variable steric effects were found to be smaller with perchloric acid than with phenol, $\Delta\Delta F°$ is apparently proportional to $\Delta\Delta H°$ (and $\Delta\Delta E_p°$) in this case, also.

With chloroform as electron acceptor, the relative frequency shift was proportional to the polarity, and, therefore, also proportional to $\Delta\Delta E_p°$.[28,31]

Thus, the relative base strengths obtained with the above electron acceptors appear to be directly comparable.

IV. Sources of Deviation in Base Strength–$\Sigma\sigma^*$-Plots.—As mentioned above, variable steric effects involving solvation appear to be minor in these series. For amide–phenol complexes in carbon tetrachloride, linear $\Delta\Delta F°$–$\Delta\Delta H°$–$\Delta\Delta S°$ relationships were exhibited,[27] which indicate negligible variable entropic or enthalpic solvent effects. With perchloric acid in nitromethane, the ion pair was essentially nonsolvated (see Discussion, part I). Variable steric effects occurred most quickly with chloroform as acid, when no added solvent was present.

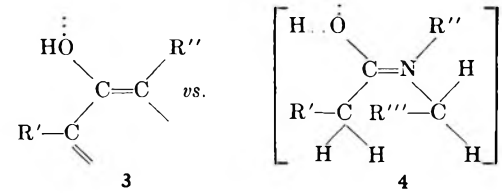
Thus, the primary source of the variable steric effects in the $\Sigma\sigma^*$–base strength plots appears to be internal rather than external. In addition, it involves steric strain rather than interference to internal motion. The latter conclusion is evidenced by the linear $\Delta\Delta F°$–$\Delta\Delta S°$ relationship in the phenol associated complexes.[27]

V. Sources of Variable Steric Strains.—In general, the potential energy term $\Delta\Delta E_p°$ may be considered as the sum of independent inductive, resonance, and steric repulsion (strain) effects.

For the planar N,N-disubstituted amide complexes, the inductive and resonance effects have been accounted for in the estimation of the polar contribution, $\Sigma\sigma^*$, for X and NY_2. However, where steric strains exist, these may result in inhibition of resonance, a reduction in the contribution of the planar structure, and a reduction of the polar contribution of the substituents.

The steric strain might be accommodated, then, by either (a) an opening or twisting of the C–O···H bond, and/or (b) steric inhibition of resonance by twisting the C–N bond.

An estimate of the contribution of (a) and (b) might be made by considering the *ortho*-substituted phenols as limiting models for the planar N,N-disubstituted amide complexes. These structures appear quite similar (structures **3** and **4**). (1) The bond lengths appear to be



3 **4**

essentially equivalent, 1.39 ± 0.02 for the C–C bond in benzene[32] or resorcinol[33] and 1.38 ± 0.05 for the C–N bond in acetamide.[34] (2) The amide structure is essen-

(23) H. Van Looy and L. P. Hammett, *J. Am. Chem. Soc.*, **81**, 3872 (1959); E. M. Arnett and C. F. Douty, *ibid.*, **86**, 409 (1964).
(24) H. K. Hall, Jr., *ibid.*, **79**, 5441 (1957).
(25) T. Gramstad, *Acta Chem. Scand.*, **16**, 807 (1962).
(26) N. N. Lichtin, "Progress in Physical Organic Chemistry," Vol. I, S. G. Cohen, *et al.*, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp. 83–84.
(27) T. Gramstad, *Spectrochim. Acta*, **19**, 497 (1963).
(28) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 262.
(29) Ref. 7, pp. 660–663.
(30) Ref. 28, pp. 76–78.
(31) L. J. Bellamy, G. Eglinton, and J. F. Morimon, *J. Chem. Soc.*, 4762 (1961).
(32) V. Schomaker and L. Pauling, *J. Am. Chem. Soc.*, **61**, 1769 (1939).
(33) J. M. Robertson and A. R. Ubbelohde, *Soc. Proc. Roy.* (London), **A167**, 122 (1938).
(34) F. Senti and D. Harker, *J. Am. Chem. Soc.*, **62**, 2008 (1940). The base strength of acetamide is in the same range as the N,N-disubstituted amides [R. Huisgen and H. Brade, *Ber.*, **90**, 1432 (1957)].

tially planar. (3) Rotational interference between $R'CH_2$ and $R'''CH_2$ groups (structure **4**) as shown by models, is minimized by a conformation in which R′ is *trans* to the nitrogen atom.

In the phenols, however, steric inhibition of resonance by twisting of the C=C bond is highly unlikely, and steric strains are accommodated only by the change in the C–O–H bond angle.[31] Published spectral data on these *ortho*-disubstituted phenols also indicate that increased size and branching of R′ and R″ is not reflected in change of the C–O–H bond angle until the substituents get much larger than in our amide complexes. That is, a reasonably linear relationship was observed between the free or the associated hydroxyl stretching vibration frequencies and the polarity ($\Sigma\sigma^*$) of the di-*ortho*-alkyl substituents up to 2,6-di-*t*-butylphenol.[31,35]

Since the free and also the associated C–O–H bonds are so resistant to accommodating steric strains in the *ortho*-disubstituted phenols, it seems likely that the C–O · · · H bond in the amide complexes would be similarly unaffected. We therefore propose that steric strain in amide complexes can be partially relieved by twisting around the C–N bond, to avoid unfavorable *cis* interactions.

This conclusion is reasonable in terms of the low energy barrier restricting internal rotation (6–9 kcal./mole) in the N,N-disubstituted amides.[2,3] Further, the eventual insensitivity of the base strength to $\Sigma\sigma^*$-values with phenol or with chloroform as acids supports the view of the C–N bond twist. Thus, if the molecule remained planar, increasingly large deviations in base strength with increase in size of the substituents would have been expected. This is seen in the enthalpy of dissociation of 2-alkylpyridine–boron trifluoride addition compounds.[36]

With continued increase in size of the substituents, restriction to internal motions (entropy effects) would eventually be superimposed on the steric strain, and the log K_{assn} for the phenol–amide complexes would then deviate significantly from a linear correlation with $\Delta\gamma_{OH}$. This was indeed reported for the phenol–ether[31] or the phenol–tertiary amine complexes.[25]

The lower N,N-disubstituted amides, then, form a group in which variable steric strains are evidenced before variable steric interference to internal motion, due to the low energy barrier to rotation around the C–N bond. This indicates an exception to the "strain–entropy" principle, which postulates that steric strains are always preceeded or accompanied by steric interference to internal motions.[37]

Experimental

I. **Solvents.**—The tetramethylurea was obtained from the Du Pont Industrial and Biochemicals Department and redistilled. The acetylpiperidine was Eastman technical grade. The N-methylpyrrolidone was obtained from the General Aniline and Film Corp. and was distilled under reduced pressure. All of the other N,N-disubstituted amides were Eastman White Label grade. These were shaken with a saturated solution of sodium bicarbonate in water until evolution of carbon dioxide ceased. The crude products were distilled under reduced pressure, treated with anhydrous sodium sulfate, then Drierite, and redistilled under reduced pressure. The 80% center cuts were retained and stored over Drierite. Data on the amides are assembled in Table I. Methanol-free chloroform was obtained by washing the stabilized product six times with equal volumes of water, followed by drying and distillation under nitrogen and storage under nitrogen. The isooctane (Phillips spectroscopic grade 2,2,4-trimethylpentane) was boiled, and a 5% foreshot removed. For spectroscopic studies, 0.1% solutions by volume (approximately 0.01 *M*) of the amides in chloroform and in isooctane were prepared in volumetric flasks which had been scoured with detergent, washed with water, rinsed with acetone, vacuum-dried, flamed under nitrogen, and prerinsed with pure solvent.

II. **Infrared Spectroscopy.**—The spectroscopic data were obtained with a Perkin-Elmer No. 21 double beam spectrometer, with NaCl optics. Temperature was 72°F., and relative humidity 50%. Calibration of frequency values was made against H_2O, CO_2 in the 5–6-μ region and checked against a grating instrument. Values were correct to within 2 cm.$^{-1}$. Infrared data for the carbonyl band on diluted samples of amides in CCl_4 or $HCCl_3$ agreed with Bellamy's data within 2 cm.$^{-1}$. (See Table II.)

III. **Determination of pK_a Values *via* Potentiometric Titrations.**—The potentiometric titration procedure used for the determination of the pK_a of these bases (where $K_a = [B][H^+]/[BH^+]$ for the reaction $BH^+ \rightleftharpoons B + H^+$) was based on the method of Streuli[12] which he applied to a variety of amines, amides, and ureas. It involves the potentiometric titration of these weak bases with perchloric acid in dilute nitromethane solution. In summary, linear $pK_{a(H_2O)}$–e.m.f.$_{(1/2)}$ correlations resulted. Some differences in slope were observed between our data and those of Streuli. However, our data for N,N-disubstituted amides and amines agreed closely with those of Streuli in relative $pK_{a(H_2O)}$ values, which was sufficient for our present purposes.

The relative pK_a values in our series, with their limited structure variation and the precautions taken in their measurement, have the desired level of precision, to about 0.03 pK units.

Titrations were performed point by point with a Beckman Zeromatic pH meter Model 9600 using a Beckman calomel aqueous sleeve electrode 4925-N60 and Beckman glass electrode 1190-80. Equivalent results were obtained with another set of glass calomel electrodes. The nitromethane was Matheson practical grade and used directly. The perchloric acid solution was prepared by diluting 4.2 ml. of 72% acid to 1 l. in nitromethane and was stored in a closed brown bottle. Streuli reported that the perchloric acid solutions were stable for about 1 month, but that the HNP (half-neutralization potential) values could vary by as much as 100 mv. over several days' time. He eliminated this difficulty by determining the ΔHNP; the difference between the HNP for the compound being tested and the HNP for a N,N′-diphenylguanidine sample (HNP $\approx$ 0) run the same day. The HNP was reproducible within 5–6 mv.

We further ensured against variation in the stock solutions by (a) using the same stock solution of CH_3NO_2 for all dilutions, and (b) determining the HNP value at the beginning and again at the end of the series of runs, which was completed within a 15-hr. period. An increase in 50 mv. was observed for the HNP of the diphenylguanidine over this period, and so the ΔHNP values for the amides titrated were appropriately corrected, depending on the time during this period in which the individual titrations were carried out. Approximately 0.0010 mole ($\approx$0.1000 g.) of compound was dissolved in nitromethane and made up to volume in a 100-ml. Kimex volumetric flask. A 25.00-ml. aliquot was diluted with 25.0 ml. of nitromethane (concentrated 0.005 *M*) and, using a magnetic stirrer, was titrated with the 0.05 *N* perchloric acid in nitromethane solution from a microburet well beyond the point of complete neutralization.

Steady e.m.f. values were obtained within 2–3 sec. of mixing in all cases except for the first 5% per cent-of-neutralization values. A typical moderate base–strong acid titration curve was obtained for bases as strong as pyridine (pK_a of the conjugate acid $\approx$ 5). With weaker bases such as the N,N-disubstituted amides (lower pK) the titration curves were reduced to an inflection point at complete neutralization. Streuli carried out his titrations at 0.00125 *M* concentrations rather than 0.005 *M*, and we observed with dimethylacetamide that a sharper inflection point did appear to result at the lower concentration. However, at the higher concentration, the inflection point still occurred at the calculated stoichiometric end point for the titration, and the e.m.f. value at half neutralization was not appreciably changed (within 10 mv.) by the increased dilution of the base (and the decreased

(35) See L. J. Bellamy and R. L. Williams, *Proc. Roy. Soc.* (London), **A254**, 119 (1960), for other supporting data.

(36) H. C. Brown and R. H. Horowitz, *J. Am. Chem. Soc.*, **77**, 1733 (1955); see also ref. 7, p. 674.

(37) Ref. 7, p. 669–670.

amount of water present) during the titration. Therefore, all titrations were carried out at 0.005 *M* concentrations. The pK_a point was always in the desired flat portion of the titration curve. The e.m.f. at half neutralization was taken as one-half the calculated stoichiometric end point. As mentioned above, the latter was always very close to the observed inflection point, and resulted in a maximum error of e.m.f. values of about 5 mv. Runs were carried out in duplicate. Repeat determinations were always within 10 mv. and generally within 5 mv. The collected Δe.m.f. values at half neutralization (ΔHNP values, referred to N,N′-diphenylguanidine) are given in Table III. A plot of these ΔHNP values *vs.* literature $pK_{a(H_2O)}$ values for several of these bases (diphenylguanidine, triethylamine, pyridine, acetamide, and urea) indicated a straight-line relationship, and so the $pK_{a(H_2O)}$ values for the series of N,N-disubstituted amides are interpolated from this line (Tables I and III).

The least-squares calculation of $pK_{a(H_2O)}$ *vs.* ΔHNP was $pK_{a(H_2O)} = 10.10 - 0.0118\Delta HNP$, with a standard deviation of 33 mv. This is appreciably different in slope from the equation calculated from Streuli's reported data for these compounds, of $pK_{a(H_2O)} = 10.10 - 0.0152\Delta HNP$.[12] On the other hand, our equation based on amides, ureas, and amines is quite close to Streuli's equation reported for amines and for N,N-disubstituted amides ($pK_{a(H_2O)} = 10.12 - 0.0129\Delta HNP_{(CH_3NO_2)}$).

Acknowledgment.—We are deeply indebted to Miss N. Schlichter, Du Pont Central Research Department, for the infrared measurements, and to Dr. H. K. Hall, Jr., Du Pont Textile Fibers Department, and Professor G. S. Hammond for stimulating discussion.

Reaction of Cyclic Phosphoramidites with Disulfides. I. A Novel Synthesis of Phosphoramidothioates

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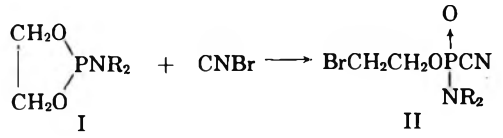
N,N-Disubstituted cyclic esters of phosphoramidous acid react readily with aromatic disulfides, tetraalkylthiuram disulfides, and certain heterocyclic disulfides to give derivatives of phosphoramidothioic acid in which the ring of the phosphoramidite has been opened. Benzhydryl and allyl disulfide are desulfurized by cyclic phosphoramidites without ring opening to give *sym*-tetraphenylethane and allyl sulfide, respectively. Simple aliphatic disulfides are not reactive towards cyclic phosphoramidites at the temperature of refluxing toluene. Alkyl aryl disulfides are cleaved by preferential attachment of the alkylthio moiety to phosphorus. A mechanistic rationalization of these experimental facts is presented.

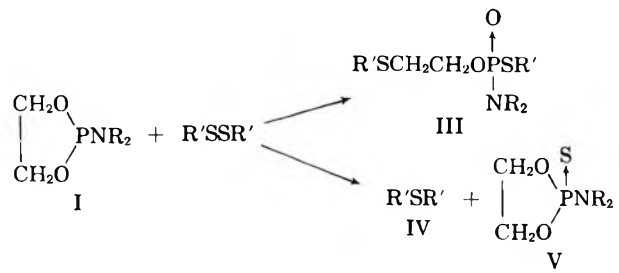
The chemistry of cyclic esters of phosphoramidous acid (I) has received only scant attention; Arbuzov found that they react abnormally with alkyl halides to form poorly defined products although they add sulfur normally[3] and apparently undergo a typical Arbuzov reaction with cyanogen bromide to give phosphoramidocyanidates (II).[4] Their brief chemistry has recently been reviewed.[5,6]



I II

We were interested in reactions of disulfides with cyclic phosphoramidites; they have not been studied although the reaction of trialkyl and triaryl phosphites with disulfides has been investigated extensively[7-11] and reviewed recently.[5,12] These latter reactions are mainly ionic and supposedly proceed by a Michaelis–Arbuzov mechanism. Since cyclic phosphoramidites are more nucleophilic than trialkyl phosphites, reaction with disulfides seemed a distinct possibility. This has been shown to be the case as discussed in more detail below.

At least two possible courses can be envisioned for the reaction of a cyclic phosphoramidite with a disulfide: Michaelis–Arbuzov rearrangement with cleavage of the phospholane ring to form the phosphoramidothioic ester (III), or desulfurization, with no ring cleavage, to form the corresponding sulfide (IV) and cyclic phosphoramidothionate (V). We have found that both reactions



I III IV V

do occur, the path being determined by the nature of the disulfide reactant. For example, when an N,N-disubstituted cyclic phosphoramidite of general structure I [R = C_2H_5, $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$] is mixed with an aromatic disulfide, a vigorously exothermic reaction occurs and an acyclic phosphoramidothiolate (III, R′ = aryl) is formed in almost quantitative yield. Tetramethylthiuram disulfide reacts analogously with cyclic phosphoramidites derived from propylene glycol (VI) to give mixed anhydrosulfides

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(3) A. E. Arbuzov and V. M. Zoroastrova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 789 (1952).

(4) G. Schrader, German Patent 949,650; *Chem. Abstr.*, **51**, 12,957 (1957).

(5) J. I. G. Cadogan, *Quart. Rev.* (London), **16**, 208 (1962).

(6) R. S. Edmundson, *Chem. Ind.* (London), 1770 (1962).

(7) H. I. Jacobson, R. G. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 6064 (1955).

(8) A. C. Poshkus and J. E. Herweh, *ibid.*, **79**, 4245 (1957).

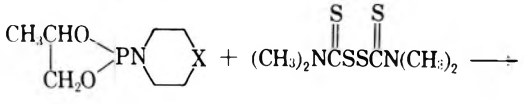
(9) J. Michalski and J. Wieczorkowski, *Bull. Acad. polon. Sci. Classe III*, **5**, 917 (1957); *Chem. Abstr.*, **52**, 6157 (1958).

(10) K. Pilgram, Ph.D. thesis, Universität Würzburg, 1959.

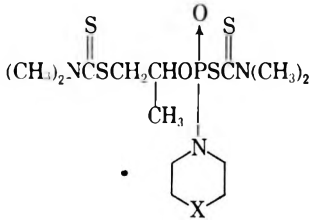
(11) R. L. McConnell, U. S. Patent 2,865,960; *Chem. Abstr.*, **53**, 12,181 (1959).

(12) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 621 (1959).

(VII).[13] Only one heterocyclic disulfide, 2-benzthiazolyl disulfide, has been investigated; it reacted with a cyclic phosphoramidite (VI, X = CH_2) to form the product analogous to VII.



VI



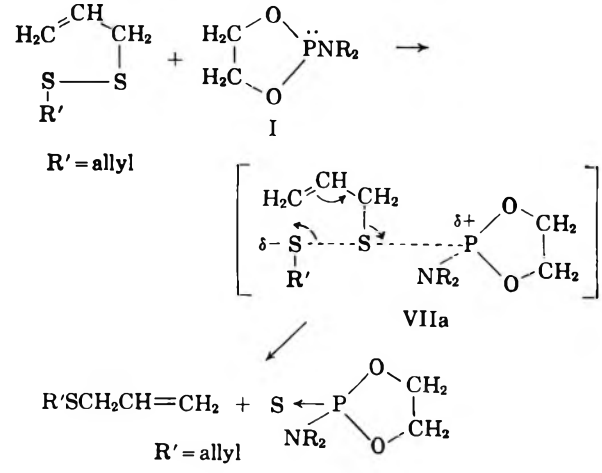
VII

Allyl disulfide reacted with a cyclic phosphoramidite (I, R = C_2H_5) at room temperature, but with only slight exothermicity; the products were those of desulfurization, *i.e.*, allyl sulfide (IV, R′ = allyl) and the cyclic phosphoramidothionate (V, R = C_2H_5). In this respect the reaction is similar to the desulfurization of allyl disulfide with triphenyl phosphine.[15]

Benzhydryl disulfide did not react with the cyclic phosphoramidite (I, R = C_2H_5) until the reaction temperature reached 150°. At this point a vigorous reaction ensued with the formation of *sym*-tetraphenylethane and, presumably, the cyclic phosphoramidothionate (V, R = C_2H_5), although the presence of the latter was not definitely established. The appearance of a transitory blue color during the course of the reaction as well as the nature of the products isolated strongly suggest a radical mechanism for this particular transformation

Simple alkyl disulfides, such as ethyl disulfide, do not react with cyclic phosphoramidites when heated to reflux in toluene solution. Benzhydryl disulfide is similarly unreactive in refluxing toluene and the strenuous conditions referred to above (150°, no solvent) had to be employed before any reaction took place.

In seeking a rationalization for the observation that alkyl disulfides are unreactive towards cyclic phosphoramidites in refluxing toluene while allyl disulfide is desulfurized by the same reagent under mild conditions, we were struck by the similarity of these results and those of Moore and Trego.[16] These workers found that alkyl disulfides are stable to the reaction of triphenyl phosphine at 140°, whereas allylic disulfides are smoothly desulfurized at 80°. The Sni′ mechanism proposed by these authors[16] seems applicable to the reaction discussed herein, and in the absence of supporting kinetic data, provides a convenient rationalization for our results. For example, allyl disulfide and



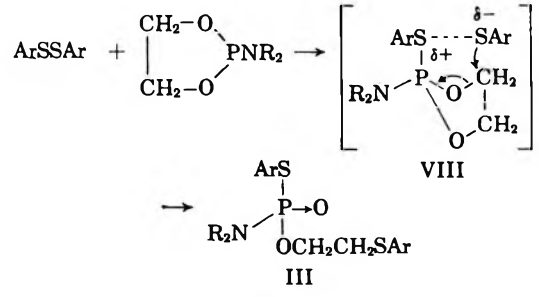
R′ = allyl

VIIa

R′ = allyl

the cyclic phosphoramidite (I, R = C_2H_5) are assumed to react by way of the transition state VIIa which can uniquely collapse to the products by the series of electronic shifts shown. A simple alkyl disulfide, lacking the unsaturation of the allyl group, would have to undergo an energetically much less favorable Sn2 attack of RS^- on a saturated carbon atom to form the same type of products, and it is consequently not surprising that an alkyl disulfide does not react with a cyclic phosphoramidite under mild conditions. The fact that triphenylphosphine requires a temperature of 80° to desulfurize allyl disulfide,[16] whereas the cyclic phosphoramidite (I, R = C_2H_5) partially desulfurizes allyl disulfide at room temperature, can be ascribed to the greater nucleophilicity of I in which the electron density about the phosphorus atom is increased by electron release from nitrogen.

The reaction of an aryl disulfide with a cyclic phosphoramidite to form phosphoramidothioate III may be regarded as a typical Michaelis–Arbuzov reaction.

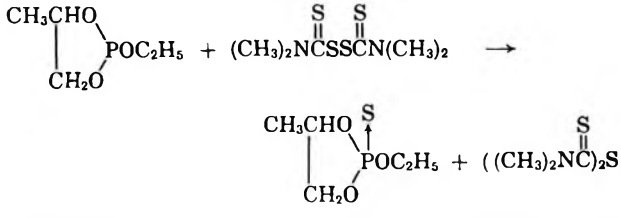


VIII

III

In the transition state VIII it is probable that stabilization of the negative charge on sulfur is necessary before the electronic shifts shown in VIII can occur to give III (see discussion above). Such stabilization is provided by delocalization of the charge throughout the aromatic ring or, as in the case of the tetraalkylthiuram disulfides which also undergo this reaction, by the $R_2NC(=S)$— group. In order to establish the importance of this stabilization, we examined the reaction between the unsym-

(13) This is in contrast to the reaction between tetramethylthiuram disulfide and ethyl propylene phosphite which we have found to take the following course.



The desulfurization of tetramethylthiuram disulfide also occurs when it is heated with triphenyl phosphine.[14]

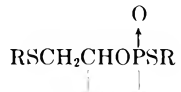
(14) A. Schonberg, *Ber.*, **68**, 163 (1935).

(15) F. Challenger and D. Greenwood, *J. Chem. Soc.*, 26 (1950).

(16) C. G. Moore and B. R. Trego, *Tetrahedron* **18**, 205 (1962); *J. Chem. Soc.*, 4205 (1962).

TABLE I

PHOSPHORAMIDOTHIOATES[a]



R	R′	X	Formula	Yield, %	B.p. (μ) or m.p., °C.	Analyses, % Nitrogen Caled.	Nitrogen Found	Phosphorus Caled.	Phosphorus Found	Sulfur Caled.	Sulfur Found
Phenyl	CH_3	Piperidino	$C_{20}H_{26}NO_2PS_2$	87	205 (0.1)	3.44	3.14	7.61	7.8	15.73	15.8
4-Nitrophenyl	H	Diethylamino	$C_{18}H_{22}N_3O_6PS_2$	100	*b*	8.88	8.9	6.56	6.7	13.55	13.8
4-Nitro-*o*-tolyl	H	Diethylamino	$C_{20}H_{26}N_3O_6PS_2$	100	*b*	8.41	8.1	6.21	6.5	12.72	12.7
6-Nitro-*o*-tolyl	H	Diethylamino	$C_{20}H_{26}N_3O_6PS_2$	100	66–67	8.41	8.7	6.21	6.3		
6-Nitro-*o*-tolyl	H	Piperidino	$C_{21}H_{26}N_3O_6PS_2$	100	*b*	8.22	8.1	6.07	6.4	12.55	12.6
3-Nitro-*o*-tolyl	H	Diethylamino	$C_{20}H_{26}N_3O_6PS_2$	100	82–83	8.41	8.6	6.21	6.7	12.72	12.9
3-Nitro-*o*-tolyl	H	Piperidino	$C_{21}H_{26}N_3O_6PS_2$	100	*b*	8.22	7.9	6.07	6.1	12.55	11.8
5-Nitro-*o*-tolyl	H	Diethylamino	$C_{20}H_{26}N_3O_6PS_2$	100	*b*	8.41	7.8	6.21	6.3	12.72	12.9
2-Methoxy-4-nitrophenyl	H	Diethylamino	$C_{20}H_{26}N_3O_8PS_2$	100	*b*	7.91	7.4	5.84	6.2		
2-Benzthiazolyl	CH_3	Piperidino	$C_{22}H_{24}N_3O_2PS_4$	100	*b*			5.95	6.0	24.6	23.8
Dimethyldithiocarbamoyl	CH_3	Piperidino	$C_{14}H_{28}N_3O_2PS_4$	25	91–92, 110–111			7.22	7.3	29.9	31.5
Dimethyldithiocarbamoyl	CH_3	4-Morpholino	$C_{13}H_{26}N_3O_3PS_4$	30	120–121	9.75	9.6	7.18	7.5	29.7	30.4

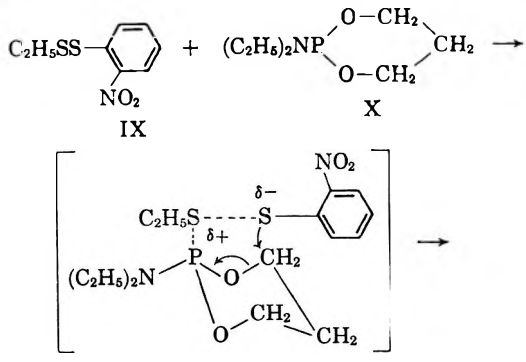
[a] All products showed characteristic >P→O absorptions in the infrared in the region of 7.8–8.0 μ. [b] Undistillable oil; thin-layer chromatography showed the presence of one component.

TABLE II

BIS(ARYL) DISULFIDES, RSSR

R	Formula	Yield, %	M.p., °C.	Analyses, % Nitrogen Caled.	Nitrogen Found	Sulfur Caled.	Sulfur Found
6-Nitro-*o*-tolyl	$C_{14}H_{12}N_2O_4S_2$	78	149	8.33	8.3	19.05	19.1
3-Nitro-*o*-tolyl	$C_{14}H_{12}N_2O_4S_2$	78.5	121	8.33	8.2	19.05	19.2
5-Nitro-*o*-tolyl	$C_{14}H_{12}N_2O_4S_2$	81	151	8.33	7.7	19.05	18.8
2-Methoxy-4-nitrophenyl	$C_{14}H_{12}N_2O_6S_2$	67.5	188.5	7.61	7.4	17.40	17.2

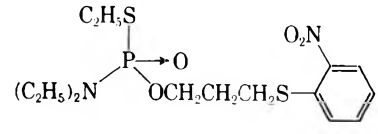
metrical disulfide IX and the phosphoramidite X. The reaction was much more exothermic than any of the diaryl disulfide examples (see Table I) and proceeded with exclusive formation of XI.[17] The absence of the



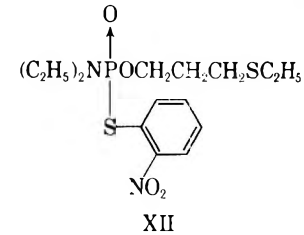
IX X

other product (XII) that would result from incipient formation of $C_2H_5S^-$ in the transition state, we regard as supporting evidence for the postulated mechanism.[18a]

This facile reaction between cyclic phosphoramidites and suitably constituted disulfides represents a convenient preparative method for phosphoramidothioates of structures III and VII. The thermal behavior of compounds of this type is described in the accompanying paper.[18b]



XI



XII

Experimental

All melting and boiling points are uncorrected. Infrared absorption spectra were determined in carbon tetrachloride solution on a Beckman IR-4 double beam instrument.

Materials.—Phenyl disulfide, tetramethylthiuram disulfide, and allyl disulfide were commercial products and were used without further purification. *p*-Nitrophenyl disulfide[19] and benzhydryl disulfide[20] were each prepared according to a literature procedure. The new disulfides listed in Table II were prepared by introducing ammonia into a suspension of the corresponding thiocyanate in ethanol following a known procedure.[21] Ethyl propylene phosphite, 2-diethylamino-1,3,2-dioxaphospholane, 2-piperidino-1,3,2-dioxaphospholane, and 2-piperidino-4-methyl-1,3,2-dioxaphospholane were prepared as previously described.[22] The latter procedure was also used to prepare the

(17) The structure of XI was proven by hydrolysis experiments, details of which may be found in the Experimental section.

(18) (a) Since the completion of this work, similar results have been reported for the reaction between triethyl phosphite and unsymmetrical disulfides by R. G. Harvey, H. I. Jacobson, and E. V. Jensen [*J. Am. Chem. Soc.*, **85**, 1618 (1963)]. These authors ascribe the difference in reactivities to a different ease of polarization in unsymmetrical disulfides. (b) K. Pilgram, D. D. Phillips, and F. Korte, *J. Org. Chem.*, **29**, 1848 (1964).

(19) T. Zincke and S. Lenhardt, *Ann.*, **400**, 2 (1913).

(20) H. Staudinger and H. Freudenberger, *Ber.*, **61**, 1576 (1928).

(21) K. Brand and H. W. Leyerzapf, *ibid.*, **70**, 288 (1937).

(22) H. G. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950).

new **2-(4-morpholino)-4-methyl-1,3,2-dioxaphospholane**, b.p. 77° (0.08 mm.), $n^{20}D$ 1.4897, 29% yield.

Reaction of Cyclic Phosphoramidites with Disulfides.—The results from the reaction of cyclic phosphoramidites with disulfides are summarized in Table I. The general procedures are illustrated by the reaction of 2-piperidino-4-methyl-1,3,2-dioxaphospholane with phenyl disulfide and by the reaction of 2-(4-morpholino)-4-methyl-1,3,2-dioxaphospholane with tetramethylthiuram disulfide.

S-Phenyl O-(2-Phenylthio-1-methylethyl)piperidinophosphonothioate.—A mixture of 2-piperidino-4-methyl-1,3,2-dioxaphospholane (18.9 g., 0.10 mole) and phenyl disulfide (21.8 g., 0.10 mole) in a 100-ml. flask fitted with a thermometer and magnetic stirrer was gradually heated to 40° at which point an exothermic reaction occurred and the internal temperature rose rapidly to approximately 175°. The resultant light yellow viscous oil was molecularly distilled to give 35.5 g. (87.3%) of the phosphoramidothioate as a colorless viscous liquid, b.p. 205° (0.1 μ), $n^{25}D$ 1.5873, and 5 g. of a light yellow residue; the latter was identical with the distilled product as shown by thin-layer chromatograms.

O-[2-(Dimethylthiocarbamoylthio)-1-methylethyl]morpholinophosphonothioate Anhydrosulfide with Dimethyldithiocarbamic Acid (VII, X = O).—To a stirred suspension of tetramethylthiuram disulfide (12.0 g., 0.05 mole) in toluene (25 ml.) was added, at room temperature, 2-(4-morpholino)-4-methyl-1,3,2-dioxaphospholane (9.55 g., 0.05 mole) in two portions. A clear solution resulted and the internal temperature rose immediately to approximately 75°. After the reaction mixture had stood overnight at room temperature, colorless crystals separated. Filtration afforded 5.5 g. (30.1%) of the desired product, m.p. 120–121° (from ethanol).

Reaction of 2-Diethylamino-1,3,2-dioxaphospholane with Benzhydryl Disulfide. A. Without Solvent.—A mixture of 2-diethylamino-1,3,2-dioxaphospholane (9.78 g., 0.06 mole) and benzhydryl disulfide (11.94 g., 0.03 mole) in a 50-ml. flask fitted with a magnetic stirrer and thermometer was gradually heated under a nitrogen atmosphere. When the temperature of the initially colorless solution reached 100°, a blue color appeared. When the temperature reached 140°, an exothermic reaction occurred and the internal temperature rose to reflux (250°). The dark blue color disappeared and, on cooling to 120°, the reaction mixture solidified. After cooling to room temperature, 100 ml. of ether was added to the red-brown reaction product, and the solid was filtered and recrystallized from 200 ml. of toluene. There was obtained 5.5 g. (54.8%) of *sym*-tetraphenylethane, m.p. 217°.

Anal. Calcd. for $C_{26}H_{22}$: C, 93.4; H, 6.6. Found: C, 92.9; H, 6.7.

The residual oil from the mother liquors (6 g.) was not investigated.

B. With Toluene as Solvent.—The same amounts of reactants as used in the preceding experiment were dissolved in toluene (50 ml.) and refluxed under a nitrogen atmosphere for 2 hr. (internal temperature 145–148°). After this time the starting materials were largely recovered.

Reaction of 2-Diethylamino-1,3,2-dioxaphospholane with Allyl Disulfide.—2-Diethylamino-1,3,2-dioxaphospholane (12.3 g., 0.076 mole) was treated with 11.0 g. (0.076 mole) of allyl disulfide at 24°. The temperature rose to 39° within 10 min. The mixture then was heated to 80° for 4 hr. and molecularly distilled to give 11.0 g. (78%) of **O,O-ethylene diethylphosphoramidothionate** (V, R = C_2H_5) as a mobile yellow oil, b.p. 100° (0.1 μ), $n^{25}D$ 1.5042.

Anal. Calcd. for $C_6H_{14}NO_2PS$: P, 15.9; S, 16.4. Found: P, 15.1; S, 16.4.

Allyl sulfide (7.0 g., 82%) was recovered from the cold trap and was identified by comparison of its infrared absorption spectrum with an authentic specimen.

Reaction of Ethyl Propylene Phosphite with Tetramethylthiuram Disulfide.[13]—Tetramethylthiuram disulfide (24.0 g., 0.1 mole) dispersed in 50 ml. of toluene was treated at 22° with 15.0 g. (0.10 mole) of ethyl propylene phosphite. The temperature rose within 10 min. to about 45° and the tetramethylthiuram disulfide slowly dissolved to give a yellow-green solution. The solution then was heated under reflux for 2 hr. and allowed to stand overnight. The yellow crystals that separated (10 g.) were filtered. On cooling in Dry Ice–acetone, the mother liquors afforded a second crop of 6 g.; the total yield of tetramethylthiuram sulfide was 77%, m.p. 110°.

The solvent was removed from the mother liquors and the residue was molecularly distilled to give 18.0 g. (99%) of **O-ethyl O,O-propylene phosphorothionate**, b.p. 100° (0.1 μ), $n^{25}D$ 1.4746.

Anal. Calcd. for $C_5H_{13}O_3PS$: S, 17.6. Found: S, 17.8.

Reaction of 2-Diethylamino-1,3,2-dioxaphosphorinane (X) with Ethyl *o*-Nitrophenyl Disulfide (IX).—Ethyl o-nitrophenyl disulfide[23] (21.5 g., 0.1 mole) was cooled to −70°, and 17.7 g. (0.1 mole) of 2-diethylamino-1,3,2-dioxaphosphorinane at 22° was added in one portion. The temperature rose to approximately 10° and remained there for about 10 min. The resultant viscous yellow oil was molecularly distilled to give 37.5 g. (95.7%) of **S-ethyl O-[3-(*o*-nitrophenyl)propyl]diethylphosphoramidothioate (XI)**, b.p. 205° (0.1 μ), $n^{25}D$ 1.5720. The product was initially a red oil, but it became yellow on standing overnight. Thin-layer chromatography showed the presence of only one component, but attempts to crystallize the distillate failed.

Anal. Calcd. for $C_{15}H_{25}N_2O_2PS_2$: N, 7.15; P, 7.91; mol. wt., 392.5. Found: N, 7.0; P, 8.0; mol. wt. (ebullioscopic in benzene), 394.

To confirm the structure of the phosphoramidothioate (XI), 22.0 g. (0.056 mole) of XI was heated with 200 ml. of 48% hydrobromic acid. After 2 hr. at 100–110°, 3.2 g. (92%) of **ethyl mercaptan** had condensed in the Dry Ice trap. The aqueous solution was extracted extensively with ether and with methylene chloride. The combined extracts were dried over magnesium sulfate, the solvents were removed *in vacuo*, and the yellow residue was crystallized from ethanol to give 11.5 g. (75%) of **3-bromopropyl *o*-nitrophenyl sulfide** as yellow crystals, m.p. 37–38°.

Anal. Calcd. for $C_9H_{10}BrNO_2S$: N, 5.07; S, 11.6. Found: N, 5.1; S, 11.3.

Acknowledgment.—The authors are indebted to Paul M. Saliman for the microanalyses and to G. E. Pollard for the infrared absorption studies.

(23) J. F. Harris, Jr., U. S. Patent 2,962,417 (1960).

Reaction of Cyclic Phosphoramidites with Disulfides. II. A Novel Synthesis of Ethylene Bis(sulfides) and Bis(dithiocarbamates)

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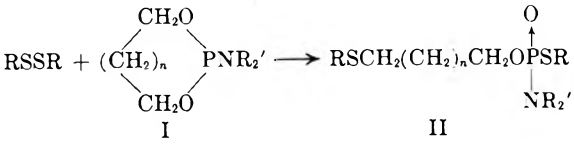
Cyclic phosphoramidites derived from ethylene glycol react with phenyl disulfide, *p*-tolyl disulfide, and benzthiazyl disulfide to form acyclic esters of phosphoramidothioic acid (II, $n = 0$) which are thermally converted to ethylene bis(sulfides) (*e.g.*, VIII). Tetraalkylthiuram disulfides react similarly to form ethylene bis(dithiocarbamates). When the cyclic phosphoramidites are derived from propylene or trimethylene glycol, the resulting phosphoramidothioates (X and II, $n = 1$) are thermally stable and may be molecularly distilled without decomposition at 205° (0.1 μ). A possible mechanism for the thermal decomposition is discussed.

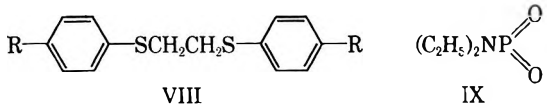
In the previous paper[3] the reaction of nitroaryl disulfides, benzthiazyl disulfide, and tetramethylthiuram disulfide with cyclic phosphoramidites (I) to give acyclic esters of phosphoramidothioic acid (II) was discussed.



I II

The failure of alkyl disulfides to undergo the reaction up to 115° and the different behavior shown by allyl and benzhydryl disulfide, which were desulfurized by the phosphoramidite (I), prompted us to study other disulfides in order to determine more precisely the scope of the reaction.

It was found that phenyl disulfide and *p*-tolyl disulfide both reacted smoothly with cyclic phosphoramidites to yield acyclic phosphoramidothioates of general structure II (see Table I). Yields were essentially quantitative and all of the products possessed the typical 8.01-μ peak in the infrared associated with the $>P\rightarrow O$ stretching vibration in a phosphoramidate.[4] On attempted purification of the phosphoramidothioates in Table I, however, it was noted that compounds derived from trimethylene glycol (*i.e.*, $n = 1$) could be molecularly distilled above 200° (0.1 μ) without decomposition while those from ethylene glycol (*i.e.*, $n = 0$, III and IV) decomposed on heating to these elevated temperatures. The products from this thermal degradation of III and IV were readily identified as the known ethylene bis(sulfides) (VIII, R = H and CH_3,



VIII IX

respectively); the phosphorus moiety resulting from the decomposition was not identified with certainty but was assumed to be the *meta* phosphoramidate (IX). When the reaction was extended to benzthiazyl disulfide and to several tetraalkylthiuram disulfides, the decomposition of the intermediate phosphoramidothioate [*e.g.*, II, R = $(CH_3)_2NC(S)$, $n = 0$] proved to be so facile in refluxing toluene that the ester was not isolated; the ethylene bis(dithiocarbamate) (see Table II) was obtained directly.

This marked difference in thermal stability between the ethylene and trimethylene phosphoramidothioates (II, $n = 0$ and $n = 1$, respectively) prompted us to examine the propylene esters (X), some of which had been prepared in our earlier work.[3] While no attempt had been made to distil the benzthiazyl compound (X, R = 2-benzthiazyl, X = piperidino) and the two dimethyldithiocarbamoyl analogs (X, R = $(CH_3)_2NC(S)$, X = piperidino and 4-morpholino) had been obtained as crystalline solids, the phenyl compound (X, R = C_6H_5, X = piperidino) was distilled at 205° (0.1 μ) without decomposition. In this respect then, the propylene compounds (X) are similar to the trimethylene compounds (II, $n = 1$) since both of them appear to be thermally stable.

A mechanism that accounts for these observations involves the quasi four-membered ring transition state shown in XII. The carbon–oxygen bond of the phosphoramidothioate (XI) is weakened by participation of the sulfur in the incipient formation of a sulfonium ion. Analogous three-membered ring sulfonium ions have long been used to explain the reactivity of β-halo sulfides and related compounds.[5] Once the carbon–oxygen bond is weakened, the electronic shifts shown in XII are a reasonable consequence; the main driving force is presumably the greater nucleophilic character of sulfur relative to oxygen and the formation of the resonance-stabilized $>P\rightarrow O$ bond.[6] The failure of the trimethylene esters (II, $n = 1$) to undergo the thermal rearrangement is understandable because the sulfur would have

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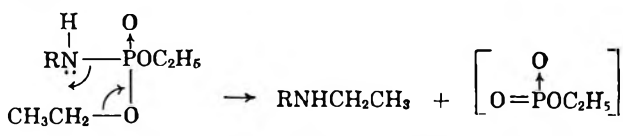
(3) K. Pilgram, D. D. Phillips, and F. Korte, *J. Org. Chem.*, **29**, 1844 (1964).

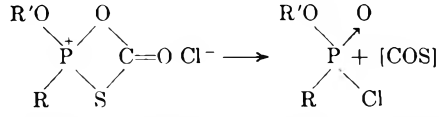
(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 258.

(5) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. 2, Chemical Publishing Co., New York, N. Y., 1960, p. 227, *et seq.*

(6) This reaction is formally similar to the alkylation of amines by phosphoric acid esters which is presumed to proceed through the phosphoramidate.[7]



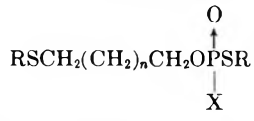
(7) B. P. Lugovkin and B. A. Arbusov, *J. Gen. Chem. USSR*, **22**, 2041 (1952). The reaction of phosgene and phosphonothioic acids has recently been suggested[8] to proceed through a similar four-membered cyclic intermediate.



(8) H. S. Aaaron, R. T. Uyeda, H. F. Frack, and J. I. Miller, *J. Am. Chem. Soc.*, **84**, 617 (1962).

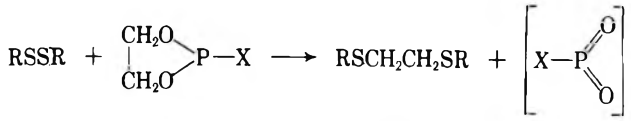
TABLE I

PHOSPHORAMIDOTHIOATES



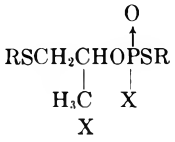
No.	R	X	n	Formula	Yield, %	B.p., °C., at 0.1 μ	—Mol. wt.— Calcd.	Found	—Nitrogen, %— Calcd.	Found	—Phosphorus, %— Calcd.	Found	—Sulfur, %— Calcd.	Found
III	C_6H_5	$N(C_2H_5)_2$	0	$C_{18}H_{24}NO_2PS_2$	100		381.5		3.67	3.7	8.12	7.5	16.75	16.7
IV	p-$CH_3C_6H_4$	$N(C_2H_5)_2$	0	$C_{20}H_{28}NO_2PS_2$	100		409.6		3.43	3.8	7.59	8.4	15.65	14.5
V	C_6H_5	$N(C_2H_5)_2$	1	$C_{19}H_{26}NO_2PS_2$	96	205	395.5				7.84	8.2	16.00	16.0
VI	C_6H_5		1	$C_{20}H_{26}NO_2PS_2$	98	200	407.5	390			7.62	8.2	15.72	15.8
VII	p-$CH_3C_6H_4$		1	$C_{22}H_{30}NO_2PS_2$	95	205	435.6	413			7.12	7.6		

TABLE II

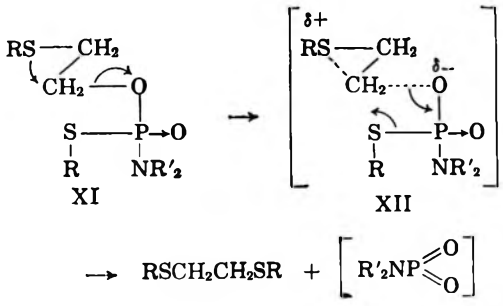


R	X	M.p., °C., of $RSCH_2CH_2SR$	Lit. m.p., °C.	Yield, %	Formula	—Nitrogen, %— Calcd.	Found	—Sulfur, %— Calcd.	Found
C_6H_5	$N(C_2H_5)_2$	67–68	65[a] 68.5[b] 69[c] 81[c]	68	$C_{14}H_{14}S_2$			26.00	26.0
p-$CH_3C_6H_4$	$N(_2CH_5)_2$	81	80[d]	63	$C_{16}H_{18}S_2$			23.35	23.5
$(CH_3)_2NC(S)$		193–194	189[e]	74	$C_8H_{16}N_2S_4$	10.44	9.9	47.75	47.8
$(C_2H_5)_2NC(S)$		93–94		69	$C_{12}H_{24}N_2S_4$	8.65	8.5	39.51	39.0
$(n$-$C_3H_7)_2NC(S)$		112–113		71	$C_{16}H_{32}N_2S_4$	7.37	7.3	33.70	32.9
$(n$-$C_4H_9)_2NC(S)$		68		64	$C_{20}H_{40}N_2S_4$	6.42	5.8	29.39	29.4
$(C_6H_5CH_2)_2NC(S)$		140	137[f]	21	$C_{32}H_{32}N_2S_4$	4.90	4.7	22.35	22.4
2-Benzthiazyl		149–150	144–145[g] 144–146[h]	62	$C_{16}H_{12}N_2S_4$	7.78	7.5	35.55	34.7

[a] C. W. Blomstrand and F. Ewerlöf, *Ber.*, **4**, 716 (1871). [b] J. Hine and W. H. Brader, Jr., *J. Am. Chem. Soc.*, **75**, 3964 (1953); [c] E. V. Bell and G. M. Bennett, *J. Chem. Soc.*, 3190 (1928). [d] E. Fromm and G. W. Raiziss, *Ann.*, **374**, 98 (1910). [e] A. W. Campbell and P. F. Tryon, *Ind. Eng. Chem.*, **45**, 125 (1953). [f] A. W. Hofmann, *Ber.*, **13**, 1231 (1880). [g] A. Sander, German Patent 811,588 (1951). *Chem. Abstr.*, **48**, 1443 (1954). [h] R. F. Brookes, J. E. Cranham, W. A. Cummings, D. Greenwood, and H. A. Stevenson, *J. Sci. Food Agr.*, **8**, 31 (1957).



to participate in the reaction through the formation of a four-membered sulfonium ion which is energetically much less favorable. Similarly, it is not surprising that an α-methyl (see X) prevents this thermal rearrangement, as it would provide considerable steric hindrance to the electronic shifts shown in XI → XII → $RSCH_2CH_2SR$.



This interesting insertion reaction provides a convenient synthesis of ethylene bis(sulfides), $RSCH_2CH_2SR$, particularly when the corresponding mercaptan is not readily available for alkylation with ethylene halides. Extension of the reaction to include other cyclic phosphorus compounds and disulfides is under study.

Experimental[9]

Materials.—The cyclic phosphoramidites (I) were prepared from the appropriate glycol and phosphorus trichloride in methylene chloride, followed by treatment with a secondary amine in

(9) All boiling and melting points are uncorrected; infrared absorption spectra were determined in carbon tetrachloride solution unless specified otherwise. Molecular distillations were carried out in a Rota-Film still, Arthur F. Smith Co., Rochester, N. Y.

ether.[10] 2-Benzthiazyl, phenyl, and *p*-tolyl disulfide were commercial products as were tetramethyl-, tetraethyl-, tetrabutyl-, and tetrabenzylthiuram disulfide; they were used without further purification.

Tetrapropylthiuram disulfide was prepared in 32% yield from dipropylamine, carbon disulfide, and iodine in ethanolic solution following a literature procedure[11] and had m.p. 50–51°.

Anal. Calcd. for $C_{14}H_{28}N_2S_4$: N, 7.95; S, 36.40. Found: N, 7.7; S, 35.6.

Reaction of Phenyl Disulfide with 2-Diethylamino-1,3,2-dioxaphospholane (I, n = 0, R′ = C_2H_5).—Phenyl disulfide (16.35 g., 0.075 mole) and 2-diethylamino-1,3,2-dioxaphospholane (12.25 g., 0.075 mole) reacted at room temperature with heat evolution; the temperature was kept below 80° by external cooling. **S-Phenyl O-[2-(phenylthio)ethyl]diethylphosphoramidothioate (III)** was obtained as a colorless viscous liquid, 28.6 g., 100% yield. Thin-layer chromatography showed one compound to be present.

Anal. Calcd. for $C_{18}H_{24}NO_2PS_2$: N, 3.67; P, 8.12; S, 16.75. Found: N, 3.7; P, 7.5; S, 16.7.

The compound was Claisen-distilled at 170–172° (0.05 mm.) to give a 95% yield of a solid complex, m.p. 62–63° (from ether–pentane), which had the same elementary analysis as above but was a mixture of two compounds as shown by thin-layer chromatography. When recrystallized from methanol, the complex was broken and **1,2-bis(phenylthio)ethane (VIII, R = H)** was obtained in 68% yield, m.p. 67–68°.

Oxidation with hydrogen peroxide in acetic acid gave the known **bis(sulfone)**,[12] m.p. 180–181°.

Anal. Calcd. for $C_{14}H_{14}O_4S_2$: S, 20.65. Found: C, 20.6.

When methanol was removed from the mother liquid by heating on the water bath *in vacuo*, a brown resin remained. Attempts to crystallize the latter failed. Treatment with aqueous sodium hydroxide eliminated diethylamine. Analysis was satisfactory for diethyl *m*-phosphoramidate (IX).

Anal. Calcd. for $C_7H_{19}NO_2P$: P, 22.95. Found: P, 22.4.

Reaction of *p*-Tolyl Disulfide with 2-Diethylamino-1,3,2-dioxaphospholane (I, n = 0, R′ = C_2H_5).—*p*-Tolyl disulfide (6.15 g., 0.025 mole) and 2-diethylamino-1,3,2-dioxaphospholane (4.08 g., 0.025 mole) reacted at room temperature with heat evolution. The temperature was kept at approximately 80° by external cooling; without cooling, the temperature rose to approximately 130°. There was obtained 10.23 g. (100%) of **S-*p*-tolyl O-[2-(*p*-tolylthio)ethyl]diethylphosphoramidothioate (IV)**, as a colorless viscous liquid; thin-layer chromatography showed the presence of only one compound.

Anal. Calcd. for $C_{20}H_{28}NO_2PS_2$: N, 3.43; P, 7.59; S, 15.65. Found: N, 3.8; P, 8.4; S, 14.5.

The reaction product was heated to 250° over a 15-min. period. On cooling to 120° the red-brown reaction mixture solidified. Dilution with methanol and recrystallization from methanol gave a 63% yield of **1,2-bis(*p*-tolylthio)ethane (VIII, R = CH_3)** as colorless crystals, m.p. 81°. Oxidation with hydrogen peroxide in acetic acid gave the known **bis(sulfone)**,[12–14] m.p. 204–205°, 99% yield.

Anal. Calcd. for $C_{16}H_{18}O_4S_2$: S, 18.95. Found: S, 18.3.

Reaction of Aromatic Disulfides with N,N-Disubstituted 2-Amino-1,3,2-dioxaphosphorinanes.—The results are summarized in Table I. The general procedure is illustrated by the reaction of phenyl disulfide with 2-diethylamino-1,3,2-dioxaphosphorinane.

Phenyl disulfide (43.6 g., 0.2 mole) was cooled to −70° and 2-diethylamino-1,3,2-dioxaphosphorinane (35.4 g., 0.2 mole), at room temperature, was added portionwise with shaking. The reaction temperature rose immediately to 10° where it remained until 75% of the phosphoramidite had been added. The cooling bath was removed and the final 25% of the phosphoramidite was added. The temperature rose to 100° and a colorless liquid resulted. Thin-layer chromatography indicated the presence of only one compound. Distillation at 205° (0.1 μ) afforded 76 g. (96%) of **S-phenyl O-[3-(phenylthio)propyl]diethylphosphoramidothioate (V)** as a colorless oil.

Anal. Calcd. for $C_{19}H_{26}NO_2PS_2$: P, 7.84; S, 16.00. Found: P, 8.2; S, 16.0.

Hydrolysis of V.—The distillate (59.25 g., 0.15 mole) was refluxed for 3 hr. in 100 ml. of 48% hydrobromic acid. After cooling, the upper oily layer was separated and the aqueous layer was extracted with ether. Oil and ether extracts were combined and dried over magnesium sulfate, ether was evaporated, and the residue was distilled to give, as a first fraction, 14.5 g. (88%) of **thiophenol**, b.p. 28° (0.08 mm.), and, as a second fraction, 25 g. (75%) of **3-bromopropyl phenyl sulfide**, b.p. 109° (0.1 mm.).

Anal. Calcd. for $C_9H_{11}BrS$: C, 46.65; H, 4.77; Br, 34.65; S, 13.85. Found: C, 47.5; H, 4.9; Br, 34.3; S, 13.74.

Reaction of 2-Benzthiazyl Disulfide and Tetraalkylthiuram Disulfides with N,N-Disubstituted 2-Amino-1,3,2-dioxaphospholanes.—The results of these reactions are summarized in Table II. The general procedure is illustrated by the reaction of tetramethylthiuram disulfide with 2-piperidino-1,3,2-dioxaphospholane.

To tetramethylthiuram disulfide (12 g., 0.05 mole) in 25 ml. of toluene was added, in three portions, 2-piperidino-1,3,2-dioxaphospholane (8.25 g., 0.05 mole). The internal temperature rose spontaneously to reflux and the tetramethylthiuram disulfide went into solution. After cooling to approximately 100°, **ethylene bis(dimethyldithiocarbamate)** crystallized, yielding 9.92 g. (74%), m.p. 193–194°.

Anal. Calcd. for $C_8H_{16}N_2S_4$: N, 10.44; S, 47.75. Found: N, 9.9; S, 47.8.

Acknowledgment.—The authors are grateful to P. M. Saliman for the microanalyses and to G. E. Pollard for the infrared absorption studies.

(10) H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950).

(11) J. v. Braun, *Ber.*, **35**, 899 (1902).

(12) R. Otto, *ibid.*, **13**, 1272 (1880).

(13) E. Froman and E. Siebert, *ibid.*, **55**, 1014 (1922).

(14) R. Otto, *J. prakt. chem.*, [2]**30**, 354 (1884); **40**, 534 (1889).

Reactions of Acetylenic Amines. VIII. Cyclization of Acetylenic Ureas

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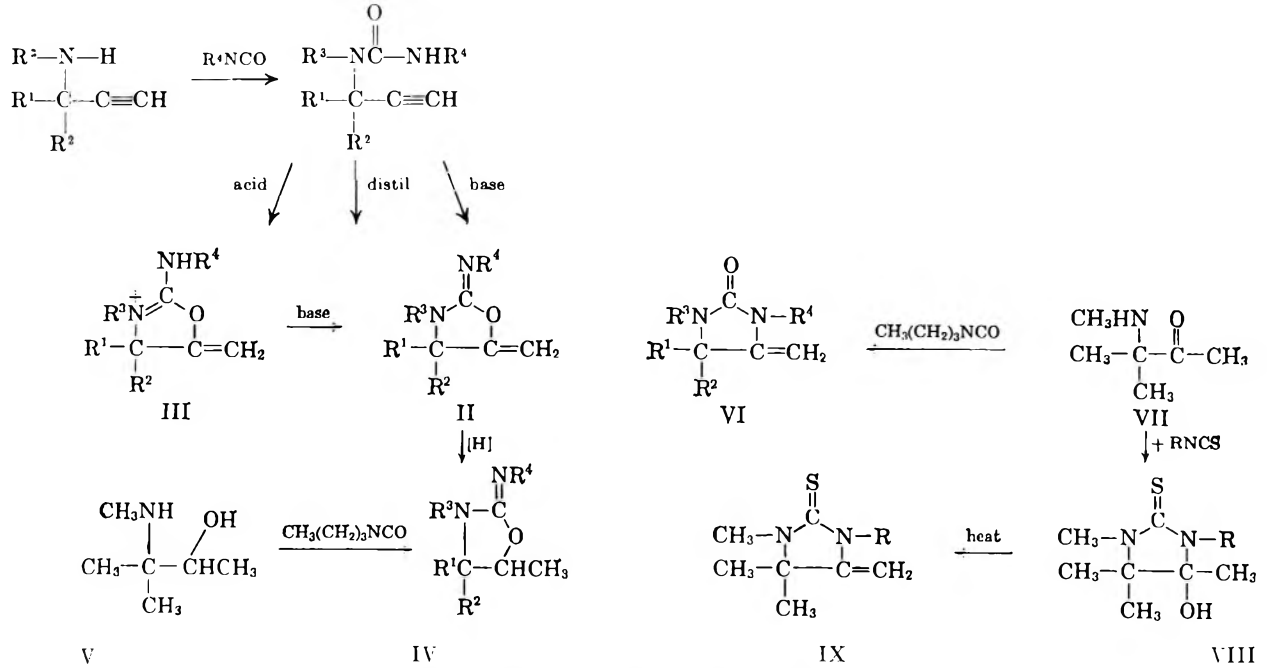
The cyclizations of ureas prepared from α,α-disubstituted propargylamines gave two isomeric heterocyclic products. Under the influence of heat or strong acid the ureas cyclized to 2-iminooxazolidines. However, base catalyzed the cyclization to imidazolidinones, which were also prepared from the reaction of isocyanates with the appropriate amino ketones. The thioureas from the reaction of the secondary α,α-disubstituted propargylamines with isothiocyanates could not be isolated since they rapidly cyclized to the 2-iminothiazolidines. The thioureas from the primary amines could be isolated but on standing also underwent S-cyclization. However, base-catalyzed cyclization of the freshly prepared thioureas gave the imidazolidinethiones.

The cyclizations of urethanes from tertiary acetylenic carbinols have been reported[1-3] recently. It has been noted[4] also that certain ureas derived from propargylamines cyclize in the presence of phosphorus pentachloride to give imidazolines. Papers[5a,b] have appeared describing the preparation of thiazoles and imidazoles from the reaction of urea or thiourea with halo acetylenes.



a, $R^1 = R^2 = R^3 = CH_3$; $R^4 = CH_3(CH_2)_3$—
b, $R^1 = R^2 = R^3 = R^4 = CH_3$
c, $R^1 = CH_3$; $R^2 = (CH_3)_2CH$—; $R^3 = R^4 = C_2H_5$
d, $R^1 = R^2 = C_2H_5$; $R^3 = CH_3$; $R^4 = CH_3(CH_2)_3$

More recently[6a,b] the same author has shown that 1-(1-methyl-2-propynyl)urea is stable to heat but on treatment with sulfuric acid cyclizes to 4,5-dimethyl-2-imidazolone, presumably through the intermediate, 4-methylene-5-methyl-2-imidazolidinone. We present our findings in this area.

The preparation of the urea Ia was accomplished by the slow addition of *n*-butyl isocyanate to an ethereal solution of N-3,3-trimethyl-1-propynylamine. However, distillation of this material produced a new compound. Since the infrared spectrum of the latter material did not show absorption in the acetylenic CH region, it was assumed that cyclization had taken place. The two most probable structures were those of the methyleneoxazolidine (II) or the methyleneimidazolidinone (VI). The n.m.r. spectrum showed doublets, centered at τ 5.44 and 5.86, which were not present in the starting urea Ia. There were available in these laboratories two excellent models for comparison with this n.m.r. spectrum: 2,3,4,4-tetramethyl-5-methylene-2-oxazolinium chloride (X), which has the $H_2C{=}\overset{|}{C}{-}O{-}$ structure[7]; 5,5-dimethyl-3-ethyl-4-methylene-2-oxazolidinone (XI), which has the $H_2C{=}\overset{|}{C}{-}N{-}$ grouping.[3] The n.m.r. spectrum of X shows two doublets centered at τ 4.93 and 5.35, whereas the n.m.r. spectrum of XI showed doublets centered at τ 5.97 and 6.08.

Although the chemical shifts for the doublets in this new compound are midway between the two models, the difference in chemical shifts between the doublets

(1) S. L. Shapiro, V. Bondurco, and L. Freedman, *J. Org. Chem.*, **26**, 3710 (1961).

(2) K. Sisido, K. Hukuoka, M. Tuda, and H. Nozaki, *ibid.*, **27**, 2663 (1962).

(3) N. R. Easton, Donald R. Cassady, and Robert D. Dillard, *ibid.*, **27**, 2927 (1962).

(4) P. J. Stoffel and A. J. Speziale, *J. Am. Chem. Soc.*, **84**, 501 (1962).

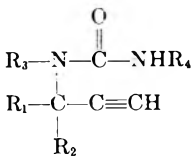
(5) (a) Y. Yura, *Chem. Pharm. Bull. Japan*, **10**, 372 (1962); (b) **10**, 376 (1962); (c) W. Batty and B. Weedon, *J. Chem. Soc.*, 786 (1949).

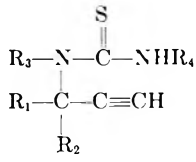
(6) (a) Y. Yura, *Chem. Pharm. Bull. Japan*, **10**, 1087 (1962); (b) **10**, 1094 (1962).

(7) N. R. Easton and R. D. Dillard, *J. Org. Chem.*, **28**, 2465 (1963).

TABLE IA

UREAS AND THIOUREAS



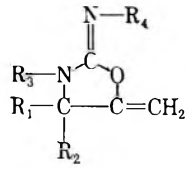


						Analyses, %					
						Calcd.			Found		
R_1	R_2	R_3	R_4	M.p., °C.	Formula	C	H	N	C	H	N
CH_3	CH_3	CH_3	C_2H_5	Liquid	$C_9H_{26}N_2O$	64.25	9.59	16.65	63.97	9.83	16.57
CH_3	CH_3	CH_3	n-$C_{18}H_{37}$	56–57[a]	$C_{25}H_{48}N_2O$	76.47	12.32	7.13	76.31	12.16	7.01
CH_3	CH_3	CH_3	C_6H_5	84–86[b]	$C_{13}H_{16}N_2O$	72.19	7.46		72.28	7.36	
CH_3	CH_3	CH_3	4-ClC_6H_4	87–88[b]	$C_{13}H_{15}ClN_2O$	62.27	6.03	11.17	62.12	6.30	10.93
C_2H_5	C_2H_5	CH_3	n-C_4H_9	Liquid	$C_{13}H_{28}N_2O$	69.59	10.78	12.49	69.55	10.87	12.65
C_6H_5	H	C_2H_5	C_6H_5	101–102[b]	$C_{18}H_{18}N_2O$	77.67	6.51	10.06	77.39	6.75	9.95
C_6H_5	CH_3	C_2H_5	CH_3	77–78[c]	$C_{14}H_{18}N_2O$	73.01	7.87	12.16	72.84	7.99	12.23
C_6H_5	C_6H_5	C_2H_5	C_6H_5	160–161[d]	$C_{24}H_{22}N_2O$	81.32	6.25		81.53	6.41	
—$(CH_2)_5$—		H	n-C_4H_9	Waxy solid[b]	$C_{13}H_{22}N_2O$	70.23	9.97	12.60	70.56	10.23	12.37
—$(CH_2)_5$—		H	C_6H_5	149–150[b]	$C_{15}H_{18}N_2O$	74.35	7.49	11.56	74.13	7.66	11.33
—$(CH_2)_5$—		CH_3	C_6H_5	83–84[b]	$C_{16}H_{20}N_2O$	74.96	7.85	10.93	74.67	7.90	10.69
—$(CH_2)_5$—		H	C_6H_5	105–106	$C_{15}H_{18}N_2S$	69.72	7.02	10.84	69.99	7.09	10.84
CH_3	$(CH_3)_2CH$	H	CH_3	118–120	$C_9H_{16}N_2S$	58.67	8.75		58.65	8.62	

[a] Recrystallized from methanol. [b] Recrystallized from benzene–petroleum ether (b.p. 30–60°). [c] Recrystallized from methylcyclohexane–benzene. [d] Recrystallized from benzene.

TABLE IIA

OXAZOLIDINES



						Analyses, %						
				B.p. (mm.) or		Calcd.			Found			
R_1	R_2	R_3	R_4	m.p., °C.	Formula	C	H	N	C	H	N	Method
CH_3	CH_3	CH_3	CH_3	64 (2)	$C_8H_{14}N_2O$	62.30	9.15	18.17	62.36	9.12	18.45	*d*
CH_3	CH_3	CH_3	n-C_3H_7	90 (1)	$C_{10}H_{18}N_2O$	65.89	9.96		66.10	10.03		*d*
CH_3	CH_3	CH_3	n-C_4H_9	100 (2)	$C_{11}H_{20}N_2O$	67.30	10.27	14.27	67.36	9.87	14.31	*b*
CH_3	CH_3	CH_3	C_6H_5	146 (5)	$C_{13}H_{16}N_2O$	72.19	7.45	12.95	72.44	7.70	12.66	*b*
CH_3	CH_3	CH_3	4-Cl-C_6H_4	39–40[a]	$C_{13}H_{15}ClNO_2$	62.27	6.03		62.07	6.16		*d*
CH_3	CH_3	3-Cl-4-$CH_3C_6H_3$	C_2H_5	77–78[a]	$C_{15}H_{19}ClN_2O$	64.42	6.86	10.05	64.57	7.10	9.93	*b*
CH_3	$(CH_3)_2CH$	$(CH_3)_2CH$	C_2H_5	110–112 (3)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.71	10.96	12.44	*c*
CH_3	$(CH_3)_3C$	C_2H_5	C_2H_5	108 (2)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.39	10.66	12.36	*c*
CH_3	C_6H_5	C_2H_5	CH_3	142 (7)	$C_{14}H_{18}N_2O$	73.01	7.81	12.16	72.92	7.95	12.31	*b*
C_2H_5	C_2H_5	CH_3	n-C_4H_9	135 (2)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.75	10.80	12.58	*b*
C_2H_5	C_2H_5	$(CH_3)_2CH$	C_2H_5	110 (2)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.88	10.56	12.06	*c*
—$(CH_2)_5$—		CH_3	C_6H_5	87–88[a]	$C_{16}H_{20}N_2O$	74.96	7.86	10.93	74.85	7.96	10.79	*d*

[a] Recrystallized from methanol. [b] Prepared by distillation of the acetylenic urea. [c] Prepared by base closure of the acetylenic urea. [d] Prepared by acid closure of the acetylenic urea.

is similar to X rather than XI. It would also be expected that the salt character of X would move the chemical shifts downfield. It was, therefore, decided that II was the more logical structure. Chemical confirmation of this structure assignment was obtained by hydrogenating II to IVa which was identical with the material prepared from the amino alcohol (V) and *n*-butyl isocyanate.

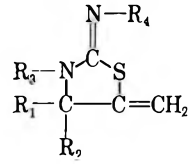
Treatment of the α,α-disubstituted acetylenic urea Ia with sodium ethoxide in ethanol resulted in a vigorous reaction which produced a new compound (VIa). The n.m.r. spectrum of this material showed a triplet at τ 6.69 (–N–CH_2–), an unsplit signal at 7.20 (–N–CH_3), additional butyl protons from 8.47 to 9.00, and an unsplit[8] signal at 6.11 assigned to the methylene protons. This compound was assigned the imidazolidinone structure, and confirmation was obtained by its independent synthesis from 3-methyl-3-methylamino-2-butanone (VII) and *n*-butyl isocyanate.

The extension of these reactions to variously substituted acetylenic amines was readily accomplished and the compounds which were prepared are reported in Tables I–III.

(8) The methylene protons of the imidazolidinones were not always a single peak. In fact, in 1-phenyl-3-methyl-4,4-pentamethylene-5-methylene-2-imidazolidinone, the n.m.r. spectrum contained two doublets with a difference in chemical shift of 11 c.p.s.

TABLE IIB

THIAZOLIDINES

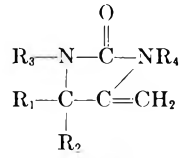


						Analyses, %						
				B.p. (mm.) or		Calcd.			Found			
R_1	R_2	R_3	R_4	m.p., °C.	Formula	C	H	N	C	H	N	Method
CH_3	CH_3	H	CH_3	88 (5)	$C_7H_{12}N_2S$	53.83	7.74		53.75	7.92		*d*
CH_3	CH_3	H	n-C_4H_9	8.3 (0.05)	$C_{10}H_{18}N_2S$	60.56	9.15		60.47	9.07		*d*
CH_3	CH_3	CH_3	CH_3	118 (5)	$C_8H_{14}N_2S$	56.43	8.28	16.45	56.69	8.49	16.46	*d*
CH_3	CH_3	CH_3	C_6H_5	53–54[a]	$C_{13}H_{16}N_2S$	13.78[c]			13.52[c]			*d*
CH_3	CH_3	C_2H_5	n-C_4H_9	120 (5)	$C_{12}H_{22}N_2S$	63.66	9.80	12.38	63.42	9.98	12.03	*d*
—$(CH_2)_5$—		H	C_6H_5	174–177[b]	$C_{15}H_{18}N_2S$	69.72	7.02	10.84	69.42	6.98	10.64	*d*
—$(CH_2)_5$—		CH_3	C_6H_5	110–111[b]	$C_{16}H_{20}N_2S$	70.54	7.40	10.29	70.68	7.44	10.19	*d*

[a] Recrystallized from benzene–petroleum ether (b.p. 30–60°). [b] Recrystallized from methylcyclohexane–benzene. [c] Sulfur analysis. [d] Prepared by distillation of the acetylenic thiourea.

TABLE IIIA

IMIDAZOLIDINONES



						Analyses, %						
				B.p. (mm.) or		Calcd.			Found			
R_1	R_2	R_3	R_4	m.p., °C.	Formula	C	H	N	C	H	N	Method
CH_3	CH_3	CH_3	C_2H_5	72 (1)	$C_9H_{16}N_2O$	64.25	9.59	16.65	63.54	9.56	16.25	*c*
CH_3	CH_3	CH_3	n-C_4H_9	102–105 (5)	$C_{11}H_{20}N_2O$	67.30	10.27	14.27	66.97	9.94	14.20	*c, d*
CH_3	CH_3	CH_3	C_6H_5	86–87[a]	$C_{13}H_{16}N_2O$			12.95			12.88	*c*
CH_3	CH_3	C_2H_5	4-Cl-C_6H_4	121–122[a]	$C_{13}H_{15}ClN_2O$	62.27	6.03	11.17	62.63	6.15	11.26	*c, e*
CH_3	CH_3	C_2H_5	C_2H_5	85 (0.1)	$C_{10}H_{18}N_2O$	65.89	9.96	15.37	65.68	9.94	15.09	*d*
CH_3	CH_3	C_2H_5	n-C_4H_9	102 (4)	$C_{12}H_{22}N_2O$	68.33	10.54	13.32	68.48	10.42	13.27	*d*
C_2H_5	C_2H_5	CH_3	n-C_4H_9	110 (5)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.48	10.75	12.60	*c*
C_6H_5	H	C_2H_5	C_6H_5	230 (1)	$C_{18}H_{18}N_2O$[f]	77.67	6.52		77.70	6.73		*c*
C_6H_5	CH_3	C_2H_5	CH_3	200 (1)	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.13	8.05	11.96	*c*
C_6H_5	C_6H_5	C_2H_5	C_6H_5	112[a]	$C_{24}H_{22}N_2O$	81.32	6.25	7.90	81.37	6.46	7.66	*c*
—$(CH_2)_5$—		H	C_6H_5	213–214[b]	$C_{15}H_{18}N_2O$	74.35	7.49	11.56	74.25	7.60	11.43	*c*
—$(CH_2)_5$—		CH_3	C_6H_5	120–121[a]	$C_{16}H_{20}N_2O$	74.96	7.86	10.93	75.02	8.06	10.76	*c*

[a] Recrystallized from benzene–petroleum ether (b.p. 30–60°). [b] Recrystallized from benzene–chloroform. [c] Prepared by base closure of acetylenic urea. [d] Prepared by dehydration of the ketourea. [e] Prepared by heating and distilling the acetylenic urea. [f] Double bond has shifted into ring: 3-ethyl-5-methyl-1,4-diphenylimidazolinone-2.

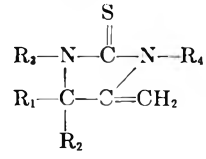
The difference in the structures of these products, compared with those reported by Yura[6a,b] for cyclization of mono α-substituted propargylureas, could be most readily explained by the steric effects of the groups substituted on the acetylenic amines. Therefore, it was of interest to examine various cyclizations of ureas in which steric effects could be expected due to the size of the different substituents.

From observations of the models of the imidazolidinones (VI) and the 2-iminooxazolidines (II), it would appear that large groups in R^1, R^2, R^3, and R^4 would inhibit the nitrogen closure to the imidazolidinone and in these cases the oxygen closure to the 2-iminooxazolidines would be favored. If the size of these groups is of sufficient importance, then, as they become large, the base-catalysis effect may be reversed. In order to test this possibility, the urea Ic [$R^1 = CH_3$; $R^3 = R^4 = C_2H_5$; $R^2 = C(CH_3)_3$] was subjected to the basic conditions which normally produce the imidazolidinones. In this example, only the 2-iminooxazolidine (IIc) was isolated, and no evidence for the presence of the imidazolidinone was seen. Therefore, it is apparent that the steric size of groups R^1, R^2, R^3, and R^4 does have an effect on the products obtained and that the larger these groups become the more difficult it is for an N-closure to take place.

It has been reported[7] that amides of substituted propargylamines cyclize to oxazolinium salts on treatment with acid. The ureas of propargylamines cyclize in the same manner and, upon neutralization of the resulting oxazolinium salts, the 2-iminooxazolidines, identical with those formed by thermal catalysis, are produced in 90–95% yields.

The only urea derived from an α-monosubstituted propargylamine which was investigated was that from the reaction of phenyl isocyanate with N-ethyl-α-phenylpropargylamine. In this instance, base closure produced 3-ethyl-5-methyl-1,4-diphenylimidazolinone-2. The double bond shifted into the ring from its exocyclic position.

TABLE IIIB
IMIDAZOLIDINETHIONES



R1	R2	R3	R4	B.p. (mm.) or m.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Method
CH_3	CH_3	CH_3	CH_3	72–73[a]	$C_8H_{24}N_2S$	56.43	8.28		55.67	8.42		*d*
CH_3	CH_3	C_2H_5	C_4H_9	140 (10)	$C_{12}H_{22}N_2S$	63.66	9.80	12.38	63.84	10.22	12.29	*d*
—$(CH_2)_5$—		H	C_6H_5	248–250[b]	$C_{15}H_{18}N_2S$	69.72	7.02	10.84	69.99	7.09	10.89	*c*

[a] Recrystallized from benzene–petroleum ether (b.p. 30–60°). [b] Recrystallized from methylcyclohexane. [c] Prepared by base closure of acetylenic thiourea. [d] Prepared by dehydration of the ketothiourea.

The reaction of these propargylamines with isothiocyanates was also studied. It was very difficult to isolate a noncyclic product when a secondary propargylamine was treated with an isothiocyanate. Absence of the 3.03-μ band in the infrared spectrum assigned to the acetylenic ≡C—H bond and the appearance of bands at 6.10 and 6.18 μ of carbonyl intensity assigned to C=N and C=C, respectively, indicated that S-cyclization to the iminothiazolidines had occurred. This was confirmed by n.m.r. spectra. The thioureas from the primary propargylamines were more stable and could be isolated. They would undergo S-cyclization on standing. The freshly prepared thioureas from the primary amines could be cyclized to imidazolidinethiones by treatment with sodium ethoxide in alcohol. The 1,3-disubstituted imidazolidinethiones could be prepared by treating the appropriate amino ketone with the proper isothiocyanate.

The n.m.r. spectrum of 3,4,4-trimethyl-5-methylene-2-methyliminothiazolidine showed two doublets centered at τ 4.80 and 4.88 for the methylene protons. Other examples showed these doublets with greater or lesser difference in chemical shift and occasionally they appeared as an unsplit signal. However, they were always further downfield from that seen for the oxygen analog.

Treatment of the amino ketones (VII) with an isothiocyanate gave the hydroxyimidazolidinethiones (VIII) which could be readily dehydrated to the methylideneimidazolidinethiones (IX).

Experimental

All melting points were taken in open capillary tubes using a Culatti electrically heating air bath melting point apparatus.

Preparation of Ureas and Thioureas.—To a mixture of 0.1 mole of the substituted propargylamine in 100 ml. of ether, there was added slowly, with stirring, 0.12 mole of the isocyanate or isothiocyanate. The temperature was kept below 30°. After addition had been completed the mixture was stirred for an additional 0.5 hr., and the ether and excess isocyanate were removed at reduced pressure (below 30°). Yields were nearly quantitative in most cases.

Purification of the ureas was difficult since heating often caused cyclization. Some of the ureas could be recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°). See Table I for physical constants of the ureas and thioureas which were stable enough to purify or were analytically acceptable in their crude states.

Thermal Cyclization of Ureas.—The ureas were distilled under reduced pressure at temperatures above 80°. Some of the members of the series were converted to the cyclic forms by standing for several days at room temperature.

Physical properties of the compounds prepared by this method are designated by method *b* in Table IIA, and method *d* in Table IIB.

Base-Catalyzed Cyclization of Ureas and Thioureas.—A solution of sodium ethoxide (from 1 g. of sodium) in 100 ml. of ethanol was added slowly, with stirring, to 10 g. of the urea. The reaction was exothermic. The stirring was continued for 1 hr. and then 500 ml. of water was added. The solution was extracted three times with 100-ml. portions of ether; the ether layers were combined and dried over magnesium sulfate and concentrated at reduced pressure. The residue was purified either by distillation or by recrystallization. Yields were 80–90%. Compounds prepared in this manner are designated by method *c* in Tables IIA, IIIA, and IIIB.

Acid-Catalyzed Cyclization of Ureas and Thioureas.—A mixture of 10 g. of the urea in 50 ml. of concentrated hydrochloric acid was heated, with stirring, in a warm water bath. Indications of a reaction were darkening and evolution of fumes. The reaction was complete when all of the solid was in solution. After the addition of 50 ml. of water, the solution was neutralized with a saturated solution of sodium bicarbonate. The mixture was extracted with ether; the ether layer was dried and concentrated at reduced pressure. The residue was either distilled at reduced pressure or recrystallized from a suitable solvent. Yields in this reaction were 90–95%. Compounds prepared in this manner are designated by method *d* in Table IIA.

Preparation of Imidazolones and Imidazolidinethiones by Reaction of α-Amino Ketones with Isocyanates or Isothiocyanates.—To a well-stirred solution of 20 g. of the α-amino ketone in 150 ml. of ether there was added dropwise an equivalent amount of isocyanate or isothiocyanate. In most cases a layer of water formed during the addition. The solvent was distilled at reduced pressure and the residue was taken up in benzene. The mixture was refluxed for 4 hr. with use of a Stark and Dean trap to remove water. The solvent was distilled at reduced pressure and the products were purified by distillation or recrystallization. Yields were 80–95%. The physical constants are recorded in Tables IIIA and IIIB and identified by method *d*.

2-*n*-Butylimino-3,4,4,5-tetramethyloxazolidine. A. By Reduction.—A solution of 30 g. of 2-butylimino-5-methylene-3,4,4-trimethyloxazolidine in 150 ml. of ethanol was treated with hydrogen under approximately 40 p.s.i.g. of hydrogen using 5% palladium on carbon as catalyst. The mixture was filtered and the solution was concentrated at reduced pressure. The product distilled at 88–90° under 5 mm. of pressure, $n^{25}D$ 1.4610.

Anal. Calcd. for $C_{11}H_{22}N_2O$: C, 66.62; H, 11.18; N, 14.13. Found: C, 66.83; H, 11.37; N, 13.87.

B. From 3-Methyl-3-methylamino-2-butanol.—To a solution of 9 g. of 3-methyl-3-methylamino-2-butanol in 200 ml. of benzene there was added, slowly with stirring, 9 g. of *n*-butyl isocyanate. After the addition of 1 g. of *p*-toluenesulfonic acid the solution was refluxed for 16 hr. During this time the water from the reaction was collected in a Stark and Dean trap. The material was purified as in method A and was identical with the product obtained by method A.

3-Methyl-3-methylamino-2-butanol.—A solution of 12 g. (0.12 mole) of 3-methyl-3-methylamino-2-butanone[9] in 100 ml. of

(9) Prepared by the method of G. F. Hennion and P. E. Butler, *J. Org. Chem.*, **26**, 3341 (1961).

ethanol was hydrogenated over 5% palladium on carbon at approximately 40 p.s.i.g. of hydrogen. The product, 10 g. (83%), boiled at 95° at 70 mm.

Anal. Calcd. for $C_6H_{15}NO$: C, 61.49; H, 12.90; N, 11.95. Found: C, 61.53; H, 12.92; N, 11.85.

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The Light-Induced Amidation of Terminal Olefins[1]

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The light-induced amidation of terminal olefins with formamide is described. The reaction can be performed both directly and through photochemical initiation by acetone. Yields of up to 90% of the 1:1 adducts are obtained.

Free-radical addition reactions to olefins are widely known in the literature.[3] These reactions have been found to involve a variety of reagents, including acetic, malonic, acetoacetic, and cyanoacetic esters.[4] The reactions are usually induced by initiators (mainly peroxides) or photochemically. Kharasch, Urry, and Kuderna[5] have shown that the addition of aldehydes to olefins to give the derived ketones can be induced by peroxides or light. This reaction, following the general scheme proposed for such additions, is described as a free-radical chain reaction. Similarly, methyl formate reacts with olefins in the presence of peroxides to give 1:1 adducts and higher telomers.[6] Urry and Juveland[7] have shown that amines add to olefins to give higher homologous amines derived by the substitution of alkyl groups for the hydrogen α to the amine group. Friedman and Shechter[8] found that substituted formamides undergo similar reactions with olefins in the presence of peroxides to give products resulting from the addition of both $\cdot CON(CH_3)_2$ and $HCON(CH_3)\dot{C}H_2$ radicals to the olefin.

A study of the addition of formamide to olefins was undertaken with the aim of finding a new process for converting olefins to higher amides, and possibly further to amines by reduction or by use of the Hofmann reaction. Since hydrolysis of the amides to the corresponding carboxylic acids can be effected by standard procedures, this reaction provides a new process for carboxylation of olefins under mild conditions at room temperature. Formamide, besides being a common reagent, has the advantage that its 1:1 adducts with olefins are highly crystalline solids which can be readily isolated.

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(3) For reviews see (a) J. I. G. Cadogen and D. H. Hey, *Quart. Rev.* (London), **8**, 308 (1954); (b) J. I. G. Cadogen, *Roy. Inst. Chem.* (London), *Lectures*, Monographs, Reports, No. 6 (1961).

(4) (a) J. C. Allen, J. I. G. Cadogen, B. W. Harris, and D. H. Hey, *J. Chem. Soc.*, 4468 (1962); (b) J. C. Allen, J. I. G. Cadogen and D. H. Hey, *Chem. Ind.* (*London*), 1621 (1962).

(5) M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).

(6) W. H. Urry and E. S. Huyser, *J. Am. Chem. Soc.*, **75**, 4876 (1953).

(7) W. H. Urry and O. O. Juveland, *ibid.*, **80**, 3322 (1958).

(8) L. Friedman and H. Shechter, *Tetrahedron Letters*, No. 7, 238 (1961).

Results

The light-induced addition of formamides to terminal olefins has been reported by us in a preliminary communication.[9] We have since found that the reaction can be initiated photochemically by acetone, and the present paper includes full details of the reactions and the products obtained.

Formamide was found to add to olefins under photochemical conditions to give mainly the 1:1 adducts resulting from anti-Markovnikov addition.

$$RCH{=}CH_2 + H{-}CONH_2 \xrightarrow{h\nu} RCH_2CH_2CONH_2$$

R = alkyl, $H_3COOC(CH_2)_2$–, $H_2NOC(CH_2)_2$–, $H_3COOC(CH_2)_8$–, $H_2NOC(CH_2)_8$–

The acetone-initiated reactions produced even higher yields of these adducts and require shorter irradiation periods. The reactions studied and the main products obtained are summarized in Table I. The 1:1 adducts

TABLE I

ADDITION PRODUCTS OF FORMAMIDE AND OLEFINS[a]

(Initiated by Acetone)

Olefin	Product, 1:1 adduct (%)	Source of light
1-Hexene	Heptanamide (50)[b]	Sun
1-Heptene	Octanamide (57)	Sun
	(61)	Ultraviolet[c]
1-Octene	Nonanamide (62)	Sun
	(51)	Ultraviolet[c]
1-Decene	Undecanamide (67)	Ultraviolet[c]
Methyl 10-undecylenate	Methyl 11-carbamoylundecanoate (53)	Ultraviolet[c]
10-Undecylenamide	Dodecanediamide (90)	Sun
Methyl 4-pentenoate	Methyl 5-carbamoylpentanoate (61)	Sun
	(58)	Ultraviolet[c]
4-Pentenamide	Adipamide (77)	Sun

[a] The mole ratio of formamide–olefin in the experiments mentioned was 18:1. [b] Yields are based on the olefins employed. The conversions are nearly quantitative in most cases. [c] Hanau Q81 high pressure mercury vapor lamps fitted into Pyrex tubes were used as the radiation source for these acetone-initiated reactions.

(9) D. Elad, *Chem. Ind.* (*London*), 362 (1962). While our work was in progress, A. Rieche, E. Schmitz, and E. Gründemann [*Angew. Chem.*, **73**, 621 (1961)] reported the addition of formamide to olefins in the presence of peroxides at elevated temperatures.

were identified by their physical properties, elementary analyses, and by comparison with authentic samples. The carbamoyl esters were hydrolyzed to the corresponding dicarboxylic acids which were compared with authentic specimens. In addition, smaller yields of higher telomers were obtained. The 2:1 telomers[10] were characterized by elementary analyses and molecular weights. In the case of propylene, the 2:1 telomer, *i.e.*, 3-methylhexanamide, was compared with an authentic sample. Products resulting from Markovnikov addition of formamide to the olefins were obtained in several cases in low yields. These amides were identified by comparison with authentic samples. Addition products of acetone and the olefins were also isolated and identified by their retention times in gas–liquid chromatography and comparison of their derivatives with authentic specimens.

Discussion

The addition of formamide to terminal olefins can be induced by light directly or initiated photochemically by acetone. In the first case the mixture of the olefin and formamide was homogenized with dry *t*-butyl alcohol and irradiated with the unfiltered light of the source.[11]

It seems that carbamoyl radicals $\cdot CONH_2$ are generated in the mixture either as a result of the collapse of the photoactivated formamide molecule or through hydrogen atom abstraction from formamide by other radicals formed. The olefin serves as a scavenger for the carbamoyl radicals to form the derived amides. The concentration of the carbamoyl radicals so produced seems to be low, and the consumption of olefins is incomplete even after 50 hr. of irradiation, resulting in low yields (~20%) of the 1:1 adducts. In the acetone-initiated reactions, the generation of the carbamoyl radicals seems to be faster and the concentration of these radicals higher. Thus, the addition of formamide to the olefins in the presence of acetone is complete within several hours and high yields of the 1:1 adducts are obtained.[12]

Light filtered through Pyrex (wave length >300 mμ) induces the acetone-initiated reactions, whereas in the absence of acetone very poor yields of the derived amides are obtained.[12b] We therefore assume that the acetone here provides the main light-absorbing system. The carbamoyl radicals $\cdot CONH_2$ are probably generated through abstraction of a hydrogen atom from formamide by the photoactivated acetone molecule.[13] The presence of acetone not only increases the yields of the amides, but also shortens the irradiation periods. Terminal olefins seem to serve as very efficient scavengers for the carbamoyl radicals, since no oxamide is produced during the acetone-initiated reactions if the addition of the olefin and the irradiation periods are controlled.

The course of the reaction may be illustrated in the following scheme.

$$H{-}CONH_2 \xrightarrow{h\nu} \cdot CONH_2 \quad (1)$$

$$H{-}CONH_2 \xrightarrow[\text{acetone}]{h\nu} \cdot CONH_2 \quad (1a)$$

$$RCH{=}CH_2 + \cdot CONH_2 \longrightarrow R\dot{C}HCH_2CONH_2 \quad (2)$$

$$R\dot{C}HCH_2CONH_2 + H{-}CONH_2 \longrightarrow RCH_2CH_2CONH_2 + \cdot CONH_2 \quad (3)$$

$$R\dot{C}HCH_2CONH_2 + RCH{=}CH_2 \longrightarrow RCH(CH_2\dot{C}HR)CH_2CONH_2 \quad (4)$$

$$RCH(CH_2\dot{C}HR)CH_2CONH_2 + H{-}CONH_2 \longrightarrow RCH(CH_2CH_2R)CH_2CONH_2 + \cdot CONH_2 \quad (5)$$

Reactions 1 and 1a (direct light-induced or initiated photochemically by acetone) are the initiation steps, whereas eq. 2 and 3 are the chain propagating steps to form 1:1 adducts. Reactions 4 and 5 lead to 2:1 telomers. Since reactions 3 and 4 compete, the low concentration of the olefin kept throughout the reaction by the slow addition of this reagent leads to high yields of the 1:1 adducts.

Chain termination results, probably, from a variety of reactions. One of the possibilities is the following,

$$R\dot{C}HCH_2CONH_2 + \cdot CONH_2 \longrightarrow RCH(CONH_2)CH_2CONH_2$$

and in fact alkylated succinamides were isolated in some cases (though in poor yields).[14] Higher concentrations of the carbamoyl radicals $\cdot CONH_2$ will favor this reaction; accordingly, the alkylated succinamides were detected only in the reactions irradiated by lamps and not by sunlight, since the concentration of the carbamoyl radicals in the former case is higher.

The experimental observations, *i.e.*, the formation of (a) 1:1 adducts, (b) telomeric products, (c) alkylated succinamides, and (d) oxamide when an olefin is absent, are consistent with a free-radical mechanism. The telomeric products obtained support the assumption of a chain reaction, being characteristic products of this type of reaction.

The point of initial attack in the free-radical addition to olefin of the type $RCH{=}CH_2$ is at the terminal carbon.[3a,b] The intermediate radical (I) produced by this process (anti-Markovnikov) has a higher degree of resonance stabilization than the alternative radical (II). Steric factors also favor the terminal addition. A Markovnikov-like addition was, however, found to take place in the present reaction and amides of the structure $RCH(CH_3)CONH_2$ were isolated in several

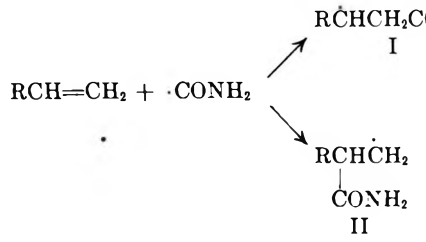
(10) *n*:1 telomer is defined as a molecule formed from *n* molecules of olefin and one molecule of formamide.

(11) Quartz immersion tubes were used for the direct light-induced reactions.

(12) (a) The photolysis of formamide in the absence of an olefin resulted in the formation of oxamide in trace amounts only, whereas the photolysis of formamide in the presence of acetone led to appreciable amounts of oxamide.[12b] (b) Unpublished results from this laboratory.

(13) (a) Because of a lack of accurate physical measurements, the possibility that acetone acts as a photosensitizer and that the generation of the carbamoyl radicals $\cdot CONH_2$ is effected by energy transfer in the triplet states[13b] cannot be excluded. However, our proposed mechanism is supported by the following observations. 2-Methylalkan-2-ols could be isolated from some reaction mixtures. These were probably obtained by addition to the olefin of the ketyl radical $(CH_3)_2\dot{C}OH$ formed by the hydrogen abstraction process. Analogously, a considerable amount of benzpinacol was obtained when benzophenone was used as an initiator.[12b] (b) *Cf.* G. S. Hammond, N. J. Turro, and P. A. Leermakers, *J. Phys. Chem.*, **66**, 1144 (1962).

(14) The possibility that oxamide and the alkylated succinamides result from radical addition to formamide cannot be excluded.



cases. The low yields (3–6%) of these amides obtained are in accordance with the view that terminal addition should predominate.[3b,4a]

The addition of acetone to olefins, induced by intiators or light, has been reported recently.[15] Such an addition was found to take place in 5–15% yield (based on olefin) during the present reactions when acetone was used as an initiator. The resulting methyl ketones are assumed to be produced from the addition of acetonyl radicals to the olefin.

$$RCH{=}CH_2 + \cdot CH_2COCH_3 \longrightarrow RCHCH_2CH_2COCH_3$$

Experimental[16]

Experiments with ultraviolet light were conducted in an apparatus similar to the one described by de Mayo[17] with slight modifications. Hanau Q81 high pressure mercury vapor lamps fitted into Pyrex immersion tubes were used as the radiation source. The lamp was immersed in the reaction mixture, which was cooled externally with running water, and oxygen-free nitrogen was passed through the mixture throughout the irradiation. The internal temperature was kept at 30–32°.

Reactions in sunlight were performed in Pyrex tubes. The system was flushed with nitrogen after each addition of the olefin.

Reagents.—Formamide, pure grade, was freshly distilled at 0.2 mm. before use; absolute acetone was used; *t*-butyl alcohol was distilled over sodium. Olefins were shaken with aqueous ferrous sulfate solution, dried (Na_2SO_4), and before use were freshly distilled and filtered through a short column of "Alcoa" activated alumina F20. 1-Hexene had b.p. 60°, $n^{28}D$ 1.3832; 1-heptene had b.p. 90–91.5°, $n^{25}D$ 1.3970; 1-octene had b.p. 119–120°, $n^{25}D$ 1.4052; 1-decene had b.p. 166°, $n^{28}D$ 1.4178; methyl 10-undecylenate had b.p. 136–137° (27 mm.), $n^{28}D$ 1.4360; and methyl 4-pentenoate had b.p. 128°, $n^{25}D$ 1.4120.

Typical experiments with ultraviolet light and sunlight are described under A. Other experiments were conducted under similar conditions unless otherwise stated.

A. 1-Heptene and Formamide with Ultraviolet Light.—A mixture of 1-heptene (0.5 g.), formamide (40 g.), *t*-butyl alcohol (35 ml.), and acetone (5 ml.) was irradiated for 45 min. A solution of 1-heptene (4.4 g.), *t*-butyl alcohol (10 ml.), and acetone (7 ml.) was then added in ten equal portions at 45-min. intervals, and irradiation was continued for another 6 hr. After removal of the solvents, formamide was distilled from the mixture at 0.2 mm. Treatment of the residue with acetone and filtration (to remove traces of oxamide), followed by the removal of the solvent and addition of water, led to an oily mixture which was crystallized from acetone–petroleum ether to give 3.2 g. of octanamide, m.p. 98–103°. A pure sample showed m.p. 105–106°, lit.[18] m.p. 105–106°.

The aqueous layer was extracted with chloroform. Treatment of the residue left after removal of the solvent with a small volume of acetone caused the separation of 200 mg. of *n*-pentylsuccinamide, which after crystallization from ethanol exhibited m.p. 218–219°.[19]

An authentic sample was prepared from-*n*-pentylsuccinic acid[20]

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 57.89; H, 9.98; N, 14.63.

The residue (2.4 g.) from the combined mother liquors was chromatographed on alumina (120 g.). Elution with acetone–petroleum ether (1:9) led to an oil (200 mg.) which is believed to contain a mixture of telomers. Further elution with the same solvent mixture gave a 2:1 telomer (400 mg.), m.p. 63–65° (*n*-pentane).

Anal. Calcd. for $C_{15}H_{31}NO$: C, 74.63; H, 12.94; N, 5.80; mol. wt., 241. Found: C, 74.47; H, 12.90; N, 5.99; mol. wt., 248.

Acetone–petroleum ether (1:9) finally eluted 220 mg. of 2-methylheptanamide. Crystallized from *n*-pentane it showed m.p. 76–77°. An authentic sample was prepared from 2-methylheptanoic acid which had been synthesized by the method of Wilson.[21] Elution with acetone–petroleum ether (3:17) yielded octanamide (850 mg.). Ethanol–acetone (3:7) eluted a glassy oil (640 mg.).

Anal. Found: C, 58.35; H, 10.66; N, 10.58.

The recovered formamide distillate was diluted with saturated aqueous sodium chloride solution and extracted with chloroform. Removal of the solvent gave an oil (1.6 g.) which furnished 320 mg. of octanamide, m.p. 90–94° upon treatment with *n*-pentane. The residue was chromatographed on alumina (70 g.). Petroleum ether eluted 2-decanone (810 mg.), whose 2,4-dinitrophenylhydrazone showed m.p. 73–75° (*n*-pentane), lit.[22] m.p. 73.5–74°.

Elution with benzene–petroleum ether (1:9) gave 2-methylnonan-2-ol (320 mg.). The 3,5-dinitrobenzoate prepared by the method of Brewster and Ciotti[23] showed m.p. 58–60° (petroleum ether).

Anal. Calcd. for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.87; N, 7.95. Found: C, 57.70; H, 7.15; N, 8.07.

1-Heptene and Formamide in Sunlight.—A mixture of 1-heptene (1 g.), formamide (40 g.), *t*-butyl alcohol (20 ml.), and acetone (5 ml.) was left in direct sunlight for 1 day, a solution of 1-heptene (3.9 g.), *t*-butyl alcohol (25 ml.), and acetone (5 ml.) was then added in four equal portions at 1-day intervals, and the solution was left in sunlight for another 2 days. It was worked up according to the procedure described above. Treatment of the oily residue with acetone–petroleum ether gave 3.23 g. of crude octanamide, m.p. 82–90°. Crystallization from acetone–petroleum ether gave a pure sample, m.p. 103–105°.

Chromatography of the residue (2.50 g.) from the combined mother liquors on alumina (120 g.) by the procedure described above afforded a mixture of telomers (450 mg.), a 2:1 telomer (400 mg.), 2-methylheptanamide (310 mg.), octanamide (620 mg.), and a glassy oil (680 mg.).

Octanamide (250 mg.), 2-decanone (950 mg.), and 2-methylnonan-2-ol (80 mg.) were isolated from the recovered formamide distillate in the usual manner as described above.

B. 1-Octene and Formamide with Ultraviolet Light.—The procedure described under A was followed using 5.6 g. of 1-octene. The usual method of work-up led to 2.9 g. of crude nonanamide, m.p. 82–86°. Crystallization from acetone–petroleum ether gave a pure sample, m.p. 99–100°, lit.[24] m.p. 99°. *n*-Hexylsuccinamide (120 mg.), m.p. 219–221° (ethanol), was isolated in the usual manner.

Anal. Calcd. for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 60.16; H, 10.06; N, 14.23.

Chromatography of the residue from the mother liquors, as described above, led to a mixture of telomers (820 mg.), and a 2:1 telomer (430 mg.), m.p. 64–66° (*n*-pentane).

(15) (a) W. Reusch, *J. Org. Chem.*, **27**, 1882 (1962); (b) A. Rieche, E. Gründemann, and E. Schmitz, *Angew. Chem.*, **74**, 182 (1962).

(16) Boiling points and melting points are uncorrected. Merck "acid-washed" alumina was used for chromatography. Petroleum ether refers to the fraction with b.p. 60–80°. Thin-layer chromatography was performed on Kieselgel G (Merck, Darmstadt); mixtures of acetone–petroleum ether were used for elution, the spots being developed by spraying with a 1% solution of iodine in chloroform. All organic solutions were dried with anhydrous sodium sulfate before removal of solvent. Gas–liquid chromatography (g.l.c.) was carried out with a "Pye" argon instrument on a 10% Apiezon M–Celite column. All products described, except the telomers, were compared with authentic samples by means of their melting point, mixture melting point, infrared spectra, and thin-layer chromatography. Liquids were characterized by their retention times in g.l.c. Molecular weights were determined by the Rast method. Analyses were carried out in our microanalytical section directed by Mr. R. Heller.

(17) P. de Mayo, "Advances in Organic Chemistry," Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 370.

(18) A. W. Hofmann, *Ber.*, **17**, 1406 (1884).

(19) In some experiments the alkylsuccinamides precipitated after the first treatment of the residue from the reaction mixture with acetone (see above).

(20) K. Bernhard and H. Lincke, *Helv. Chim. Acta*, **29**, 1457 (1946).

(21) C. V. Wilson, *J. Am. Chem. Soc.*, **67**, 2161 (1945).

(22) P. J. G. Kramer and H. Van Duin, *Rec. trav. chim.*, **73**, 63 (1954).

(23) J. H. Brewster and C. J. Ciotti, *J. Am. Chem. Soc.*, **77**, 6214 (1955).

(24) W. A. Hofmann, *Ber.*, **15**, 977 (1882).

Anal. Calcd. for $C_{17}H_{35}NO$: C, 75.77; H, 13.09; N, 5.20; mol. wt., 269. Found: C, 75.85; H, 13.14; N, 5.40; mol. wt., 259.

Also found were 2-methyloctanamide (110 mg.), m.p. 79–80° (*n*-pentane), lit.[25] m.p. 80.8°; nonanamide (1.0 g.); and a glassy oil (820 mg.) which showed the following analysis.

Anal. Found: C, 68.04; H, 11.34; N, 6.88.

Nonanamide (150 mg.), 2-undecanone (860 mg.), and 2-methyldecan-2-ol (250 mg.) were isolated from the recovered formamide distillate by the usual manner. The 2,4-dinitrophenylhyrazone of the ketone showed m.p. 63–64° (*n*-pentane), lit.[22] m.p. 64.5–65°. The 3,5-dinitrobenzoate of the tertiary alcohol exhibited m.p. 47–48° (petroleum ether).

Anal. Calcd. for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.67. Found: C, 59.00; H, 7.15; N, 7.65.

1-Octene and Formamide in Sunlight.—The procedure described under A was followed using 5.6 g. of 1-octene; the mixture was worked up in the usual way. The crude nonanamide obtained (3.75 g.) melted at 92–96°.

The residue from the mother liquors was chromatographed on alumina to yield a mixture of telomers (100 mg.), a 2:1 telomer (430 mg.), 2-methyloctanamide (400 mg.), nonanamide (1 g.), and a glassy oil (840 mg.).

Nonanamide (150 mg.), 2-undecanone (530 mg.), and 2-methyldecan-2-ol (170 mg.) were isolated from the recovered formamide distillate.

C. 1-Decene and Formamide with Ultraviolet Light.—Seven grams of 1-decene were used for this experiment. The usual manner of work-up led to 5.45 g. of crude undecanamide, m.p. 80–85°. Crystallization from acetone–petroleum ether gave a pure sample, m.p. 99–100°, lit.[26] m.p. 103°. *n*-Octylsuccinamide (100 mg.), m.p. 220–222° (ethanol), was obtained by the usual procedure.

Anal. Calcd. for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.60; N, 12.27. Found: C, 63.60; H, 10.77; N, 12.13.

Chromatography of the residue from the mother liquors yielded a mixture of telomers (1.21 g.). A pentane solution of the oil left at 0° deposited 200 mg. of a 2:1 telomer, m.p. 60–62° (*n*-pentane).

Anal. Calcd. for $C_{21}H_{43}NO$: C, 77.48; H, 13.32; N, 4.30; mol. wt., 326. Found: C, 76.85; H, 13.28; N, 4.50; mol. wt., 292.

Also found were 2-methyldecanamide (550 mg.), m.p. 81–82° (*n*-pentane), lit.[25] m.p. 81.4°; undecanamide (640 mg.); and a glassy oil (860 mg.) which had the following analysis.

Anal. Found: C, 70.38; H, 11.46; N, 6.69.

Undecanamide (110 mg.) and 2-tridecanone (250 mg.) were isolated from the recovered formamide distillate. The 2,4-dinitrophenylhydrazone of the ketone showed m.p. 68–70° (*n*-pentane), lit.[22] m.p. 70–71°.

D. Methyl 10-Undecylenate and Formamide with Ultraviolet Light.—The general procedure, using 9.9 g. of methyl 10-undecylenate, was followed and led to 3.9 g. of crude methyl 11-carbamoylundecanoate, m.p. 92–95°. Crystallization from acetone–petroleum ether gave a pure sample, m.p. 96–98°, $\nu_{max}^{CHCl_3}$ 1661 and 1726 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.17; H, 10.28; N, 5.89.

The product gave dodecanedioic acid upon alkaline hydrolysis.

The aqueous layer was worked up in the usual manner.[27] The residue from the mother liquors was chromatographed on alumina leading to an oil (2.7 g.), crystallization of which from *n*-pentane yielded 2.1 g. of methyl 13-oxotetradecanoate, m.p. 40–41°, lit.[15b] m.p. 38–40°. An authentic sample was prepared by the method of Robinson.[28] The 2,4-dinitrophenylhydrazone melted at 81–83° (ethanol).

Anal. Calcd. for $C_{21}H_{32}N_4O_6$: C, 57.78; H, 7.39; N, 12.84. Found: C, 57.61; H, 7.53; N, 12.95.

A 2:1 telomer (600 mg.) was found and had m.p. 64–66° (acetone–petroleum ether).

Anal. Calcd. for $C_{25}H_{47}NO_5$: C, 67.99; H, 10.73; N, 3.17; mol. wt., 442. Found: C, 67.94; H, 10.63; N, 3.25; mol. wt., 393.

Also found were methyl 11-carbamoylundecanoate (2.55 g.) and a glassy oil (1.1 g.) which showed the following analysis.

Anal. Found: C, 62.92; H, 10.07; N, 5.13.

E. 10-Undecylenamide and Formamide in Sunlight.—A mixture of 10-undecylenamide (2 g.), formamide (40 g.), *t*-butyl alcohol (25 ml.), and acetone (5 ml.) in a Pyrex conical flask stoppered under nitrogen was left in direct sunlight. (A solid started precipitating at the end of the second day.) After 2 days, a solution of 10-undecylenamide (7.15 g.) in *t*-butyl alcohol (55 ml.) and acetone (7 ml.) was added in five equal portions at 2-day intervals, and the mixture was left in sunlight for another 2 days. The precipitate was washed with acetone to yield 9 g. of dodecanediamide, m.p. 172–180°. Crystallization from ethanol gave a pure sample, m.p. 185–187°, lit.[29] m.p. 189°.

The formamide was removed from the filtrate in the usual way. Boiling the residue with acetone left an insoluble material (1.3 g.) which was filtered off rapidly. It melted at 183–185° (ethanol) and was identified as dodecanediamide.

From the filtrate the amide of 13-oxotetradecanoic acid (1.12 g.), m.p. 117–118° (acetone), was obtained.

Anal. Calcd. for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.28; N, 5.80. Found: C, 69.67; H, 11.17; N, 5.98.

The 2,4-dinitrophenylhydrazone showed m.p. 131–132° (ethanol).

Anal. Calcd for $C_{20}H_{31}N_5O_5$: C, 56.99; H, 7.41; N, 16.62. Found: C, 56.70; H, 7.49; N, 16.85.

F. Methyl 4-Pentenoate and Formamide with Ultraviolet Light.—Methyl 4-pentenoate (5.7 g.) was used for the reaction. Saturated aqueous sodium chloride solution was added to the residue obtained in the usual manner, leading to 3.25 g. of crude methyl 5-carbamoylpentanoate, m.p. 82–88°. Crystallization from acetone–petroleum ether gave a pure sample, m.p. 94–96°, $\nu_{max}^{CHCl_3}$ 1668 and 1724 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.85; H, 8.00; N, 8.86.

The product yielded adipic acid upon alkaline hydrolysis. The residue from the mother liquors was chromatographed on alumina to yield a mixture of telomers (660 mg., eluted with acetone–petroleum ether 3:7), methyl 5-carbamoylpentanoate (1.3 g., eluted with acetone–petroleum ether 1:1), and a glassy oil (1.03 g.) which showed the following analysis.

Anal. Found: C, 49.80; H, 7.78; N, 8.25.

Workup of the recovered formamide distillate led to an oil (1.4 g.) which contained a ketone. The 2,4-dinitrophenylhydrazone showed m.p. 83–85° (ethanol) and was identical with the same derivative of methyl 7-oxooctanoate, prepared by the method of Robinson.[28]

Anal. Calcd. for $C_{13}H_{20}N_4O_6$: C, 51.13; H, 5.72; N, 15.90. Found: C, 51.12; H, 5.85; N, 15.80.

Methyl 4-Pentenoate and Formamide in Sunlight.—A yield of 4.3 g. of crude methyl 5-carbamoylpentanoate, m.p. 84–91°, was obtained from 5.7 g. of methyl 4-pentenoate. Chromatography of the residue from the mother liquors led to an additional crop of methyl 5-carbamoylpentanoate (510 mg.).

Work-up of the recovered formamide distillate gave an oil (1.5 g.), from which methyl 7-oxooctanoate was isolated as its 2,4-dinitrophenylhydrazone derivative.

G. 4-Pentenamide and Formamide in Sunlight.—A mixture of 4-pentenamide (1 g.), formamide (40 g.), *t*-butyl alcohol (20 ml.), and acetone (5 ml.) in a Pyrex conical flask stoppered under nitrogen was left in direct sunlight. (Precipitation of the product started at the end of the second day.) After 2 days, a solution of 4-pentenamide (4 g.), *t*-butyl alcohol (50 ml.), and acetone (5 ml.) was added in five equal portions at 2-day intervals, and the mixture was left in sunlight for another 2 days. The precipitate was washed with hot acetone to yield 4.4 g. of adipamide, m.p. 210–215°. Crystallization from ethanol gave a pure sample, m.p. 224–226°, lit.[30] m.p. 220°.

Formamide was removed from the filtrate in the usual way. Treatment of the residue with acetone–ethanol led to the isolation of an additional crop (1.17 g.) of adipamide.

The residue from the mother liquor was treated with water and extracted with chloroform. Removal of the solvent gave a solid

(25) C. de Hoffmann and E. Barbier, *Bull. soc. chim. Belges*, **45**, 565 (1936).

(26) P. A. Levene and C. J. West, *J. Biol. Chem.*, **18**, 463 (1914).

(27) In some experiments a solid, m.p. 187–189° (acetone), was obtained at this stage by treatment of the residue with a small volume of acetone. *Anal.* Calcd. for $C_{14}H_{26}N_2O_4$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.68; H, 9.28; N, 9.49. The elemental analysis suggests that this compound might be methyl 10,11-dicarbamoylundecanoate, in analogy with other cases.

(28) G. M. Robinson, *J. Chem. Soc.*, 1543 (1934).

(29) C. R. Barnicoat, *ibid.*, 2926 (1927).

(30) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. 1, Eyre and Spottiswoode, London, 1953, p. 33.

(620 mg.), m.p. 90–91° (acetone–petroleum ether), which was identified as the amide of 7-oxooctanoic acid.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.84; H, 9.51; N, 8.91.

The 2,4-dinitrophenylhydrazone showed m.p. 142–144° (ethanol).

Anal. Calcd. for $C_{14}H_{19}N_5O_5$: C, 49.84; H, 5.68; N, 20.76. Found: C, 49.86; H, 5.85; N, 20.95.

H. 1-Hexene and Formamide in Sunlight.—Heptananide (1.31 g.), m.p. 98–100° (acetone–petroleum ether), lit.[31] m.p. 96°, was obtained from 4.2 g. of 1-hexene. The residue[32] from the combined mother liquors was chromatographed and yielded a mixture of telomers (800 mg.), and a 2:1 telomer (510 mg)., m.p. 67–68° (*n*-pentane).

Anal. Calcd. for $C_{13}H_{27}NO$: C, 73.18; H, 12.76; N, 6.57; mol. wt., 213. Found: C, 73.00; H, 12.78; N, 6.40; mol. wt., 206.

Also found were heptanamide (1.3 g.) and a glassy oil (720 mg.) which had the following analysis.

Anal. Found: C, 64.21; H, 11.60; N, 7.68.

An additional 600 mg. of heptanamide was obtained in the usual manner from the recovered formamide distillate.

I. Propylene and Formamide in Sunlight.—A mixture of propylene (3.5 ml. as liquid), formamide (40 g.), *t*-butyl alcohol (25 ml.), and acetone (15 ml.) was left in direct sunlight in a sealed Pyrex tube for 1 week. After work-up, an oil (1.1 g.) was obtained and was chromatographed on alumina (55 g.) to yield 360 mg. of crude 3-methylhexanamide, m.p 55–60°. Crystallization from acetone–petroleum ether gave a pure sample, m.p. 96–97°, lit.[33] m.p. 97°, and 130 mg. of crude butyramide which was sublimed on a steam bath and showed m.p. 114–116°, lit.[34] m.p. 115°.

J. 1-Octene and Formamide without Acetone.—A mixture of 1-octene (5.6 g.), formamide (40 g.), and *t*-butyl alcohol (55 ml.) was irradiated for 44 hr. (A quartz immersion tube was used for this experiment.) Work-up led to 400 mg. of crude nonanamide, m.p. 90–92°.

The residue from the mother liquors (2.6 g.) was chromatographed on alumina (130 g.) to yield a mixture of telomer (1.0 g.), a 2:1 telomer (350 mg.) which was identical with the 2:1 telomer obtained from the acetone-initiated reaction, nonanamide (710 mg.), and an oil (460 mg.) which had the following analysis.

Anal. Found: C, 69.45; H, 11.48; N, 7.05.

Acknowledgment.—We are indebted to Professor F. Sondheimer for his interest and encouragement and to The Weizmann Graduate School in the Natural Sciences for maintenance of a Fellowship to one of us (J. R.).

(31) J. S. Lumsden, *J. Chem. Soc.*, **87**, 90 (1905).

(32) In experiments carried out with ultraviolet light (unpublished results from this laboratory) *n*-butylsuccinamide, m.p. 216–217° (ethanol), was isolated. *Anal.* Calcd. for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.97; H, 9.40; N, 16.49.

(33) A. Dewall and A. Weckering, *Bull. soc. chim. Belges*, **33**, 495 (1924).

(34) W. A. Hofmann, *Ber.*, **15**, 977 (1882).

Ester Formation and Coupling at Phosphorus on Reaction of Diphenylphosphinous Chloride with Diols and Tertiary Amines[1]

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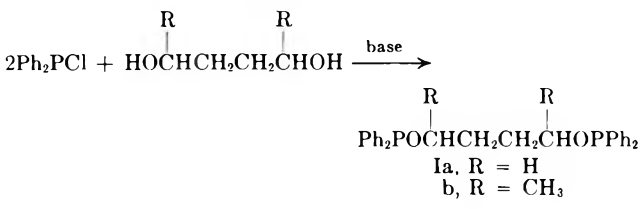
1,4-Butanediol and 2,5-hexanediol reacted smoothly with diphenylphosphinous chloride in the presence of diethylaniline to yield solid bisphosphinites. Ethylene glycol failed to yield a solid bisphosphinite; on distillation the product of the Arbuzov rearrangement of this ester, ethylene bis(diphenylphosphine oxide), was obtained. From the diol reaction mixtures, trace to appreciable amounts of a by-product identified as tetraphenyldiphosphine dioxide were obtained. It was also found that the reaction of ethanol with diphenylphosphinous chloride gave this unusual by-product, apparently not previously observed in such reactions.

Phosphinous chlorides are known to react with alcohols to form phosphinites in the presence of a tertiary amine.[3] We have used this reaction[4] to prepare bisphosphinites, desired for anticancer screening, from certain glycols and diphenylphosphinous chloride.

1,4-Butanediol and 2,5-hexanediol reacted smoothly with diphenylphosphinous chloride in the presence of diethylaniline in ether solution. The bisphosphinites



so produced were recovered as low-melting, crystalline solids. Compound Ia showed strong infrared absorption at 1045 cm.$^{-1}$, attributable to the P–O–C group.[4] The spectrum of Ib possessed two medium intensity peaks (1000 and 1055 cm.$^{-1}$) in the P–O–C region. Neither ester exhibited absorption in the phosphoryl region (1175–1250 cm.$^{-1}$), and thus Arbuzov rearrangement to isomeric phosphine oxides had not occurred. In further confirmation of their structures, esters Ia and Ib rapidly decolorized iodine solutions, and on neutral hydrolysis gave diphenylphosphine oxide, identified by its infrared spectrum and by its chloral adduct.[5] Hydrolysis of phosphinites to *sec*-phosphine oxides has been observed previously.[6]

Compound Ia was converted to the known[7] tetramethylene bis(diphenylphosphine oxide) by Arbuzov rearrangement with a small amount of ethyl iodide in refluxing heptane. Phosphoryl absorption for this compound occurred as a singlet at 1177 cm.$^{-1}$; in the spectrum of ethylene bis(diphenylphosphine oxide) (*vide infra*), a doublet at 1170–1180 cm.$^{-1}$ is present. No rearrangement was detected on simply heating Ia at 150–200° for 2 hr. Compound Ib failed to undergo rearrangement in the presence of ethyl iodide in either refluxing heptane or dodecane at 145°.

Attempts to prepare ethylene bis(diphenylphosphinite) (II) have been unsuccessful. A nearly quanti-

(1) Supported in part by Research Grant CA-05507 from the National Cancer Institute, Public Health Service.

(2) Philip Morris Research Assistant, 1962–1963.

(3) A. E. Arbuzov and K. V. Nikonorov, *Zh. Obshch. Khim.*, **18**, 2008 (1948).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, Chapter 18.

(5) L. D. Quin and R. E. Montgomery, *J. Org. Chem.*, **28**, 3315 (1963).

(6) (a) M. Sander, *Ber.*, **93**, 1220 (1960); (b) M. I. Kabachnik and E. N. Tsvetkov, *Dokl. Akad. Nauk. SSSR*, **135**, 323 (1960).

(7) A. Mondon, *Ann.*, **603**, 115 (1957).

tative yield of amine hydrochloride resulted when diphenylphosphinous chloride and ethylene glycol reacted as above, but the ether solution left a noncrystallizing oil on evaporation. This oil consumed only about one-half of the calculated amount of iodine on titration. Its infrared spectrum was complex and indicative of a gross mixture, but P–H and phosphoryl absorptions were recognizable. Numerous attempts to recover any II present by distillation were unsuccessful. Distillates did not possess the expected composition or infrared spectra, and were indicated by the former to contain an excess of oxygen and by the latter to contain phosphoryl groups.

In all distillations, there remained a large amount of a crystalline residue whose infrared spectrum showed no P–O–C absorption, but did show strong phosphoryl absorption. A pure sample had m.p. 273° and was identified as ethylene bis(diphenylphosphine oxide) (IV). This compound has been prepared previously by different methods[8]; a recently reported[8d] melting point is 273–275°. Compound IV could have two precursors in the mixture subjected to distillation. It could have arisen either from bisphosphinite II by double Arbuzov rearrangement or from the half-rearranged compound III. If III were the precursor, then an Arbuzov rearrangement must also have occurred prior to attempted distillation, perhaps during the initial reaction. The phosphoryl absorption and iodine titer of the oil obtained initially suggest this to have occurred. No further effort was made to eluci-

$$\underset{\text{II}}{Ph_2POCH_2CH_2OPPh_2} \longrightarrow \underset{\text{III}}{Ph_2\overset{\overset{O}{\uparrow}}{P}CH_2CH_2OPPh_2} \longrightarrow \underset{\text{IV}}{Ph_2\overset{\overset{O}{\uparrow}}{P}CH_2CH_2\overset{\overset{O}{\uparrow}}{P}Ph_2}$$

date the course of the ethylene glycol–diphenylphosphinous chloride reaction; the system was markedly different from the others examined, and appeared unlikely to yield a bisphosphinite.

On allowing the ether filtrate from any of the diol–phosphinous chloride reaction mixtures to stand for a day or two, deposition of a white, crystalline solid occurred. While only small amounts formed in preparations of Ia and Ib, significant amounts were obtained in reactions involving ethylene glycol. The yield was as high as 22% in one reaction, but values around 10% were more common. This compound, m.p. 167°, showed strong phosphoryl absorption at 1175 cm.$^{-1}$. Analysis indicated the empirical formula, $(C_6H_5)_2PO$, and suggested the structure, $(C_6H_5)_2P(O)$-$P(O)(C_6H_5)_2$, a most unexpected product. This compound, tetraphenyldiphosphine dioxide (V), has been prepared previously by a different method.[9] It had m.p. 167° and an infrared spectrum identical with our sample. It was reported to be readily cleaved by alkaline hydrolysis to diphenylphosphinic acid, and we also observed this property. In addition, we found neutral hydrolysis to effect cleavage of the P–P bond.

$$(C_6H_5)_2P(O)P(O)(C_6H_5)_2 \xrightarrow{H_2O} (C_6H_5)_2P(O)H + (C_6H_5)_2P(O)OH$$

This milder treatment allowed recovery of the other product of cleavage, diphenylphosphine oxide, which in an alkaline medium is rapidly disproportionated.

In some other work, we had occasion to prepare ethyl diphenylphosphinite by the same general reaction. On distillation, 50–75% yields of the ester were obtained. The distillation residue crystallized on cooling. It was initially assumed that this residue was either diphenylethylphosphine oxide, formed from Arbuzov rearrangement of the ester during distillation, or diphenylphosphinic acid, as mentioned by Arbuzov and Nikonorov.[3] However, the residue was later examined and found to be largely insoluble in sodium bicarbonate and to have a crude melting point of 147–150°. The tertiary phosphine oxide has m.p. 121°.[10] On recrystallization, the residue had m.p. 167–169° and an infrared spectrum identical with that of tetraphenyldiphosphine dioxide. The yield was 11.4%. This compound must have been formed in a side reaction accompanying the esterification reaction; it did not form during distillation of the ester, as none was produced when a pure sample of the ester was heated.

The formation of this diphosphine derivative in alcohol–phosphinous chloride–amine reactions apparently has not been detected previously. In their identification of the distillation residue as diphenylphosphinic acid, Arbuzov and Nikonorov[3] performed a recrystallization from ethanol. The diphosphine dioxide is readily cleaved by nucleophiles, one product being diphenylphosphinic acid, and it is possible that some of the acid they obtained came from this source. We have also observed that recrystallization of V often gives the phosphinic acid if the solvent is not adequately dried.

The origin of V is of some interest, as the P–P bond is not generally encountered so casually.[11] Work is now in progress to identify the reaction giving rise to V.[12]

Experimental

General.—Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting and boiling points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 137 spectrophotometer. Reactions of diphenylphosphinous chloride were conducted in a nitrogen atmosphere.

Diphenylphosphinous chloride was kindly donated by Victor Chemical Division, Stauffer Chemical Co., Chicago, Ill. It was redistilled before use. Glycols were dried with sodium and distilled. Diethylaniline and solvents were dried and distilled.

Preparation of Tetramethylene Bis(diphenylphosphinite).—To a solution of 4.5 g. (0.05 mole) of 1,4-butanediol and 22.4 g. (0.15 mole) of diethylaniline in 75 ml. of ether was added in 1 hr. a solution of 22.1 g. (0.10 mole) of diphenylphosphinous chloride. The temperature was held at 20–25°. After stirring an additional 2 hr., the precipitated amine salt was removed by filtration. The filtrate on standing 2 days deposited 0.1 g. of a solid, m.p.

(8) (a) K. Issleib and D. W. Muller, *Ber.*, **92**, 3175 (1959); (b) G. M. Kosolapoff and R. F. Struck, *J. Chem. Soc.*, 2423 (1961); (c) M. I. Kabachnik, T. Y. Medved, Y. M. Polikarpov, and K. S. Yudina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2029 (1961); (d) P. T. Keough and M. Grayson, *J. Org. Chem.*, **27**, 1817 (1962).

(9) W. Kuchen and H. Buchwald, *Ber.*, **91**, 2871 (1958).

(10) A. Michaelis and H. von Soden, *Ann.*, **229**, 295 (1885).

(11) The subject has been recently reviewed: J. E. Huheey, *J. Chem. Educ.*, **40**, 153 (1963).

(12) NOTE ADDED IN PROOF.—It has since been observed that exposure to the atmosphere of an ether solution of a diarylphosphinous chloride and a tertiary amine results in the formation of the tetraaryldiphosphine dioxide in good yield. It is likely that this is the source of tetraphenyldiphosphine dioxide found in the present study. L. D. Quinn and H. G. Anderson, *J. Am. Chem. Soc.*, **86**, 2090 (1964).

167–169°, later identified as tetraphenyldiphosphine dioxide. The ether solution was stripped, leaving an oil that rapidly crystallized. The solid was washed with ice-cold pentane; 18.3 g. (80%) of m.p. 67–70° was obtained. A sample recrystallized from pentane had m.p. 74–75°. It was reasonably resistant to air oxidation; no special precautions were taken in the recrystallization.

Anal. Calcd. for $C_{28}H_{28}O_2P_2$: C, 73.35; H, 6.16; P, 13.51. Found: C, 73.05; H, 6.20; P, 13.41.

Arbuzov Rearrangement of Tetramethylene Bis(diphenylphosphinite).—A 1-g. sample of Ia was heated in a bath at 150° for 1 hr., and then at 200° for 1 hr. The melting point of the sample was unchanged.

A 1.3-g. (0.0028 mole) sample of Ia in 25 ml. of heptane was treated with 4 drops of ethyl iodide. A crystalline solid began to form after several hours at reflux. After 16 hr., the mixture was filtered while hot. The residue was washed with cold acetone, leaving 0.65 g. (50%) of tetramethylene bis(diphenylphosphine oxide). After recrystallization from ethanol–ether, m.p. 259–261° was obtained (lit.[7] m.p. 256–257°). Strong phosphoryl absorption at 1177 cm.$^{-1}$ was noted and no decolorization of iodine occurred.

Preparation of 1,4-Dimethyltetramethylene Bis(diphenylphosphinite).—A solution of 22.1 g. (0.1 mole) of diphenylphosphinous chloride in 75 ml. of ether was added over 1.3 hr. to a solution of 5.9 g. (0.05 mole) of 2,5-hexanediol and 22.4 g. (0.15 mole) of diethylaniline in 125 ml. of ether held at 18–20°. After stirring 9 hr., the precipitate was removed. The filtrate deposited a trace of tetraphenyldiphosphine dioxide overnight. The solvent was removed from the filtrate, and the residual oil was mixed with acetone. Crystallization occurred on chilling in a Dry Ice bath. The product (15.8 g., 65.0%) was recrystallized from acetone, m.p. 73°.

Anal. Calcd. for $C_{30}H_{32}O_2P_2$: C, 74.06; H, 6.63; P, 12.74. Found: C, 74.26; H, 6.50; P, 12.65.

Hydrolysis of Bisphosphinites.—A 1.25-g. (0.0027 mole) sample of Ia was placed in 20 ml. of water and refluxed for 5 hr. The mixture then was extracted with ether; the ether was removed from the extract; and the semisolid residue (0.95 g., 86%) was dried *in vacuo*. The infrared spectrum of the residue was identical with that of diphenylphosphine oxide, prepared by hydrolysis of diphenylphosphinous chloride.[5] Further confirmation was obtained by preparing the chloral adduct, whose melting point and infrared spectrum agreed with a known specimen. Little hydrolysis of Ib occurred after 3-hr. reflux, but a 79.6% yield of diphenylphosphine oxide was obtained after 16 hr.

Tetraphenyldiphosphine Dioxide from Ethylene Glycol–Diphenylphosphinous Chloride Reactions.—The following procedure is typical of several runs. A solution of 3.1 g. (0.05 mole) of ethylene glycol and 29.8 g. (0.20 mole) of diethylaniline in 75 ml. of ether was treated with a solution of 22.1 g. (0.10 mole) of diphenylphosphinous chloride in 75 ml. of ether. Addition time at 18–20° was 1 hr. After stirring for 2 hr. longer, the amine salt was removed by filtration and the filtrate was allowed to stand. White crystals slowly formed on the flask walls. After 2 days, 1.5 g. (8%) was recovered by filtration. Following recrystallization from ethyl acetate or toluene, the solid had m.p. 167–169°. The recrystallization requires dry solvents to prevent phosphinic acid formation.

Anal. Calcd. for $C_{24}H_{20}O_2P_2$: C, 71.64; H, 5.01; P, 15.40. Found: C, 71.37; H, 4.93; P, 15.18.

The compound decolorized iodine and neutral potassium permanganate solutions. On refluxing 0.66 g. with 5% sodium hydroxide for 3 hr. followed by acidification, diphenylphosphinic acid (0.7 g.), m.p. 193–195°, was obtained. On refluxing 0.76 g. in 25 ml. of water for 30 min., 0.23 g. of diphenylphosphinic acid, m.p. 192°, precipitated. Evaporation of the water left 0.38 g. of an oil having an infrared spectrum essentially identical with that of a known specimen of diphenylphosphine oxide, and which formed a chloral adduct, m.p. 168°, lit.[5] m.p. 171.5–172.5°, whose infrared spectrum agreed with that of a standard.

Ethylene Bis(diphenylphosphine oxide) from Ethylene Glycol and Diphenylphosphinous Chloride.—The filtrate from removal of tetraphenyldiphosphine dioxide, in a preparation such as that above, was evaporated to leave a noncrystallizing oil. Its infrared spectrum was complex, but P–H (2275 cm.$^{-1}$) and phosphoryl (1180–1220 cm.$^{-1}$) absorptions were present. Its trivalent phosphorus content was 6.9% (calcd. for $C_{26}H_{28}O_2P_2$, 14.4%). On distillation at 0.01 mm., a fraction was received at 150–160°; thereafter, no further distillation without decomposition occurred. The pot contents crystallized on cooling. After two recrystallizations from toluene, this solid had m.p. 271–273°, lit.[8c] m.p. 273–275°. The infrared spectrum included a doublet at 1170–1180 cm.$^{-1}$ for the phosphoryl group. The yield of this compound was variable, but generally was around 30–40%.

Anal. Calcd. for $C_{26}H_{24}O_2P_2$: P, 14.39. Found: P, 14.71.

The distillation fractions gave some diphenylphosphinic acid after refluxing 2 hr. in 10% sodium hydroxide, and generally showed infrared absorption characteristic of P–H at 2350 cm.$^{-1}$, phosphoryl groups at 1190 and 1220 cm.$^{-1}$, and P–O–C at 1025 cm.$^{-1}$. Variable results, inconsistent with any definite compound, were obtained on analysis of the distillates.

Modifications involving reversal of reagent addition, use of benzene or dioxane as solvents, and purification of the oil by washing with dilute hydrochloric acid and sodium bicarbonate prior to distillation led to substantially the same results. In no case was evidence for the desired bisphosphinite obtained.

Reaction of Ethanol with Diphenylphosphinous Chloride.—A mixture of 11.5 g. (0.25 mole) of ethanol and 37.3 g. (0.25 mole) of diethylaniline in 125 ml. of ether was treated over a period of 1.5 hr. with a solution of 44.2 g. (0.20 mole) of diphenylphosphinous chloride in 75 ml. of ether. The temperature was held at 20°. After 2 hr., the mixture was filtered and the filtrate was distilled. Ethyl diphenylphosphinite (34.8 g., 76%) was collected at 111–114° (0.45–0.50 mm.). On cooling, the pot residue crystallized and had m.p. 147–150°. It was washed with ether and dilute sodium bicarbonate, leaving 4.6 g. (11.4%) of white solid. After recrystallization from toluene, it had m.p. 167–169° and an infrared spectrum identical with that of tetraphenyldiphosphine dioxide.

Effect of Heat on Ethyl Diphenylphosphinite.—A 3.6-g. sample of ethyl diphenylphosphinite was held for 8 hr. just below reflux at atmospheric pressure. A pale yellow viscous oil remained on cooling. Addition of ether caused formation of a crystalline mass and extracted some unchanged ethyl diphenylphosphinite, detected by infrared spectroscopy. A benzene solution of the crystallized solid was extracted with sodium bicarbonate; this extract on acidification gave 0.70 g. of diphenylphosphinic acid (crude m.p. 188–190°). The benzene solution on evaporation left 1.40 g. of diphenylethylphosphine oxide, m.p. 118–119°, lit.[10] m.p. 121°, having an infrared spectrum in agreement with that of a known specimen.

Anomalous Reaction of Epichlorohydrin with Trimethylamine

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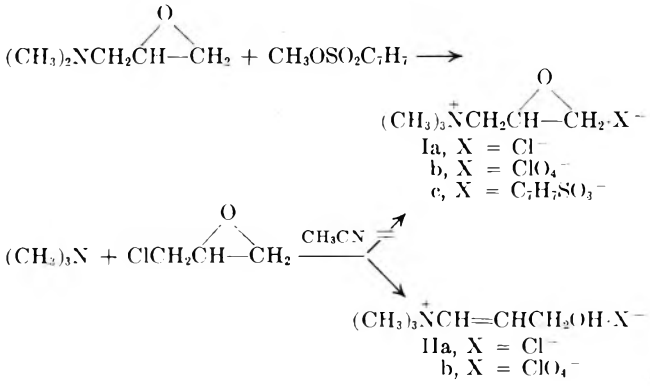
The reaction of epichlorohydrin and trimethylamine in acetonitrile does not give the expected product, N-(2,3-epoxypropyl)trimethylammonium chloride (Ia) but, instead, N-(3-hydroxy-1-propenyl)trimethylammonium chloride (IIa). Evidence is presented to show that Ia is a likely intermediate in the reaction, and that its rearrangement to IIa occurs readily in the presence of trimethylamine. The reaction has been extended to the long-chain amine, N,N-dimethyldodecylamine.

The preparation and reactions of epoxides which contain quaternary ammonium functions have been of recent interest.[1] These salts were readily prepared from tertiary glycidyl amines by alkylation with suitable agents. Thus, N-(2,3-epoxypropyl)trimethylammonium *p*-tosylate (Ic) was obtained in good yield from N-(2,3-epoxypropyl)dimethylamine and methyl *p*-tosylate. Since the glycidyl amine is not readily available, and must first be prepared from epichlorohydrin, an alternate procedure, the direct alkylation of trimethylamine with epichlorohydrin was considered. This reaction has led to an anomalous result, namely, the formation of the isomeric compound, N-(3-hydroxy-1-propenyl)trimethylammonium chloride (IIa).



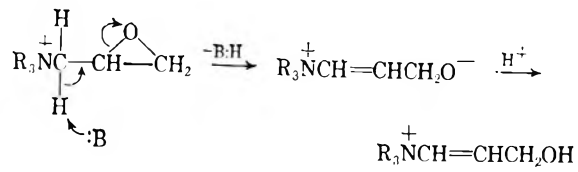
Although the reaction of epichlorohydrin with tertiary amines to produce epoxypropyl quaternary salts is mentioned in the literature,[2] including technical brochures, original references to the reaction with trimethylamine are very old and in them the products were not definitely characterized. Reboul[3] heated equal volumes of trimethylamine and epichlorohydrin in a sealed tube at 100° and reportedly obtained Ia as a viscous sirup. Somewhat later, Schmidt and Hartmann[4] in a similar reaction, but, using a 2:1 ratio of amine to epichlorohydrin, obtained a small amount of Ia; the chief product was the bis salt, 2-hydroxypropane-1,3-bis(trimethylammonium chloride) (III). The reaction of a long-chain tertiary amine with epichlorohydrin has also been reported to produce an epoxide salt, but without documentary proof.[5,6]

The reaction of epichlorohydrin and trimethylamine in acetonitrile was found to occur readily, under ambient conditions, to give good yields of a product consisting largely of the 3-hydroxy-1-propenyl salt (IIa) which is isomeric with epoxide Ia. The presence of a small amount of the epoxide was indicated by an epoxy oxygen analysis and by the n.m.r. spectrum of the product. The major product has not previously been reported in the literature nor have the properties of the expected epoxide. Although the elemental analysis of the product was consistent with Ia, an extremely low epoxy oxygen value and the presence of a strong hydroxyl band in the infrared spectrum indicated a product other than the unexpected compound.

The results of the first attempt at identification by n.m.r. were misleading in that the spectrum appeared to indicate the presence of two CH_2 groups in the molecule. The only structure compatible with this finding and other data is the highly improbable enolic form, $(CH_3)_3N^+CH_2CH(OH)=CH_2\cdot Cl^-$, of acetonyltrimethylammonium chloride. The spectrum did confirm the presence of the OH group for the single proton resonance at τ 6.66; this shifted to the position of water resonance when a small amount of D_2O was added. It soon became apparent that the two protons appearing as a triplet at τ 3.66 are the olefinic protons of structure IIa, an instance in which two protons in completely different environments have essentially identical displacements in a magnetic field. The 3,5-dinitrobenzoate ester, on the other hand, gives an n.m.r. spectrum which is not only consistent with that of the hydroxy compound but which shows a normal separation of the olefinic protons. This has the appearance of an AB multiplet, each line of the doublet at higher field being split into a triplet.

Final confirmation of structure IIa for the product derived from its decolorization of permanganate and hydrogenation of the perchlorate salt (IIb) to N-(3-hydroxypropyl)trimethylammonium perchlorate.

The mechanism of formation of IIa from the reaction of epichlorohydrin and trimethylamine appears to proceed *via* the epoxide Ia as an intermediate. The latter may be formed by direct alkylation of the amine with the chloride or, alternatively, by a ring-opening step as is characteristic of reactions of epichlorohydrin with primary and secondary amines.[7] The rearrangement, occurring under catalysis by excess trimethylamine, may then proceed as follows.



(1) D. M. Burness and H. O. Bayer, *J. Org. Chem.*, **28**, 2283 (1963).

(2) A. M. Paquin, "Epoxyverbindungen und Epoxyharze," Springer-Verlag, Berlin, 1958, p. 202.

(3) E. Reboul, *Compt. rend.*, **93**, 423 (1881).

(4) E. A. Schmidt and H. Hartmann, *Ann.*, **337**, 116 (1904).

(5) E. I. du Pont de Nemours and Co., Inc., British Patent 477,981 (March 30, 1936).

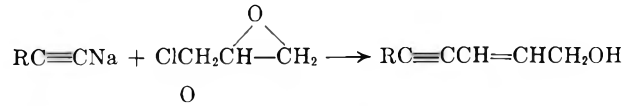
(6) When this work was substantially complete, Ia was made available in research quantities by Shell Chemical Co., to whom we are indebted for a sample. Details of their synthesis have not yet been published.

Confirmation of the intermediacy of the epoxide in this reaction was found in the ease and efficiency with which epoxides Ia and Ib rearranged under the reaction conditions to IIa and IIb. In one instance, a minor amount of the diquaternary salt, 2-hydroxypropane-1,3-bis(trimethylammonium perchlorate), was formed as a minor by-product. This probably arose from attack by trimethylamine on the terminal carbon of the epoxide ring, with resultant ring cleavage at this point.

The possibility that the chloride ion, when present in the reaction medium, may serve as the catalyst which promotes the rearrangement of Ia[8] may be discounted by the failure of Ia to rearrange to any appreciable extent in the absence of trimethylamine. In *refluxing* acetonitrile, a trace of the amine was detectable after 3 hr.; nevertheless, the bulk of the epoxide was recovered unchanged. Efforts to catalyze the rearrangement with triethylamine or triethylenediamine, under the usual ambient conditions, were notably unsuccessful. In the case of triethylamine, the increased steric requirement could be responsible; triethylenediamine is a considerably weaker base.

Although propylene oxide has recently been reported[9] to rearrange to allyl alcohol with a basic lithium phosphate catalyst, it underwent polymerization rather than rearrangement under the conditions of these reactions. Trimethylamine has previously been mentioned as a polymerization catalyst[10]; however, it was found that little reaction occurred at 25° in the absence of acetonitrile. Although other solvents have not been tried in the reactions under investigation, other highly polar solvents should also promote these ionic reactions.

The formation of an allylic alcohol in the reaction of epichlorohydrin with a basic reagent is not unique. Various workers[11-13] have found that epichlorohydrin and related compounds react with sodium acetylides to give such products. The rearrangement of the epoxide, benzylethylene oxide, to cinnamyl alcohol has been effected with a molar equivalent of sodamide in liquid ammonia.[11] Milder agents were ineffective.



An indication that the anomalous result obtained with trimethylamine is not unique and may be of considerable scope was found in the only other similar reaction attempted so far, *i.e.*, with dodecyldimethylamine. This reaction, which required more vigorous conditions than trimethylamine, resulted in an approximately 50% crude yield of a product which consisted largely of N-dodecyl-N-(3-hydroxy-1-propenyl)dimethylammonium chloride.

Experimental[14]

N-(3-Hydroxy-1-propenyl)trimethylammonium Chloride (IIa) and Derivatives.—A solution of 75 g. (0.81 mole) of epichlorohydrin (dried over Drierite) and 300 ml. of acetonitrile (Eastman Grade, dried over Drierite) in a flask equipped with stirrer, gas addition tube, and Dry Ice condenser was cooled to −20°, and 53 g. (0.90 mole) of anhydrous trimethylamine was passed in gradually. After 1.5 hr. at −10 to −20°, the solution was allowed to warm to 25°, and the temperature was maintained at 20–25° for 19 hr. Most of the trimethylamine was contained during this period by the condenser. The oil which gradually separated soon crystallized. The solid was removed and washed with acetonitrile and ether, 107-g. (87%) crude yield, m.p. 147–156°. A single recrystallization from *ca.* 400 ml. of absolute ethanol, with charcoal, and addition of ether to the cloud point produced 72 g. (58%) of a colorless, hygroscopic solid of m.p. 163–164° dec. A sample recrystallized further from absolute ethanol melted at 164–165° dec.

Anal. Calcd. for $C_6H_{14}ClNO$: C, 47.5; H, 9.3; Cl, 23.4; N, 9.2. Found: C, 47.2; H, 9.5; Cl, 23.6; N, 9.3.

An epoxy oxygen analysis indicated the possible presence of 9–10% of the epoxide Ia[15]; the infrared spectrum showed a strong hydroxyl absorption at 3.0.

The product failed to form a dinitrophenylhydrazone and failed to decolorize a solution of bromine in acetic acid. It did, however, decolorize aqueous permanganate, whereas the epoxide salt I gave a negative test with this reagent. The failure to react with bromine is in agreement with the result reported[16] with N-vinylpyridinium perchlorate.

The perchlorate salt (IIb), prepared from the chloride with concentrated aqueous sodium perchlorate, formed colorless plates of m.p. 181.5–183.5°. The n.m.r. spectrum of a 10% solution (w./v.) in acetonitrile shows a singlet at τ 6.76 (nine protons), two doublets at 5.82 (two protons), a triplet at 3.66 (two protons), and a triplet at 6.66 (one proton).

Anal. Calcd. for $C_6H_{14}ClNO_5$: S, 33.4; H, 6.5; Cl, 16.5; N, 6.5. Found: C, 33.7; H, 6.5; Cl, 16.8; N, 6.9.

An epoxy oxygen analysis indicated the possible presence of a small amount (0–2.5%) of Ib.[15]

The **3,5-dinitrobenzoate** was prepared from 1.5 g. of IIa and 2.3 g. of 3,5-dinitrobenzoyl chloride by boiling the solution for 5 min. in 60 ml. of nitromethane. Isolation of the ester and recrystallization from absolute ethanol–ether afforded 1.3 g. of nearly colorless crystals of m.p. 157.5–158° dec. The n.m.r. spectrum of a 5% solution (w./v.) in dimethy sulfoxide shows a singlet at τ 6.65 (9 protons), a doublet at 4.93 (2 protons), a multiplet at 3.25 (2 protons), and three aromatic protons further downfield.

Anal. Calcd. for $C_{13}H_{16}ClN_3O_6$: C, 45.1; H, 4.6; Cl, 10.3; N, 12.15. Found: C, 45.3; H, 4.8; Cl, 10.2; N, 11.9.

N-(2,3-Epoxypropyl)trimethylammonium Perchlorate (Ib).—The tosylate salt[1] was converted to the perchlorate using sodium perchlorate in acetonitrile. After filtration of the sodium *p*-toluenesulfonate and removal of the solvent, the pure perchlorate was obtained from methanol in 87% yield, m.p. 132.5–133.5°.

Anal. Calcd. for $C_6H_{14}ClNO_5$: C, 33.4; H, 6.5; Cl, 16.5; N, 6.5. Found: C, 33.7; H, 6.2; Cl, 16.5; N, 6.9.

Acetonyltrimethylammonium Chloride and Perchlorate.—A solution of 50 g. of chloroacetone in 250 ml. of acetonitrile, held

(7) *Cf.* S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 27.

(8) This possibility, suggested by Dr. Stanley Smith, of the University of Illinois, arises from known instances in which eliminations and rearrangements in acetonitrile and other polar organic solvents have been strongly catalyzed by halide ions. *Cf.* D. N. Kevill, P. H. Hess, P. W. Foster, and N. H. Cromwell, *J. Am. Chem. Soc.*, **84**, 983 (1962); R. P. Holysz, *ibid.*, **75**, 4432 (1953); H. W. Heine, M. E. Fetter, and E. M. Nicholson, *ibid.*, **81**, 2202 (1959).

(9) Olin Mathieson Chemical Corp., British Patent 902,953; *Chem. Abstr.*, **58**, 13,794 (1963).

(10) C. S. Marvel and E. C. Horning, "Organic Chemistry," Vol. I, 2nd Ed., H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 771.

(11) L. J. Haynes, I. Heilbron, E. R. H. Jones, and F. Sondheimer, *J. Chem. Soc.*, 1583 (1947).

(12) C. F. Hiskey, H. L. Slates, and N. L. Wendler, *J. Org. Chem.*, **21**, 429 (1956).

(13) T. L. Jacobs, D. Dankner, and A. R. Dankner, *J. Am. Chem. Soc.*, **80**, 864 (1958).

(14) Melting points were taken in a capillary and are corrected. The method for epoxy oxygen determinations was an adaptation, by D. G. Bush of these laboratories, of one published by A. J. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956). With quaternary salts, it has been found necessary to employ excess hydrogen bromide and to back-titrate after 30 min. with tetra-*n*-butylammonium hydroxide, using crystal violet as indicator. The n.m.r spectra were obtained on a Varian 60-Mc. dual purpose spectrometer, Model V-4302, using tetramethylsilane as an internal reference. The τ-values given are those of G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(15) Although good accuracy is ordinarily obtained in these analyses, the values appear to run a bit high (0–2.5%) in the presence of the allylic hydroxyl group.

(16) I. N. Duling and C. C. Price, *J. Am. Chem. Soc.*, **84**, 578 (1962).

at 10°, was treated with 33 g. of gaseous trimethylamine. After 2 hr., the chloride was filtered and recrystallized from acetonitrile to give 36 g. of a colorless, hygroscopic solid of m.p. 155–157°. Conversion to the perchlorate in acetonitrile produced a colorless solid of m.p. 96–100° after recrystallization from 2-butanone.

Anal. Calcd. for $C_6H_{14}ClNO_5$: C, 33.4; H 6.5; Cl, 16.5. Found: C, 33.3; H, 6.4; Cl, 16.7.

Neither of these salts is reported in the literature.

N-(3-Hydroxypropyl)trimethylammonium Perchlorate and Tetraphenylboride. A. By Hydrogenation of IIb.—A solution of 4.3 g. of IIb in 90% aqueous methanol was hydrogenated at 25° and 45 p.s.i. using a platinum oxide catalyst; the theoretical amount of hydrogen was absorbed in 10 min. The solvent was removed and the residue was washed with ether to give 3.3 g. of crude product of m.p. 123–128° (melt not clear). Although the infrared spectrum compared favorably with that of the perchlorate prepared below, a troublesome impurity, indicated by bands in the spectrum at 3.7 and 10.2 μ to be trimethylammonium perchlorate, interfered with an attempted purification by recrystallization. The product thus was converted to the tetraphenylboride (TPB) salt, using aqueous sodium tetraphenylboron. After recrystallization from acetone, the TPB salt, consisting of colorless plates, melted at 228° dec. A mixture with the authentic compound, prepared as described in the next section, was not depressed, and the respective infrared and n.m.r. curves were identical.

B. By Quaternization of 3-Dimethylamino-1-propanol.—A sample of 3-dimethylamino-1-propanol (Eastman Practical Grade) was alkylated by methyl *p*-toluenesulfonate in benzene and converted to the perchlorate in acetonitrile. Recrystallization from methanol gave colorless plates of m.p. 163–164.5°.

Anal. Calcd. for $C_6H_{16}ClNO_5$: C, 33.1; H, 7.35. Found: C, 33.5; H, 7.3.

Conversion by aqueous sodium tetraphenylboron to the TPB salt resulted in a colorless solid of m.p. 229° dec.

Anal. Calcd. for $C_{30}H_{36}BNO$: C, 82.4; H, 8.2; N, 3.2. Found: C, 82.5; H, 8.6; N, 3.4.

Rearrangement of N-(2,3-Epoxypropyl)trimethylammonium Salts. A. Using Trimethylamine with the Perchlorate.—A solution of 5 g. of Ib in 37 g. of acetonitrile was treated briefly with trimethylamine. (All materials were dried *via* anhydrous calcium sulfate.) Within a very few minutes, colorless crystals began to separate. After 16 hr. at 25°, the mixture was filtered, producing 4.35 g. (87% yield) of crude IIb, m.p. 166–168° dec.; the infrared spectrum was a close match with that of pure IIb obtained from the reaction product of epichlorohydrin with trimethylamine. Attempted recrystallization from methanol failed to raise the melting point to that of the pure compound, perhaps owing to a persistent impurity which was isolated in 0.2-g. yield by fractional crystallization, m.p. 322° dec. This proved to be 2-hydroxypropane-1,3-bis(trimethylammonium perchlorate); the infrared spectrum was compatible with this structure.

Anal. Calcd. for $C_9H_{24}Cl_2N_2O_9$: C, 28.8; H, 6.4; Cl, 18.9; N, 7.5. Found: C, 29.0; H, 6.1; Cl, 19.1; N, 7.3.

B. Using Trimethylamine with the Chloride.—A suspension of 7.4 g. of Ia (Shell Chemical Co.) in 85 ml. of acetonitrile was treated as in A. The colorless product weighed 6.75 g. (91% yield), m.p. 157–161°; the infrared spectrum was identical with that of the product obtained directly from the reaction of epichlorohydrin and trimethylamine in acetonitrile.

A 3-g. sample of Ia (m.p. 138.5–141°) in 25 ml. of acetonitrile was stirred without added catalyst for 18 hr. at 25°. A nearly quantitative recovery of the unchanged epoxide (m.p. 137–140.5°) was achieved. When such a solution containing 2.5 g. of Ia was heated at reflux for 3 hr., a slight odor of trimethylamine developed and 92% of the original material was recovered in two crops: (1) 1.75 g. of m.p. 115–125°, and (2) 0.55 g. of m.p. 133–138°. The infrared spectra of both fractions were essentially identical with that of Ia, although crop 1 was shown to contain small amounts of IIa and another unknown contaminant.

C. Attempted with Other Catalysts.—Small-scale experiments using triethylamine or triethylenediamine as catalysts in reactions with Ib under the conditions used in A failed to produce any crystalline product, although the infrared spectra of the solutions indicated the presence of small amounts of hydroxy compound. After 3 days, a solution containing 2% triethylenediamine contained a very small crop of crystals.

In another experiment, equivalent amounts (*ca.* 20 mole % based on the epoxide) of trimethylamine and triethylamine (in a little methanol) were added to separate solutions of Ib in acetonitrile. After 41 hr., the trimethylamine-catalyzed reaction had produced a 50% yield of crude IIb, and 28% of unchanged Ib was recovered from the filtrate. The triethylamine-catalyzed reaction failed to produce crystals; removal of the solvent left a crystalline residue which was shown by its infrared spectrum to contain a very small amount of IIb. By recrystallization of the material from methanol, 75% of pure Ib was recovered. It is obvious that triethylenediamine and triethylamine are less effective catalysts for this rearrangement.

N-Dodecyl-N-(3-hydroxy-1-propenyl)dimethylammonium Perchlorate.—A mixture of 21.4 g. (0.1 mole) of N-dodecyldimethylamine and 9.3 g. (0.1 mole) of epichlorohydrin in 75 ml. of acetonitrile was stirred under reflux for 10 hr. (After 15 min., solution was complete.) On cooling, the reaction mixture deposited 15.2 g. (50% yield) of a colorless, hygroscopic solid, which showed a definite CH_2OH peak in the infrared. Reaction with sodium perchlorate in acetonitrile produced the perchlorate which melted at 57–70° (from ethyl acetate). There was no change in melting point on repeated recrystallization. The n.m.r. spectrum closely resembled that of IIb, confirming the structure indicated.

Anal. Calcd. for $C_{17}H_{36}ClNO_5$: C, 55.2; H, 9.7; Cl, 9.6. Found: C, 54.9; H, 9.6; Cl, 9.7.

Reaction of Propylene Oxide in the Presence of Trimethylamine. A. Neat.—Propylene oxide (Eastman Grade, 38 g.) was treated briefly with anhydrous trimethylamine and allowed to stand at 25–30° for 70 hr. The mixture during this period became slightly yellow and the index of refraction ($n^{25}D$) increased from 1.3633 to 1.3642, indicating only a slight degree of reaction.

B. In Acetonitrile.—A solution of 40 g. of propylene oxide and 10 g. of acetonitrile was treated as in A. The solution soon developed an amber color. After 70 hr., the solution was a deep red-brown and the $n^{25}D$ had increased from 1.3586 to 1.3739. Removal of the solvent left 8.2 g. of red oil, $n^{25}D$ 1.4565, which was indicated by the infrared spectrum to be a polyether.

Acknowledgment.—The author gratefully acknowledges the contributions of Mr. C. M. Combs and Dr. J. K. O'Loane with respect to n.m.r. spectra and their interpretation, and of Miss Thelma Davis for similar help with infrared spectra.

The Condensation Reaction between Sulfamide and Monoketones

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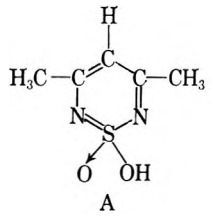
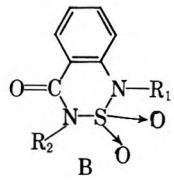
Sulfamide and various monoketones condense in the presence of hydrogen chloride to yield substituted cyclic thiadiazine 1,1-dioxides. Isobutyraldehyde undergoes a comparable reaction. Infrared and proton nuclear magnetic resonance data have been used to establish the existence of the ring system and to suggest the natures of the various substituted groups. The reaction product obtained from 2-butanone has been separated into two geometrical isomers.

The direct reactions between sulfamide and carbonyl groups have received comparatively little attention. Prior to 1940,[1] only the benzal,[2] methylol,[3] and dixanthyl[4] derivatives had been described. More recently, Paquin[5] pointed out analogies between the reaction of formaldehyde with sulfamide and with urea, and Degering and Wilson[6] obtained a cyclic product (A) from the condensation of sulfamide with 2,4-pentanedione. A number of closely related compounds (B) have been obtained from sulfamyl chloride.[7] Other cyclic structures have been obtained from reactions involving crotonaldehyde,[8] malonic acid dichloride,[9] and anthraquinone.[9] The ring system formed with crotonaldehyde probably differs from those described herein (C) only in having hydrogen atoms at the R_2, R_3, R_4, and R_5 positions.



A



B

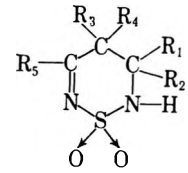
Interestingly enough, reactions between sulfamide and monoketones have not been reported, although the formation of cyclic structures as a consequence of the formally analogous reactions of urea with ketones[10] or guanidine with mesityl oxide[11] suggests that they are reasonable. During a study of the interactions of sulfamide with metal ions, a reaction involving copper (II) chloride in acetone was found to yield a white product. This substance proved to be a condensation product of an acid-catalyzed reaction between sulfamide and acetone. Subsequent study has shown that hydrogen chloride is a more effective catalyst both for this reaction and for comparable reactions with 2-butanone, 2-pentanone, 3-pentanone, and acetophenone. On the other hand, self-condensation in the presence of hydrogen chloride prevented similar reactions with 3-methyl-2-butanone and 4-methyl-2-pentanone. Isobutyraldehyde, however, also gave a condensation product.

(1) L. F. Audrieth, M. Sveda, H. H. Sisler, and M. J. Butler, *Chem. Rev.*, **26**, 49 (1940).
(2) W. Traube and E. Reubke, *Ber.*, **56**, 1656 (1923).
(3) F. C. Wood and A. E. Battye, *J. Soc. Chem. Ind.*, **52**, 346T (1933).
(4) F. C. Wood, *Nature*, **136**, 837 (1935).
(5) A. M. Paquin, *Angew. Chem.*, **60A**, 316 (1948).
(6) E. F. Degering and J. E. Wilson, *J. Org. Chem.*, **17**, 339 (1952).
(7) E. Cohen and B. Klarberg, *J. Am. Chem. Soc.*, **84**, 1994 (1962).
(8) A. M. Paquin, *Kunstoffe*, **37**, 165 (1947).
(9) I. G. Farbenindustrie, A.-G. (G. Kränzlein and K. Renn, investors), German Patent 673,389 (March 24, 1939); *Chem. Abstr.*, **33**, 4436 (1939).
(10) K. Folkers and T. B. Johnson, *J. Am. Chem. Soc.*, **55**, 3361 (1933).
(11) W. Traube and R. Schwarz, *Ber.*, **32**, 3163 (1899).

The compounds obtained are listed in Table I, together with information on their syntheses and properties. All are white crystalline solids that dissolve readily in acetone, pyridine, ethyl acetate, and acetonitrile; they dissolve less readily in chloroform, with difficulty in water, and not at all in petroleum ether. They are best recrystallized from a mixture of ethyl acetate and petroleum ether (b.p. 80–110°).

Unlike the condensation product from sulfamide and 2,4-pentanedione,[6] which is a strong acid in aqueous solution, these compounds (in *ca.* 2×10^{-2} *M* solution) are essentially neutral (pK_a *ca.* 9.8 for compound I, Table I). In alkaline solution, each of these compounds reduces the diamminesilver(I) ion to the free metal.

It is not unreasonable to assume, in the light of experimental observation that each condensation requires 2 moles of ketone to 1 mole of sulfamide, that the products have structure C. Such a structure would



C, R = H, alkyl, or aryl

would permit, *via* geometrical isomerism, the existence of two 2-butanone derivatives as indicated in Table I, but its validity could be better established from physical data.

The infrared spectra (600–4000 cm.$^{-1}$) of all the compounds are closely similar (Table II), suggesting that the same structural type is characteristic of all of them. The following features are of significance: (1) the N–H stretching frequency at *ca.* 3250 cm.$^{-1}$; (2) the C–H stretching frequency at *ca.* 2900–3000 cm.$^{-1}$; (3) the C=N stretching frequency at *ca.* 1620 cm.$^{-1}$ (although this band appears at a slightly lower frequency than is generally found, this may be a consequence of the presence of this bond in a cyclic structure); (4) the S=O stretching frequencies at 1310–1330 and 1150–1180 cm.$^{-1}$; (5) numerous additional absorptions in the 700–1500-cm.$^{-1}$ region that appear to reflect ring deformation and skeletal vibrations. Each pattern is characteristic, but all are relatively similar. These data indicate, of course, the presence of certain groupings, but are not completely structurally definitive.

Proton nuclear magnetic resonance spectra of 10% solutions in deuteriochloroform are given in Fig. 1. The letter designations refer to the interpretations summarized in structural formulas I–VII. For compound I, the ratio of areas under the resonance peaks is

TABLE I

PROPERTIES AND ANALYSES OF CONDENSATION PRODUCTS

Compound[a]	Empirical formula	Carbonyl compound used	Yield, %	M.p.,[b] °C.	Molecular weight[c] Calcd.	Found	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found	Sulfur Calcd.	Found
I	$C_8H_{12}N_2O_2S$	Acetone	66.5	142	176	180	40.90	41.29	6.87	6.89	15.90	15.60	18.17	17.94
II	$C_{16}H_{16}N_2O_2S$	Acetophenone	20.8	137	300	312	64.00	63.51	5.33	5.33	9.33	9.55		
III	$C_8H_{16}N_2O_2S$	2-Butanone	40.7	130	204	197	47.06	47.07	7.84	7.74	13.72	13.43	15.69	16.10
IV	$C_8H_{16}N_2O_2S$	2-Butanone	1.6	158	204	204	47.06	47.07	7.84	7.88	13.72	13.34	15.69	15.80
V	$C_{10}H_{20}N_2O_2S$	3-Pentanone	24.8	117	232	232	51.72	52.02	8.62	8.71	12.07	11.72		
VI	$C_{10}H_{20}N_2O_2S$	2-Pentanone	33.1	78	232	238	51.72	51.88	8.62	8.58	12.07	11.80		
VII	$C_8H_{16}N_2O_2S$	Isobutyraldehyde	42.8	193	204		47.06	47.37	7.84	7.94	13.72	13.17	15.69	15.45

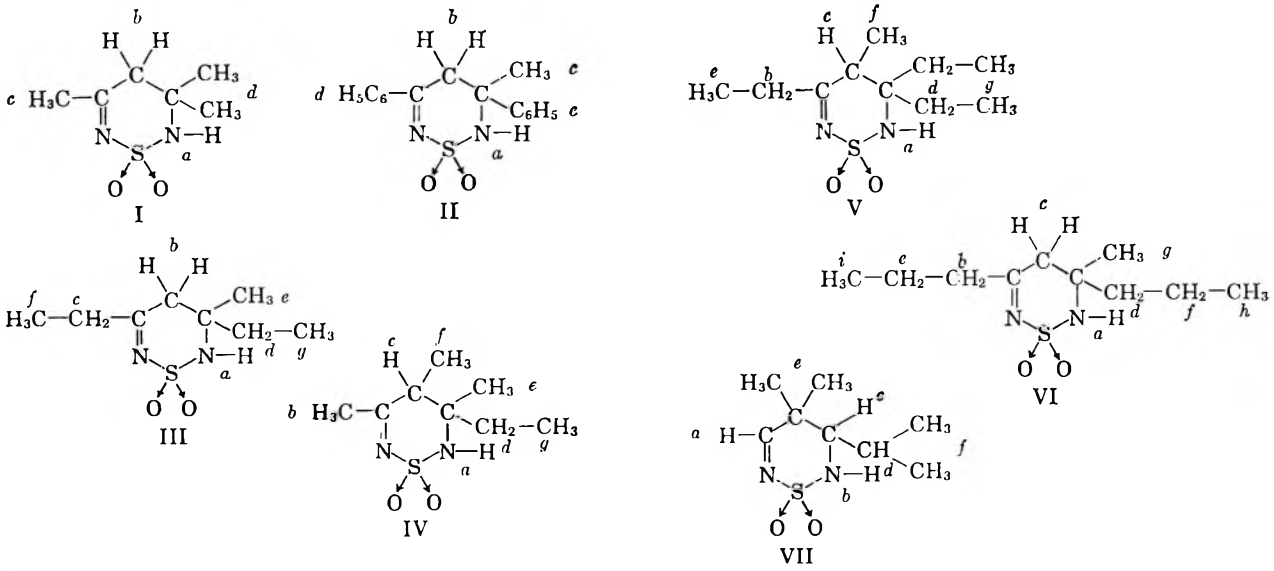
[a] Designation uniform throughout. [b] Uncorrected. [c] In acetone.

TABLE II

INFRARED SPECTRA OF CONDENSATION PRODUCTS

Compound	Frequency, cm.$^{-1}$ N–H	C–H	C=N	S=O	Others[a]
I	3200	2950	1628	1333	1465, 1427, 1412, 1370
				1175, 1163	1270, 1210
					988, 957, 915, 880, 814, 788, 710
II	3250	3080	1605	1330	1450, 1423, 1410, 1380, 1360
		3000	1598	1170, 1155	1258
			1568		1095, 1025, 950, 910, 850, 798, 760, 695
III	3260	2960	1620	1320	1460, 1412, 1385, 1372
				1170	1220, 1197
					1090, 1078, 990, 950, 900, 818, 795, 763, 675
IV	3260	2960	1620	1320	1460, 1412, 1385, 1370
				1170	1220, 1195
					1090, 1080, 990, 948, 895, 820, 798, 762, 675
V	3280	2990	1620	1325	1462, 1418, 1360
				1150	1215, 1180
					1098, 1090, 980, 960, 890, 805, 787, 748, 667
VI	3210	2960	1623	1322	1460, 1425, 1405, 1388, 1360
		2880		1165	1260
					1090, 1038, 985, 965, 935, 890, 795, 748, 715
VII	3280	2980	1615	1350	1470, 1430, 1395, 1380
				1180	1305, 1290, 1135
					1035, 1015, 1000, 950, 933, 905, 795, 740,695

[a] Major peaks only.



$a:b:c:d$ = 1:2:3:6. The assigned structure (I) is thus a reasonable one, insofar as the types of protons present are concerned. Correspondingly, the ratio of the areas for compound II is $a:b:c$ = 1:2:3, in agreement with the assignments indicated for the nonphenyl protons in structure II. In addition, two broad peaks appear in the *ca.* 1.8–2.9-p.p.m. region. These represent, reasonably, proton resonances associated with the two phenyl groups (*d* and *e*). Inasmuch as resonance *a* (compounds I–VI inclusive) disappears both when a pyridine solution is used and when an acetonitrile solution of a compound is treated with a drop of deuterium oxide, the validity of associating it with an N–H proton is supported.

Assignment of structures III and IV to the isomeric products resulting from reaction with 2-butanone has been effected in the same general fashion. Structures

V and VI for the 3- and 2-pentanone products, respectively, are again reasonable interpretations of the nuclear magnetic resonance spectra.

The spectrum of compound VII differs significantly from the other spectra, particularly in the presence of a new peak at *ca.* 2.38 p.p.m. This peak is believed to indicate the presence of *a*-type protons (structure VII). That peak *b* is a consequence of the presence of N–H protons is suggested by its disappearance, as a consequence of H–D exchange, upon addition of deuterium oxide. The area under peak *f* is less than the theoretical value, and peak *e* is split into two components. Ring or side-chain interactions may be the cause of these departures. Hydrolytic decomposition of the compound in aqueous or ethanolic solution containing hydrogen chloride yielded ammonium sulfate (40% yield, determined as barium sulfate) and mesityl oxide (20% yield, determined as 1-(4-nitro-phenyl)-3,5,5-trimethylpyrazoline[12]).

Compound I was also synthesized, in almost the same yields (60–65%) as from the acetone–sulfamide reaction, by the hydrogen chloride catalyzed reaction of sulfamide with either mesityl oxide or diacetone alcohol.

Experimental

3,3,5-Trimethyl-1,2,6,2H-thiadiazine 1,1-Dioxide.—Five grams (0.052 mole) of sulfamide[13] and 30 ml. (*ca.* 0.41 mole)[14] of acetone were mixed in a standard-taper, 100-ml., round-bottomed flask and the mixture was treated with a stream of dry hydrogen chloride for 5 min. The mixture was then heated under a reflux condenser for 6 hr. at 70°.[15] The remaining acetone was removed *in vacuo* at 50–60°, and the residue was treated with chloroform. After filtration to remove unchanged sulfamide, the chloroform was removed *in vacuo* at 50–60°, and the product was recrystallized two times from a 1:1 mixture of acetone and petroleum ether (b.p. 80–110°). It was dried at room temperature under reduced pressure.

Other products were obtained similarly with the ketone or isobutyraldehyde in at least fourfold excess.[16] Compounds III and IV were separated from each other by crystallization from ethyl acetate, compound IV being much less soluble at lower temperatures. Compounds III–VII were all recrystallized conveniently from ethyl acetate–petroleum ether (b.p. 80–110°) mixtures. These compounds were dried *in vacuo* at room temperature.

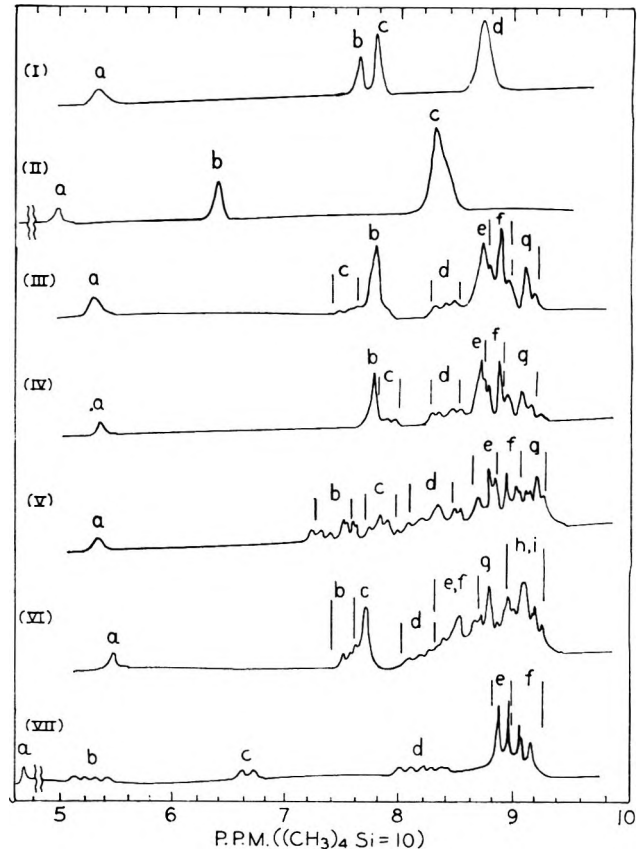


Fig. 1.—Proton nuclear magnetic resonance spectra.

Spectra.—Infrared spectra were obtained by the potassium bromide disk procedure with a Perkin-Elmer Model 21 instrument. Nuclear magnetic resonance spectra were obtained with a Varian Model A-60 instrument.

Acknowledgment.—Support received for this investigation under Contract DA-31-124-ARO(D)-35 is gratefully acknowledged, as are also useful discussions by Dr. P. Nannelli and Dr. T. Fujii.

(12) K. von Auwers and A. Kreuder, *Ber.*, **58**, 1974 (1925).

(13) Obtained from Allied Chemical Corp., General Chemical Division, Morristown, N. J. and had m.p. 93°, after recrystallization from ethanol.

(14) A substantial excess of acetone is essential for a good yield.

(15) Higher temperatures, prolonged heating, or insufficient acetone yields a black, oily by-product that is removed only with difficulty by means of activated charcoal. It is better to stop the reaction before the system becomes black and turbid.

(16) Up to one-half of the ketone may be substituted by ethanol without affecting the yield.

Alkylation of Lithium Enolates of 2-Methylcyclohexanone

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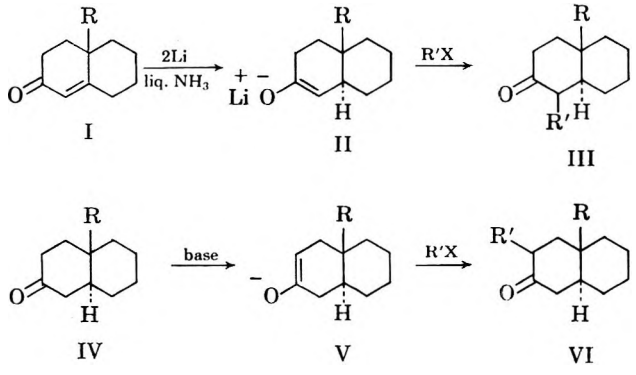
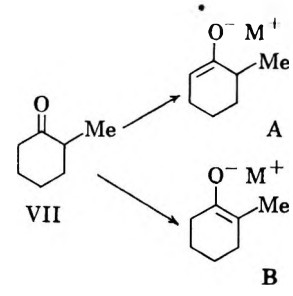
The products of methylation of lithium enolates of 2-methylcyclohexanone (VII) have been investigated. Reduction of 6-chloromercuri-2-methylcyclohexanone with lithium in liquid ammonia and methylation of the Δ^6-enolate product with methyl iodide in 1,2-dimethoxyethane gave 2,6-dimethylcyclohexanone (VIII) as by far the major monoalkylation product. VII, when treated with trityllithium in liquid ammonia–ether under kinetic conditions followed by methylation with methyl iodide in 1,2-dimethoxyethane and in tetrahydrofuran, gave mainly VIII *via* the less substituted lithium enolate. Under reaction conditions where equilibration of lithium enolates of VII was intentionally effected or unavoidable prior to the addition of the alkylating agent, 2,2-dimethylcyclohexanone (IX) derived from the more substituted enolate was found to be the major monomethylation product. The behavior of kinetic *vs.* equilibrium mixtures of lithium enolates of VII is compared, and the alkylations of metal enolates of VII with regard to the nature of the cation are considered.

It has recently been shown by Stork, Rosen, and Goldman[2] that the lithium–ammonia reduction of α,β-unsaturated ketones of the type I leads to the lithium enolate II which can be alkylated in liquid ammonia to produce *trans*-1-alkyl 2-decalones, *e.g.*, III. The enolate II is the less stable one of the *trans*-2-decalone system (IV) and direct alkylation of IV in the presence of strong base leads mainly to 3-alkyl substituted products (VI)[3] *via* the more stable enolate V. The success of the reductive alkylation of I to produce III depends on the fact that in liquid ammonia C-alkylation of the lithium enolate II is more rapid than its equilibration to the more stable enolate V by proton exchange with initially alkylated neutral ketone. From this result it seemed likely that alkylation could be directed to a specific α-carbon of an unsymmetrical ketone such as 2-methylcyclohexanone (VII) through

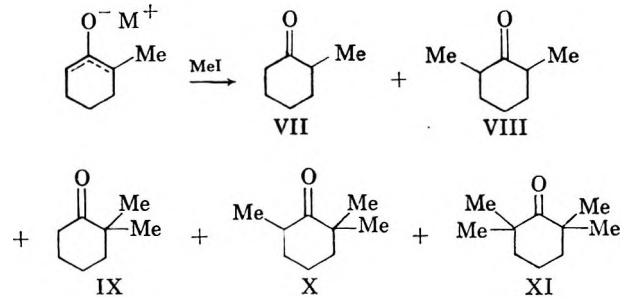


the corresponding lithium enolate.[4] This objective has been achieved in part by (1) generation of the Δ^6-enolate of VII (A, M = Li) by reduction of 6-chloromercuri-2-methylcyclohexanone (XIII) with lithium in liquid ammonia, and (2) utilization of lithium enolates of VII formed kinetically with trityllithium in liquid ammonia–ether.

An unsymmetrical alicyclic ketone like VII can lose a proton to give either of two possible metal enolates, *i.e.*, A or B; it is well known[5] that, in the alkylation of



such ketones with alkyl halides in the presence of strong base, mixtures of products are obtained and that the monoalkylation product derived from reaction at the more highly substituted carbon atom predominates. The ketone is usually converted to the enolate anion with strong base and alkylated in a suitable solvent with excess alkyl halide. The products of alkylation of VII with methyl iodide under these usual preparative conditions have been reinvestigated. A typical run which involved alkylation of the potassium enolate of VII with excess methyl iodide in 1,2-dimethoxyethane led as expected to a mixture of all possible products: unchanged VII, 2,6-dimethylcyclohexanone (VIII), 2,2-dimethylcyclohexanone (IX), 2,2,6-trimethylcyclohexanone (X), and 2,2,6,6-tetramethylcyclohexanone (XI). IX was the major product. The results of analysis of the recovered mixture of ketone by v.p.c. and n.m.r. as described in the Experimental are shown in Table I, item 1. Very similar results have recently been obtained by House and Kramer[6]; they have carried out a comprehensive study of the factors involved in the alkylation of unsymmetrical acyclic and alicyclic ketones, including VII, and conclude that the most important factor in product control is the equilibrium con-



(1) (a) National Institutes of Health Postdoctoral Fellow, 1961–1962; (b) Department of Chemistry, Georgia Institute of Technology, Atlanta, Ga. 30332.

(2) G. Stork, P. Rosen, and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961).

(3) Y. Mazur and F. Sondheimer, *ibid.*, **80**, 5220 (1958).

(4) This idea and some of the results reported herein have been discussed by G. Stork, Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 23M.

(5) *Cf.*, *inter alia*, H. M. E. Cardwell, *J. Chem. Soc.*, 2442 (1951).

(6) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963). The author wishes to thank Professor House for making a copy of this manuscript available in advance of publication.

TABLE I

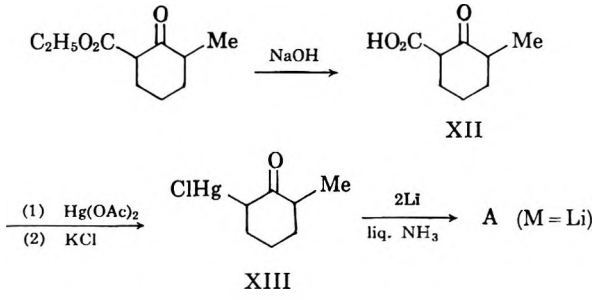
ALKYLATION OF METAL ENOLATES OF 2-METHYLCYCLOHEXANONE (VII) WITH METHYL IODIDE

Item	Method of generation of enolates	Solvent for alkylation[a]	% recovered ketones VII	VIII[b]	IX[b]	X	XI
1	KNH_2 in liq. ammonia	DME[c]	25	~10	41	24	1
2	Reduction of 6-chloromercuri-2-methylcyclohexanone (XIII) with Li in liq. ammonia	DME	16	72	<10	12	
3	$Ph_3C^-Li^+$ in liq. ammonia–ether (kinetic conditions)[d]	DME	11	55	27	7	
4	$Ph_3C^-Li^+$ in liq. ammonia–ether (kinetic conditions)	THF[e]	35	47	<10	13	
5	$Ph_3C^-Li^+$ in liq. ammonia–ether (equilibrium conditions)[f]	DME	14	13	73		

[a] After enolate formation was complete, the solvent system employed for that purpose was removed by distillation and replaced by the indicated solvent prior to methylation. [b] These values are considered to be accurate within 10% (see Experimental). [c] 1,2-Dimethoxyethane. [d] Excess trityllithium present at the end of the addition of VII. [e] Tetrahydrofuran. [f] Slight excess of VII to trityllithium added.

centration among the possible enolate anions.[7] Thus in the alkylation of potassium as well as sodium enolates[8] of VII, regardless of the kinetic concentrations of enolates A and B, equilibration among the anions by proton transfer reactions with initially produced alkylated ketone is faster than the alkylation reaction, and roughly the same product composition is always observed.

To demonstrate that alkylation of a specific lithium enolate of VII would occur faster than equilibration to the equilibrium mixture of A and B, the course of alkylation of the enolate A (M = Li) generated by indirect means has been investigated. The report by Nesmeyanov, *et al.*,[9] that chloromercuriacetaldehyde can be reduced to the lithium salt with lithium in liquid ammonia prompted investigation of a similar reaction of XIII for the purpose of generating A (M = Li). Using 6-carbethoxy-2-methylcyclohexanone as a starting material, XIII was prepared essentially according to the procedure of Nesmeyanov, *et al.*,[10] for the preparation of 2-chloromercuri-2-methylcyclohexanone. The β-keto ester was converted to 6-carboxy-2-methylcyclohexanone (XII)[11] on shaking with dilute sodium hydroxide at room temperature followed by acidification, and XIII was prepared by treating XII with aqueous



mercuric acetate solution, heating to effect decarboxylation of the mercuric salt, and addition of potassium chloride solution. Compound XIII precipitated as a gummy white semisolid and resisted further purification by recrystallization.[12] Thus the crude compound was dissolved in 1,2-dimethoxyethane and added to 2 equiv. of lithium in liquid ammonia. After the ammonia had been removed and additional 1,2-dimethoxyethane added, reaction with methyl iodide led to a mixture of ketones having the compositions listed in Table I, item 2. The 2,6-dimethylcyclohexanone(VIII) which amounted to 72% of the product was obtained as an approximately 6:4 mixture of *cis* and *trans* isomers. However, for purposes of analysis, the entire reaction mixture was treated with 10% hydrochloric acid to convert the 2,6-dimethylcyclohexanones to the equilibrium mixture of which the *cis* isomer constitutes approximately 92%.[13] This result indicated that the less substituted lithium enolate of VII, *i.e.*, A (M = Li), was generated by the reduction of XIII and that indeed this enolate was alkylated in 1,2-dimethoxyethane with methyl iodide prior to significant equilibration among the enolates A and B. However, in view of the small amount of trimethyl ketone X and of recovered VII observed, the possibility that some proton exchange did occur before alkylation was complete cannot be excluded.

With the achievement of the objection of directing the alkylation of VII to the less substituted α-position *via* indirect formation of the enolate A (M = Li), the products of alkylation of lithium enolates of VII produced with strong base were investigated next. When methylations of VII were carried out using lithium amide in 1,2-dimethoxyethane and lithium *t*-butoxide in dimethyl sulfoxide, 2,2-dimethylcyclohexanone IX was found to account for 84% and 75%, respectively, of the monoalkylation products. These results compare closely with those obtained on methylation of potassium and sodium enolates of VII. In the former case, the covalent nature and low solubility of the lithium amide probably do not allow irreversible generation of the enolate, while in the latter case the result can be explained if enolate anion formation is reversible, or if in the solvent dimethyl sulfoxide proton transfer leading to equilibration is faster than C-alkylation.[2]

In search of a base that would allow for irreversible enolate formation, the products of methylation of the enolate of VII produced with trityllithium were next in-

(7) The work of House and Kramer (ref. 6) has proved incorrect the assumption by Cardwell (ref. 5) that the more highly substituted enolate of an unsymmetrical ketone is the more stable. They showed that in the case of acyclic ketones the less substituted enolate is definitely favored at equilibrium, and that in alicyclic ketones the more substituted enolate is only slightly favored. In 1,2-dimethoxyethane, the equilibrium concentrations of the potassium enolates of VII were found to be 48 ± 7% A and 52 ± 7% B.

(8) The composition of the mixture of ketones obtained by alkylation with methyl iodide of the sodium enolate of VII prepared from sodium hydride in 1,2-dimethoxyethane was very close to that obtained for the potassium enolate. Similar results have been reported for alkylations of the sodium enolate of VII in ether [see W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, **28**, 2184 (1963)].

(9) N. Nesmeyanov, I. F. Lutsenko, and R. M. Khomutov, *Dokl. Akad. Nauk SSSR*, **120**, 1043 (1958); *Chem. Abstr.*, **52**, 19,315 (1958).

(10) A. N. Nesmeyanov, I. F. Lutsenko, and S. N. Anachenko, *Uch. Zap. Mosk. Gos. Univ.*, **No. 132**, 136 (1950); *Chem. Abstr.*, **49**, 3836 (1955).

(11) E. J. Corey, T. H. Topie, and W. A. Wozniek, *J. Am. Chem. Soc.*, **55**, 5415 (1955).

(12) On heating in organic solvents XIII underwent extensive decomposition with the formation of mercurous salts. Similar behavior has been observed for chloromercuricyclohexanone [see J. H. Robson and G. F. Wright, *Can. J. Chem.*, **38**, 1 (1960)].

(13) B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962).

vestigated. The method described by Hauser, *et al.*,[14] was employed for the preparation of this base. This involved addition of triphenylmethane in ether to lithium amide in liquid ammonia. Since reversion of the reaction to the hydrocarbon and lithium amide occurs when the liquid ammonia is removed, the enolates of VII were formed by addition of the ketone to the trityl lithium in the liquid ammonia–ether solvent. Reactions were carried out under kinetic and equilibrium conditions of enolate formation. Under kinetic conditions sufficient base was employed so that the red color of the tritylllithium remained at the end of the dropwise addition of the ketone in ether. Under these conditions, if enolate formation is irreversible, the concentrations of the enolates A and B produced would depend on the relative rates of proton removal from C-6 and C-2, respectively. Under equilibrium conditions a slight excess of the ketone to tritylllithium was added, as evidenced by the discharge of the red color of the base. Here the added excess neutral ketone should allow complete equilibration among the enolates A and B *via* proton transfer reactions. The results of methylations in 1,2-dimethoxyethane and tetrahydrofuran under kinetic conditions of enolate formation are shown in Table I, items 3 and 4, while item 5 shows the results obtained under equilibrium conditions. In both cases where the enolate was formed kinetically 2,6-dimethylcyclohexanone (VIII) was the major monoalkylation product, whereas under equilibrium conditions the 2,2-isomer IX predominated. As has been pointed out previously, alkylation of potassium and sodium enolates of VII yields mainly IX; but, by making use of the fact that under the proper conditions C-alkylation of a kinetic mixture of lithium enolates of this ketone occurs faster than proton exchange to the equilibrium mixture of enolates, it appears that this trend can be reversed in favor of VIII.

In both cases where methylations of kinetic mixtures of lithium enolates were carried out, recovered VII and the dialkylation product X were obtained along with the monoalkylation products. This result indicates that some proton transfer did occur during alkylation. Thus, attempts to relate the distribution of monoalkylation products (VIII and IX derived from VII) to the kinetic concentrations of the enolates A and B are of course questionable. However, if the structurally isomeric enolates react with methyl iodide at similar rates,[6] it appears likely that the less substituted enolate of VII (A, M = Li) is definitely preferred kinetically under the reaction conditions employed for enolate formation. Rosen[15] has shown that the sodium enolate of VII prepared kinetically with sodium amide in liquid ammonia yields 6-carbomethoxy-2-methylcyclohexanone on reaction with solid carbon dioxide in 1,2-dimethoxyethane followed by acidification and treatment with ethereal diazomethane. The carbonation reaction is rapid and unlike methylation presumably occurs without equilibration among the sodium enolates.[5] Since 6-carbomethoxy-2-methylcyclohexanone is derived from the enolate A (M = Na), it appears likely that the less substituted enolate of VII is preferred kinetically when sodium amide in liquid ammonia, as well as tritylllithium in liquid ammonia–ether, is employed for enolate formation.

House and Kramer[6] have shown that the nature of the cation has considerable influence on the equilibrium concentrations of structurally isomeric enolates, and that in certain acylic ketones the less substituted lithium enolate is favored at equilibrium as compared with cases where sodium and potassium are used as the cations. In these cases methylation of the equilibrium mixture of lithium enolates was found to yield mainly monoalkylation products derived from the less substituted enolate anion. However, the data in Table I, item 5, do not indicate similar behavior for VII, since IX, derived from the more substituted enolate B, was obtained as the major monoalkylation product when equilibration of the lithium enolates was intentionally effected prior to methylation. The 2,2-isomer IX also was found to predominate when equilibration of enolates was unavoidable, as when lithium amide and lithium *t*-butoxide were used as the bases for enolate formation.

Studies are now in progress to determine the kinetic concentrations of enolates of unsymmetrical ketones produced under various conditions and to make further use of the reduction of α-chloromercuri ketones for generating specific metal enolates of unsymmetrical ketones.

Experimental[16]

Materials.—All ether solvents were purified by reflux over lithium aluminum hydride and distillation. The dimethyl sulfoxide (DMSO) was distilled from calcium hydride at reduced pressure. Anhydrous liquid ammonia was obtained by distillation from sodium directly into the reaction vessel.

The sample of 2-methylcyclohexanone (VII) employed for the work was prepared by oxidation of 2-methylcyclohexanol and after fractionation showed a boiling point of 165.0–165.2°. It was shown by v.p.c. to be of greater than 99% purity. The n.m.r. spectrum of VII showed broad absorption in the region of τ 7.5–8.8 (9H) and a doublet (J = 6 c.p.s.) centered at 9.07 (3H, CH_3–CH<).

Authentic samples[17] of the equilibrium mixture of *cis*- and *trans*-2,6-dimethylcyclohexanone (VIII) and of 2,2-dimethylcyclohexanone (IX) showed the following n.m.r. absorptions: VIII showed broad absorption at τ 7.5–8.8, an intense doublet (J = 6 c.p.s.) at 9.07 (CH_3–CH<, *cis* isomer), and very weak absorption at 8.92 corresponding to one peak of a doublet (J = 6 c.p.s.) centered at 8.97 (CH_3–CH<, *trans* isomer); the ratio of the total methyl to methylene and methinyl absorption was 6:8. The unsymmetrical isomer IX showed broad absorption at τ 7.5–7.9 (2H, CH_2–CO) and 8.0–8.5 (6H) and a singlet at 8.95 (6H).

Sufficient quantities of the trimethylated ketone X and the tetramethylated ketone XI for collection by v.p.c. were obtained by methylation of the sodium enolate of VII in DMSO. To a solution of sodium methyl sulfinyl carbanion[18] [prepared from 1.22 g. (0.055 mole) of sodium hydride and 80 ml. of DMSO] in DMSO was added dropwise 5.61 g. (0.05 mole) of VII in 20 ml. of DMSO over 30 min. at room temperature. The solution was stirred for 1 hr. and 8.5 g. (0.06 mole) of methyl iodide was added. After 2 hr. of stirring at room temperature, the reaction mixture was poured into ice–water, the mixture of methylated ketones was extracted with ether, and the ethereal solution was dried over anhydrous sodium sulfate. After removal of the solvent, v.p.c. analysis (see below) showed that the mixture was composed of

(14) C. R. Hauser, D. S. Hoffenberg, W. H. Puterbaugh, and F. C. Frostick, *J. Org. Chem.*, **20**, 1531 (1955).

(15) P. Rosen, Ph.D. dissertation, Columbia University, 1962.

(16) Melting points were determined by the open capillary method and are corrected. Boiling points are uncorrected. The v.p.c. separations were effected at 140° using a 10 ft. × 0.25 in. column containing 20% silicone SE-30 on Chromosorb-W. N.m.r. spectra were obtained in carbon tetrachloride solution with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard.

(17) Kindly supplied by Dr. S. Dowd and Dr. S. D. Darling.

(18) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).

VII (14%), the dimethylcyclohexanones VIII and IX (40%), the trimethyl ketone X (33%), and the tetramethyl ketone XI (12%). Collected samples of X and XI showed the following n.m.r. absorptions: X gave broad absorption at τ 7.3–7.7 (1H) and at 8.0–8.5 (6H) and peaks at 8.90, 9.00, and 9.12 (9H) in the ratio 3:4.5:1.5; these three peaks correspond to the two methyl groups at C-2 (τ 8.90 and 9.00) and to one peak (9.12) of a doublet (J = 6 c.p.s.) centered at 9.07. The tetramethyl ketone XI showed broad absorption at τ 8.3–8.5 (6H) and a singlet at 8.97 (12H).

Analysis of Products.—After the usual work-up of the reaction mixture from the methylation of the metal enolates of VII, the percentage compositions of the products listed in Table I were determined by a combination of v.p.c. and n.m.r. spectroscopy. Using the silicone gas chromatography column, the methylated cyclohexanones were eluted as follows: first peak, unchanged 2-methylcyclohexanone (VII); second peak, the equilibrium mixture of dimethylcyclohexanones VIII and IX[19]; third peak, 2,2,6-trimethylcyclohexanone (X); and the fourth peak, 2,2,6,6-tetramethylcyclohexanone (XI). Thus by determining the relative areas (by multiplying the peak width at one-half height by the height) of the four peaks, the per cent of VII, the mixture of VIII and IX, X, and XI were obtained. The mixture of VIII and IX then was collected by v.p.c. and its composition was determined by integration of the methyl region of the n.m.r. spectrum at a 50-c.p.s. sweep width. Although slight overlap existed between the singlet at τ 8.95 and the low-field peak of the doublet at τ 9.07, a determination of the compositions of known mixtures of VIII and IX showed this method to be accurate within 10%.

Alkylation of the Potassium Enolate VII with Methyl Iodide in 1,2-Dimethoxyethane.—To 100 ml. of stirred anhydrous liquid ammonia containing a trace of anhydrous ferric chloride was added 0.98 g. (0.025 g.-atom) of freshly cut potassium metal. The blue color produced on addition of the metal soon disappeared, indicating the formation of potassium amide. After the solution had been stirred for 15 min., 2.24 g. (0.020 mole) of VII in 40 ml. of 1,2-dimethoxyethane was added dropwise over a period of 45 min. When the addition was complete, stirring was continued for 30 min. The liquid ammonia then was removed by warming the reaction vessel with warm water and 40 ml. of 1,2-dimethoxyethane was added to replace it. The 1,2-dimethoxyethane suspension of the enolate was heated to reflux, cooled to room temperature, and 28.4 g. (0.2 mole) of methyl iodide was added in one portion. After 2 hr. at reflux, the reaction mixture was cooled, and poured into water; the aqueous mixture was extracted with ether. After the organic layer had been washed with water and dried, and the solvent removed under pressure, analysis of the mixture as described previously showed VII (25%), VIII (~10%), IX (41%), X (24%), and XI (1%).

Methylation of Lithium Enolates of VII. A. From Reduction of 6-Chloromercuri-2-methylcyclohexanone with Lithium in Liquid Ammonia.—6-Carbethoxy-2-methylcyclohexanone,[20] 10.1 g. (0.055 mole), was shaken for 16 hr. at room temperature with 3.32 g. (0.083 mole) of sodium hydroxide in 30 ml. of water. The basic solution then was extracted with 50 ml. of ether, acidified to pH 3 with 5% hydrochloric acid, and again extracted with three 50-ml. portions of ether. The ethereal solution was dried over sodium sulfate and, on removal of the solvent at reduced pressure at room temperature, 6.40 g. (75%) of the acid XII, m.p. 88–91° dec. (lit.[11] m.p. 90–91° dec.), was obtained.

To 13.4 g. (0.042 mole) of mercuric acetate in 35 ml. of water was added 6.24 g. (0.040 mole) of XII in 10 ml. of 95% ethanol, and the mixture was warmed at 75° to effect decarboxylation of the mercuric salt of the acid. The hot solution then was filtered, cooled to room temperature, and treated with 2.98 g. of potassium chloride. A white precipitate of the chloromercuri compound XIII immediately formed and the mixture then was allowed to stand in an ice bath overnight. The product then was extracted with chloroform and the chloroform solution was dried over sodium sulfate. On removal of the chloroform under reduced pressure, 6.95 g. of XIII which could not be purified by recrystallization was obtained. Crude XIII, 5.63 g. (0.017 mole), then was dissolved in 40 ml. of 1,2-dimethoxyethane and added dropwise[21] to 0.25 g. (0.036 g.-atom) of lithium in 60 ml. of anhydrous liquid ammonia. As the last few drops were added, the blue color of the lithium in ammonia faded but was easily restored by the addition of a small piece of lithium metal. The mixture then was stirred for 30 min. and the ammonia was removed and replaced by 60 ml. of 1,2-dimethoxyethane. The reaction mixture then was brought to reflux, cooled to room temperature, and treated with 5.68 g. (0.04 mole) of methyl iodide and again brought to reflux for 1 hr. The precipitated lithium iodide and elemental mercury then were removed by filtration and the filtrate was poured into cold water. Work-up of the reaction mixture in the usual way with ether yielded 1.97 g. of a mixture of ketones. Preliminary v.p.c. of this mixture indicated that it consisted mainly of *cis*- and *trans*-2,6-dimethylcyclohexanone in a ratio of *ca.* 6:4. The mixture then was refluxed with 10% hydrochloric acid overnight and analyzed as previously described. The products were VII (16%), VIII (72%), and X (12%). Less than 10% of 2,2-dimethylcyclohexanone (IX) was present by n.m.r.

B. From Lithium Amide in 1,2-Dimethoxyethane.—To a slurry prepared from 0.58 g. (0.025 mole) of lithium amide in 50 ml. of 1,2-dimethoxyethane which had been brought to reflux under nitrogen was added 2.24 g. (0.020 mole) of VII, and the reaction mixture was refluxed overnight. The mixture then was cooled to room temperature, 5.68 g. (0.04 mole) of methyl iodide was added, and reflux resumed for 2 hr. After work-up of the mixture of products in the usual way with ether, removal of the solvent gave 1.5 g. of a mixture of methylated ketones which was found to contain VII (24%), VIII (10%), IX (55%), and X (11%). No tetramethylcyclohexanone XI was observed.

C. From Lithium *t*-Butoxide in DMSO.—A mixture composed of 0.184 g. (0.023 mole) of lithium hydride and 1.70 g. (0.023 mole) of *t*-butyl alcohol in 50 ml. of DMSO was warmed at 70° under nitrogen until homogeneous (14 hr.). The solution then was cooled to room temperature and 2.24 g. (0.020 mole) of VII in 10 ml. of DMSO was added dropwise with stirring over 30 min. When the addition was complete, the mixture was stirred for 2 hr. at room temperature, 3.6 g. (0.025 mole) of methyl iodide then was added, and the mixture was stirred for 1 hr. longer. The mixture was poured into ice–water and extracted with ether; the ethereal solution was dried over sodium sulfate. Removal of the solvent under reduced pressure yielded 2.0 g. of a mixture of methylated cyclohexanones which was found to contain VII (35%), VIII (14%), IX (42%), and X (9%). No XI was detected.

D. From Tritylithium in Liquid Ammonia–Ether. A. Kinetic Conditions with Methylation in 1,2-Dimethoxyethane.—The procedure by Hauser, *et al.*,[14] was employed for the preparation of tritylithium. To 75 ml. of anhydrous ammonia containing a trace of anhydrous ferric chloride was added 0.236 g. (0.034 g.-atom) of freshly cut lithium wire. The mixture then was stirred at liquid ammonia reflux temperature until the formation of lithium amide was complete as indicated by the disappearance of the blue color of lithium in liquid ammonia. Triphenylmethane, 8.30 g. (0.034 mole), in 100 ml. of anhydrous ether then was added at such a rate that the ammonia was condensed efficiently with the Dry Ice–acetone condenser. The red color of the tritylithium developed immediately on addition of the first few drops of the solution of triphenylmethane and at the end of the addition the lithium amide had dissolved and a deep red suspension of tritylithium remained. To this suspension was added dropwise with stirring 2.69 g. (0.024 mole) of VII in 25 ml. of ether over 40 min. The red color of the tritylithium persisted throughout the course of the addition and while stirring was continued for 30 min. thereafter. The liquid ammonia then was removed in the usual way (the red color of the excess tritylithium disappeared at this point), and the ether was distilled and replaced by 100 ml. of 1,2-dimethoxyethane. When the temperature of the distillate had reached 70°, the reaction mixture was cooled to room temperature, 16.0 g. (0.12 mole) of methyl iodide was added, and the reaction mixture refluxed for 2 hr. (An aliquot taken after 10

(19) In cases where significant quantities of *trans*-2,6-dimethylcyclohexanone were obtained in the alkylation reactions, a shoulder attributable to this material appeared on the second v.p.c. peak. However, since complete separation of this mixture of ketones could not be effected on the column employed, for purposes of analysis the entire mixture of ketones was refluxed with 10% hydrochloric acid to convert the 2,6-dimethylcyclohexanones to the equilibrium mixture.

(20) Prepared by Mr. C. Miller by the procedure of E. B. McCall and B. B. Willard, *J. Chem. Soc.*, 1911 (1959).

(21) Immediately on exposure of the 1,2-dimethoxyethane solution of XIII to ammonia vapor a copious precipitate, presumably a complex of XIII and ammonia, formed. However, the precipitate remained in suspension and the mixture could be added successfully to the lithium ammonia solution using a Hershberg dropping funnel.

min. showed the same composition by v.p.c. as did the product obtained after 2 hr.) Work-up of the reaction mixture in the usual way yielded VII (11%), VIII (55%), IX (27%), and X (7%). No XI was observed.

B. Kinetic Conditions with Methylation in Tetrahydrofuran (THF).—Tritylllithium was prepared as described above by the addition of triphenylmethane, 8.30 g. (0.034 mole), in 100 ml. of anhydrous ether to lithium amide (from 0.236 g., 0.034 g.-atom, of lithium) in 75 ml. of liquid ammonia. To the red solution was added dropwise with stirring 2.69 g. (0.024 mole) of VII in 25 ml. of ether over 30 min. The liquid ammonia then was removed in the usual way (the red color of the excess tritylllithium disappeared at this point) and was replaced by 100 ml. of THF. The ether was distilled from the reaction mixture until the temperature of the distillate reached 50°. The reaction mixture was cooled to room temperature, 16.0 g. (0.12 mole) of methyl iodide was added, and the mixture refluxed for 2 hr. After work-up of the reaction mixture and equilibration of the 2,6-dimethylcyclohexanones with 10% hydrochloric acid, analysis of the products gave VII (35%), VIII (47%), IX (<10%), and X (13%).

C. Equilibrium Conditions with Methylation in 1,2-Dimethoxyethane.—Tritylllithium was made by addition of 8.30 g. (0.034 mole) of triphenylmethane in 100 ml. of ether to lithium amide (from 0.236 g., 0.034 g.-atom, of lithium) in 75 ml. of liquid ammonia and 3.36 g. (0.030 mole) of VII in 25 ml. of ether was added dropwise with stirring over 30 min. When the last few drops of ketone were added, the disappearance of the red color of the tritylllithium indicated that a slight excess of ketone to this base was present. After the liquid ammonia had been removed and 100 ml. of 1,2-dimethoxyethane added to replace it, ether was distilled from the reaction mixture until the temperature of the distillate reached 70°. After cooling to room temperature and the addition of 16.0 g. (0.12 mole) methyl iodide, the reaction mixture was refluxed for 2 hr. Work-up in the usual way yielded a mixture of ketones which contained VII (14%), VIII (13%), and IX (73%). No other methylation products were observed.

Acknowledgment.—The author is sincerely grateful to Professor Gilbert Stork for his advice and assistance throughout the course of the work.

The Reaction of Lithium Acetylide·Ethylenediamine with Ketones

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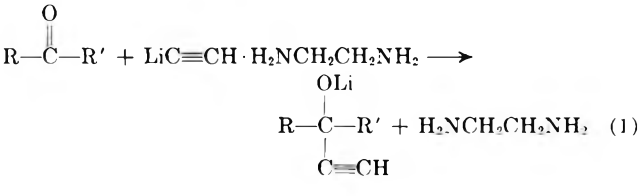
The reaction between lithium acetylide·ethylenediamine and a variety of ketones has been studied in several organic solvents under argon and acetylene atmospheres. High yields of ethynylcarbinols were obtained. A relationship between the yield of ethynylcarbinol and the dielectric constant of the solvent is discussed.

In a recent paper[1] we reported the preparation and some properties of lithium acetylide·ethylenediamine. This crystalline complex is stable up to about 45°, in contrast to uncomplexed lithium acetylide which is stable only in liquid ammonia at −33°.[2]

This new reagent with its higher stability has a potential of being used over a wide range of temperatures in a variety of organic solvents and in standard equipment. In this paper, this new versatility is discussed, and the effect of some of the variables on the reaction with ketones to form ethynylcarbinols is shown.

Lithium acetylide·ethylenediamine was found to add readily across a ketonic linkage to produce the lithium salt of the corresponding ethynylcarbinol.



(1)

The yield obtained was found to vary widely, depending upon the reaction conditions and the solvent.

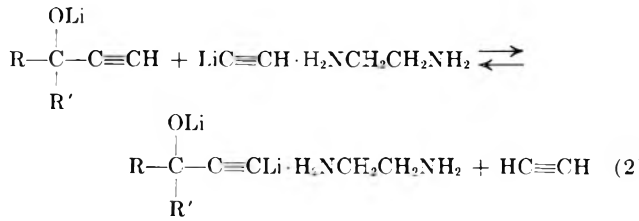
Table I summarizes the results obtained when stoichiometric quantities of lithium acetylide·ethylenediamine were allowed to react with the various ketones. Yields are based on starting materials added, and no correction is made for recovered ketone. Several runs were made with 10% excess acetylide where low yields were experienced with stoichiometric quantities. Yield was determined by analysis, not by isolation. Duplicate runs gave yields varying up to 2%.

If the yields given in Table I are plotted against the dielectric constant of the solvent, an interesting curve is obtained for each ketone. These curves can be grouped into several different types (see Fig. 1–4) and reflect two major side reactions.

In low dielectric solvents (such as benzene) there is usually a drop in yield. In most cases this loss is due mainly to base-catalyzed enolization. Evidence for this is the fact that after hydrolysis all of the starting ketone can be accounted for either as ethynylcarbinol or as unchanged ketone. Additional evidence is the relationship between the yields obtained in benzene and the base-catalyzed enolization constants determined by H. Shechter, *et al.*,[3] and listed in Table II.

The two marked exceptions to this simplification are the diaromatic ketones benzophenone and 9-fluorenone. Although it is impossible for them to enolize, they have the most dramatic drop in yield in low dielectric solvents. In fact, 1,1,4,4-tetraphenyl-2-butyne-1,4-diol is the major product obtained from benzophenone in benzene. This anomoly will be discussed in more detail under metalation.

At the high end of the dielectric scale (and to a lesser extent over the entire range), the reduction in yield appears to be due to metalation of the resulting ethynylcarbinol. This product may react further with an-



(2)

(1) O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963).

(2) M. Corbellini and L. Turner, *Chim. Ind.* (Milan), **42**, 251 (1950); *Chem. Abstr.*, **54**, 19,250 (1960).

(3) H. Shechter, M. J. Collins, R. Dessy, Y. Okuzumi, and A. Chen *J. Am. Chem. Soc.*, **84**, 2095 (1962).

TABLE I

YIELDS OF ETHYNYLCARBINOL FROM LITHIUM ACETYLIDE·ETHYLENEDIAMINE[a]

	Benzene[b]		Tetrahydrofuran–benzene[c]		Tetrahydrofuran[c]		N,N-Dimethylacetamide–benzene[b]		N,N-Dimethylacetamide[d]	
	C_2H_2[e]	Ar	C_2H_2[e]	Ar	C_2H_2[e]	Ar	C_2H_2[e]	Ar	C_2H_2[e]	Ar
Cyclopentanone	76	65	88 89[f]	76	82 86[f]	72	81	68	74	16
Cyclohexanone	89	91	98	90	90	84	100	84	89	73
Cycloheptanone		98			100	99		97	98	85
Acetone	62	55	92	69	75 86[f]	74	99	78	75	50
2-Butanone	89	76	99	81	98	83	100	96	87	61
3-Pentanone	94	87	99	96	96	94	100	87	95	66
2-Octanone	96	82	98	90	95	90		100	90	69
3-Octanone	97	91	100	98	97	94	100	92	92	63
Diisopropyl ketone		100		99		100				100
2-Cyclohexylcyclohexanone[g]		91		92	100	91				
2-Cyclohexylcyclohexanone		69			64				79	
Methyl vinyl ketone[h]	27	20	75	61	86 98[f]	75	68	45	41	34
Methyl vinyl ketone		13			53	43				
Isophorone[g]	81	78	87 93[f]	86	58	46	32	11	0	0
Isophorone		74		73	41	44		9	8	0
Mesityl oxide		80		93	97	99		63	25	25
Benzal acetone		99		100	100	100		100	93	79
Dibenzal acetone		97		97		97				95
Acetophenone	55	46	64	53	57 79[f]	57	75 80[f]	60	64	37
Propiophenone	81	73	88	84	80 98[f]	78	76	67	47	37
Benzophenone	47	46		50	62	58	81	71	92 96[f]	77
9-Fluorenone		33		40	42 56[f]	47	77	82	82 90[f]	76
1-Indanone	66	45	74	69	82 83[f]	70	76	41	63	39

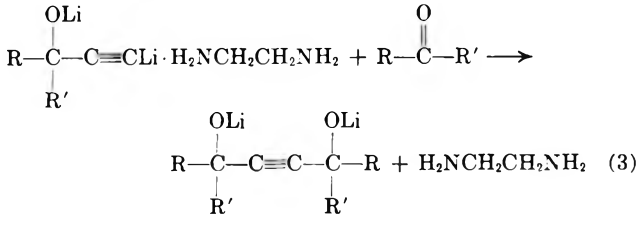
[a] Mixed solvents were 50:50 vol.%; yield was based on analysis; stoichiometric quantities, 0.25-hr. addition, and 1 *M* concentration were used unless otherwise specified. [b] Reaction temperature 35°, reaction time 1.75 hr. [c] Reaction temperature 35°, reaction time 2.75 hr. [d] Reaction temperature 25°, reaction time 1.75 hr. [e] The solvent was presaturated with acetylene and acetylene was bubbled through the mixture throughout the reaction. [f] A 10% excess of lithium acetylide·ethylenediamine was used. [g] Reaction temperature 45°, reaction time 6 hr. [h] Concentration 0.25 *M*, addition time 2.5 hr., reaction time 3 hr.

TABLE II

EFFECT OF BASE-CATALYZED ENOLIZATION ON YIELD

Ketone	Base-catalyzed enolization constant[a] $k^{40°} \times 10^7$	Yield with $LiC_2H \cdot H_2NCH_2CH_2NH$ in benzene–acetylene
Acetophenone	2200	55
Cyclopentanone	680	76
Propiophenone	490	81
Cyclohexanone	100	89
Cycloheptanone	19	98
Diisopropyl ketone	0.6	100

other molecule of ketone to form an acetylenic glycol or the reaction may stop here depending on the ketone and the reaction conditions. In either case, a loss in yield of ethynylcarbinol occurs if equimolar quantities of acetylide and ketone are used.



(3)

Although nothing could be done about enolization, except to change solvents, metalation could be minimized or eliminated. The use of a solvent presaturated with acetylene is sufficient to increase the yield markedly. The use of an acetylene atmosphere in addition to saturating the solvent will sometimes give an additional increase. The use of acetylene is felt to reverse eq. 2.

Interestingly, with benzophenone and 9-fluorenone, not only were the corresponding acetylenic glycols

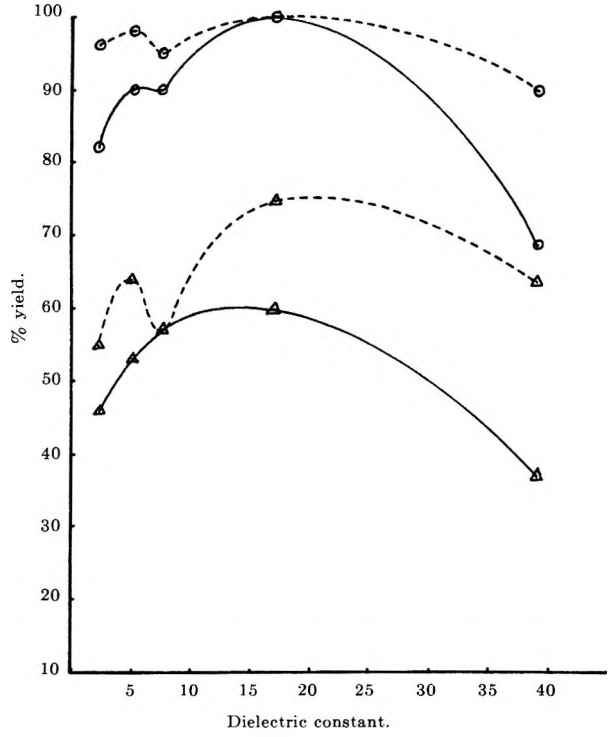


Fig. 1.—Yield of ethynylcarbinol *vs.* dielectric constant of the solvent: O, from 2-octanone; △, from acetophenone; ---------, acetylene atmosphere; ———, argon atmosphere.

formed in all solvent but the formation was far greater at low dielectrics. It was possible to minimize this acetylenic glycol formation in high dielectric solvents through the use of acetylene, but this did not help in low dielectric solvents. Either a different mechanism

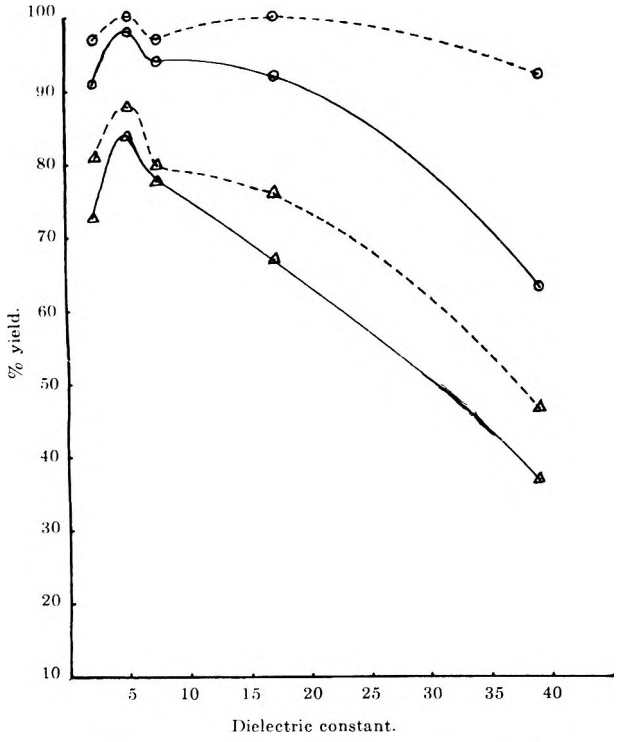


Fig. 2.—Yield of ethynylcarbinol *vs.* dielectric constant of the solvent: O, from 3-octanone; Δ, from propiophenone; ---------, acetylene atmosphere; ———, argon atmosphere.

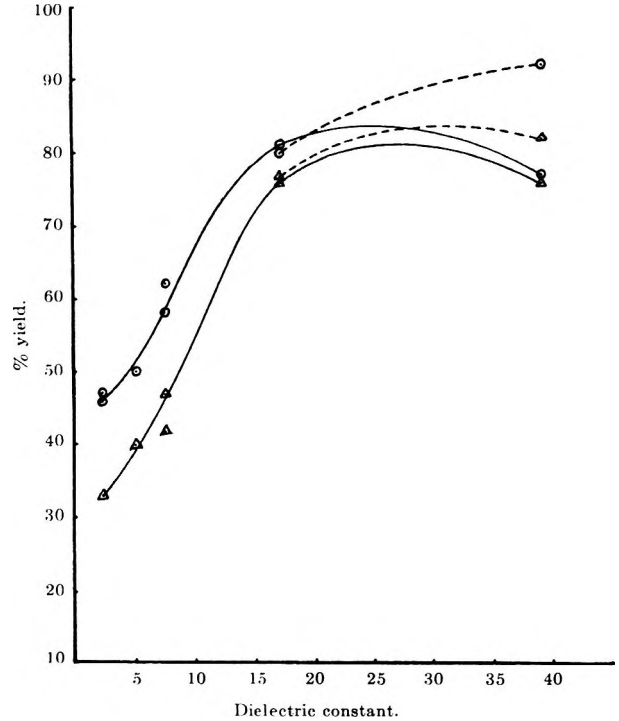


Fig. 3.—Yield of ethynylcarbinol *vs.* dielectric constant of the solvent: O, from benzophenone; Δ, from 9-fluorenone ---------, acetylene atmosphere; ———, argon atmosphere.

is responsible for the formation of these acetylenic glycols at low dielectrics or for some unknown reason acetylene fails to prevent metalation of the corresponding diaromatic ethynylcarbinols. Possibly the failure of excess acetylene to prevent metalation in the low dielectric solvents may be attributed to the low solubility of acetylene in these solvents.

The problem of steric hindrance was experienced only with 2-cyclohexylcyclohexanone, and forcing conditions (6 hr. at 45°) were necessary in order to obtain yields over 80%. It was not possible to use these conditions with N,N-dimethylacetamide as the solvent, since it reacts appreciably with the acetylide at this temperature.

It usually takes about an hour longer for the reaction between lithium acetylide-ethylenediamine and ketones to go to completion in tetrahydrofuran than in any other solvent. During this period, any side reaction has a greater opportunity to compete with the main reaction. This is apparently the reason why many of the ketones give a lower yield in tetrahydrofuran than would be predicted by a smooth yield *vs.* dielectric constant curve (Fig. 1 and 2).

Three of the ketones used in this study are subject to polymerization. When the standard conditions used to ethynylate the other ketones were used with methyl vinyl ketone, isophorone, and mesityl oxide, polymerization did occur to a considerable extent, especially in high dielectric solvents. It was found that with slow addition of the ketone, combined with greater dilution, it was possible to minimize polymerization. Lowering the reaction temperature lowered the yield.

Table I gives results using both sets of conditions for methyl vinyl ketone and isophorone. For mesityl oxide this change was felt unnecessary since excellent yields could be obtained in tetrahydrofuran using standard conditions.

Lithium acetylide-ethylenediamine appears to be an excellent reagent for the ethynylation of ketones. It offers high yields combined with the convenience of storage stability and simplicity of use. It should be possible, with the aid of Table I, to obtain good yields of ethynylcarbinol from most ketones.

Experimental

General.—The lithium acetylide-ethylenediamine used was all from the same lot. The analysis[1] was lithium acetylide-ethylenediamine, 92.3%; dilithium acetylide, 0.2%; N-lithioethylenediamine, 2.7%; lithium hydroxide, 0.6%; ethylenediamine, 2.8%; and 1.4% unknown.

All liquid ketones were distilled prior to use except for methyl vinyl ketone and 2-cyclohexylcyclohexanone.[4] Solid ketones were used as received. Benzene was thiophene-free and dried over sodium wire. Tetrahydrofuran (refined) and N,N-dimethylacetamide were used as received. Acetylene (welding) was purified by passage through columns containing activated alumina.

Reaction of Lithium Acetylide-Ethylenediamine with Ketones.—A 1-l., three-necked flask fitted with a dropping funnel, condenser, stirrer, and thermometer served as the reactor; a glass "T" above the condenser served as a means for argon cover and as an exit for escaping gas.

Lithium acetylide-ethylenediamine (40.1 g., 0.40 mole) was placed in the argon-flushed reactor, followed by 400 ml. of solvent. Stirring was started and the mixture was warmed to 35°. Ketone (0.40 mole) was added dropwise over a period of 15 min. while maintaining 35° by cooling. The mixture was stirred at room temperature for an additional 1.75 hr.

Water (100 ml.) was added slowly to hydrolyze the mixture. The contents were brought to gentle reflux and held for 1 hr. to remove any dissolved acetylene. After cooling to room temperature, the two layers were separated, weighed, and analyzed.

Solid ketones were dissolved in a minimum amount of solvent for the addition. This solvent was subtracted from the 400-ml. initial solvent charge.

(4) Obtained from Allied Chemical Co.

The procedure was the same for all solvents under argon with the following exceptions.

(1) In N,N-dimethylacetamide–benzene, 200 ml. of each solvent was used. (2) In tetrahydrofuran, 2.75 hr. was allowed for the reaction to go to completion instead of 1.75 hr. (3) In tetrahydrofuran–benzene, 200 ml. of each solvent was used and 2.75-hr. reaction time was allowed. (4) In N,N-dimethylacetamide, the reaction temperature was 25°.

Reactions under acetylene were carried out in the same manner as specified above for each solvent system except that the solvents were presaturated with acetylene and acetylene was bubbled through the solution throughout the reaction.

The following modifications were employed in a second set of runs for methyl vinyl ketone and isophorone: (1) 1600 ml. of solvent was used in a 2-l. reactor; (2) the ketone was added over a period of 2.5 hr.; and (3) the mixture was stirred at room temperature for an additional 3 hr.

For 2-cyclohexylcyclohexanone, the reaction temperature was raised to 45° and maintained for 6 hr. in all solvent systems except N,N-dimethylacetamide and benzene–N,N-dimethylacetamide.

With Benzophenone and 9-Fluorenone.—Benzophenone (0.327 mole) dissolved in benzene (120 ml.) was added to a slurry of lithium acetylide ethylenediamine (0.327 mole) in benzene (207 ml.) at 35° over a period of 15 min. The resultant slurry was stirred at room temperature for 1.75 hr., hydrolyzed with water (100 ml.), refluxed for 1 hr., cooled to room temperature, and filtered.

Analysis of the filtrate indicated a 46% yield of 1-ethynyldiphenylcarbinol. The white, crystalline solid was air-dried, giving m.p. 156–160°, 28.1 g. (44%). After recrystallization from methanol–water, it had m.p. 191–192°; lit.[5] (for 1,1,4,4-tetraphenyl-2-butyne-1,4-diol) m.p. 192°.

Anal. Calcd. for $C_{28}H_{22}O_2$: C, 86.12; H, 5.68. Found: C, 86.06; H, 5.82.

Similarly, using 9-fluorenone, 9,9′-ethynylenebis-9-fluorenol was obtained as an orange, crystalline solid, m.p. 236°, lit.[6] m.p. 238°.

Anal. Calcd. for $C_{28}H_{18}O_2$: C, 87.02; H, 4.69. Found: C, 86.78; H, 4.63.

With 2-Cyclohexylcyclohexanone.—1-Ethynyl-2-cyclohexylcyclohexanol is a previously unreported compound, b.p. 115° (1 mm.).

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.49; H, 10.75. Found: C, 81.73; H, 10.93.

With Isophorone.—1-Ethynyl-3,5,5-trimethyl-2-cyclohexenol is a previously unreported compound, b.p. 82° (3 mm.).

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.36; H, 9.87.

Determination of Dielectric Constants of Mixed Solvents.—Equipment consisted of a Q meter type 260-A from the Boonton Radio Corp., operating at 700 kc. with a 30-mmfd. capacitor detuned to 4.20 mmfd. The dielectric constants found were benzene, 2.31; benzene–tetrahydrofuran (50:50 vol. %), 4.98; tetrahydrofuran, 7.55; benzene–N,N-dimethylacetamide (50:50 vol.%), 16.90; and N,N-dimethylacetamide, 39.40.

Method of Analyses. A. Introduction.—The ethynyl alcohols were analyzed *in situ* by measuring the acetylenic hydrogen function.[7] It was necessary to determine the solvent conditions and reaction time for each ethynyl alcohol.

Ketones were analyzed by the hydroxylamine hydrochloride method.[8]

B. Procedure for Ethynyl Alcohol Determination.—A weighed sample of solution to be analyzed was placed in a 400-ml. beaker containing 100 ml. of proper solvent mixture (Table III) and equipped with a pH meter and magnetic stirrer. The solution was neutralized with 0.1 *N* sulfuric acid (2 *N* sulfuric acid used if considerable basic material present) to pH 4.00. Silver nitrate solution, 10% by weight (10 ml. per 25-ml. titration), was added and the liberated acid was titrated to pH 4.00 with 0.1 *N* sodium hydroxide.

Care must be exercised in determining the final end point, since tailing is prevalent in many compounds (Table III). The electrode tips tend to gum over and must be cleaned before the final end point is taken. The per cent yield was determined with the following equation.

$$\% \text{ yield} = \frac{\text{wt. of layer} \times \text{ml. of NaOH} \times N \text{ of NaOH}}{\text{wt. of sample} \times \text{moles of ketone} \times 10}$$

Blanks were run under the various solvent conditions using 1-ethynylcyclohexanol as standard and were found to be negligible. A blank was also run with lithium acetylide-ethylenediamine and N,N-dimethylacetamide at 35° for 2.5 hr. After working the mixture in the usual manner, no acetylenic hydrogen could be detected.

Table IV is a summary of the method applied to several pure ethynylcarbinols.

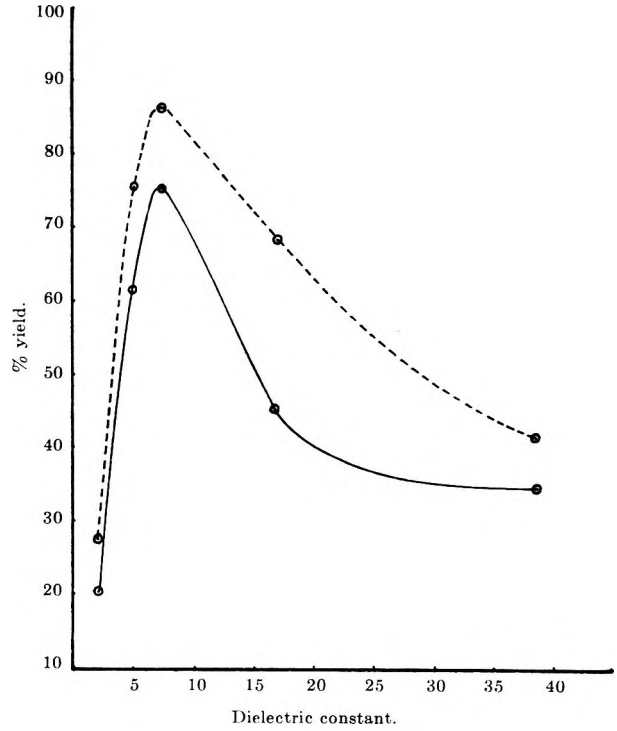


Fig. 4.—Yield of ethynylcarbinol *vs.* dielectric constant of the solvent: O, from methyl vinyl ketone; ---------, acetylene atmosphere; ———, argon atmosphere.

TABLE III

CONDITIONS USED FOR THE ANALYSIS OF ETHYNYLCARBINOLS

Parent ketone	Volume of water, ml.	Volume of methanol, ml.	Time,[a] min.
Cyclopentanone	50	50	20
Cyclohexanone	100	0	10
Cycloheptanone	50	50	20
Acetone	50	50	45
2-Butanone	50	50	45
3-Pentanone	50	50	30
2-Octanone	40	50	30
3-Octanone	50	50	30
Diisopropyl ketone	25	75	10
Methyl vinyl ketone	50	50	150
Isophorone	100	0	150
Mesityl oxide	50	50	60
Benzal acetone	25	75	30
Dibenzal acetone	25	75	30
Acetophenone	25	75	15
Propiophenone	50	50	20
Benzophenone	50	50	20
9-Fluorenone	25	75	45
1-Indanone	25	75	45
2-Cyclohexylcyclohexanone	25	75	30

[a] Total time to reach end point due to tailing.

(5) A. Babyan, *Izv. Akad. Nauk Arm. SSR*, **5**/**6** (10/11), 121 (1941).
(6) E. Bergmann, H. Hoffmann, and D. Winter, *Ber.*, **66B**, 46 (1933).
(7) T. L. Jacobs, *Org. Reactions*, **5**, 45 (1960).
(8) J. Mitchell, Jr., "Organic Analysis," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1953, p. 243.

TABLE IV

ANALYTICAL RESULTS FROM PURE ETHYNYLCARBINOLS

Parent ketone	B.p., °C.	M.p., °C.	Assay, %
Cyclohexanone	178	32–33	99.5 ± 0.1
Diisopropyl ketone	163–165	...	98.7 ± 0.2
Acetophenone	85 (3 mm.)	...	99.2 ± 0.1
2-Butanone	119–121	...	99.5 ± 0.1
2-Cyclohexylcyclohexanone	115 (1 mm.)	...	98.3 ± 0.2
Methyl vinyl ketone	50–51 (54 mm.)	...	99.9 ± 0.1
2-Octanone	72–73 (4 mm.)	...	99.9 ± 0.1
1-Indanone	...	70.1	99.9 ± 0.1
9-Fluorenone	...	107	98.4 ± 0.1

C. Procedure for Ketone Determinations.—A weighed sample of solution to be analyzed was placed in a 400-ml. beaker containing 200 ml. of water and equipped with a pH meter and magnetic stirrer. The solution was neutralized to pH 4.00 with 0.1 *N* hydrochloric acid and 0.8 *N* hydroxylamine hydrochloride was added (10 ml. per 40-ml. titration). The liberated hydrochloric acid was back-titrated with 0.1 N sodium hydroxide.

This method was applied to cyclohexanone, acetone, cyclopentanone, 2-butanone, 3-pentanone, and 2-octanone.

Acknowledgment.—We wish to thank Dr. Ralph G. Verdieck for determining the dielectric constants and John G. Maroski for his assistance in carrying out many of the analyses.

Fluoro Ketones. II. Reactions with Trialkyl Phosphites

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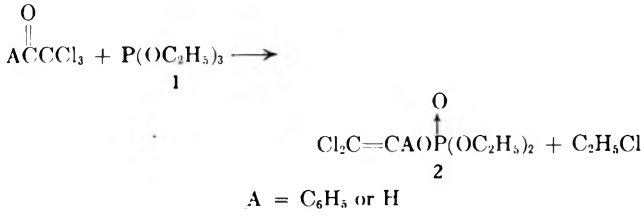
Contribution No. 924 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington 98, Delaware

Received December 11, 1963

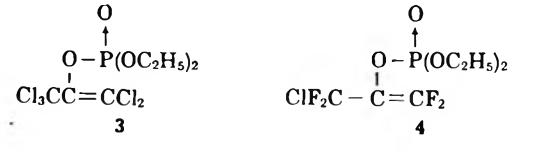
sym-Dichlorotetrafluoroacetone and *sym*-difluorotetrachloroacetone have been found to undergo the Perkow reaction with trialkyl phosphites to give the corresponding dialkyl perhaloisopropenyl phosphate and alkyl chloride. Perfluoro ketones undergo a new reaction with trialkyl phosphites to yield alkyl enol ethers of the ketones and dialkyl phosphorofluoridate.

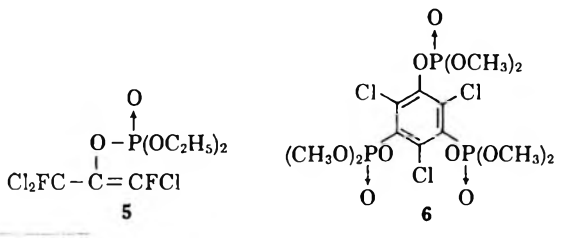
The reaction of α-halogenated aldehydes, ketones, esters, and amides with phosphites containing at least one alkyl ester group yields vinyl phosphates.[1-3] For example, the reaction of chloral[2,3] or trichloroacetophenone[2] with triethyl phosphite (1) yields the dichlorovinyl esters 2 and ethyl chloride.



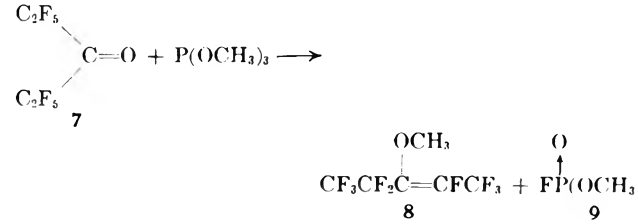
This paper describes some examples of reaction of alkyl phosphites with perhalogenated ketones and the abnormal reaction products from perfluorinated ketones.

When hexachloro-, *sym*-dichlorotetrafluoro-, or *sym*-difluorotetrachloroacetone react with triethyl phosphite, the corresponding diethyl perhaloisopropenyl phosphates (**3**, **4**, and **5**) are formed along with ethyl chloride. Interestingly, no ethyl fluoride was formed in the latter two reactions. With 3 moles of trimethylphosphite, hexachloro-1,3,5-cyclohexanetrione[4] gave the aromaticized product **6**. The isopropenyl phosphates are sensitive to water, react with bromine, and appear to undergo SN2′ reactions with anions such as iodide and cyanide.





Surprisingly, the perfluorinated ketones were found to react exothermically at 0° with trialkyl phosphites with no alkyl fluoride evolution to give the alkyl enol ether of the starting ketone and a dialkyl phosphorofluoridate. For example, perfluoro-3-pentanone (**7**) reacted with trimethyl phosphite to give 3-methoxyperfluoro-2-pentene (**8**) and dimethyl phosphorofluoridate (**9**). The enol ether **8** was obtained as a 1:1 mixture of *cis* and *trans* isomers, separable by gas chromatography. The proof of structure requires comment only in that the isomer with methoxy and fluorine groups *trans* had no infrared absorption in the region associated with C=C stretching frequency in marked contrast to the *cis* isomer (Fig. 1). Both isomers showed C=C Raman absorptions. The structural assignment is based on the interpretation of the F^{19} n.m.r. spectra (Fig. 2) given in Experimental.



The reaction appeared to be quite general for perfluoro ketones giving enol ethers with perfluoro-4-hep-

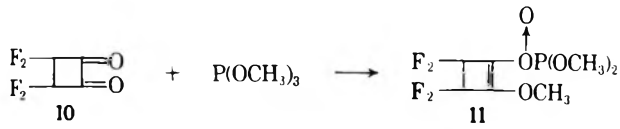
(1) F. Cramer, *Angew. Chem.*, **72**, 236 (1960); F. N. Lichtenhaler, *Chem. Rev.*, **61**, 607 (1961).

(2) M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.*, **20**, 1356 (1955).

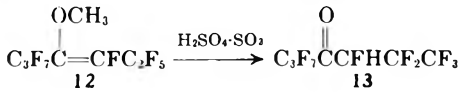
(3) W. Perkow, *Ber.*, **87**, 755 (1954).

(4) T. Zincke and O. Kegel, *ibid.*, **22**, 1467 (1889).

tanone and hexafluoroacetone. Perfluorobutyraldehyde gave a low yield of the corresponding enol ether, and hexafluorocyclobutanone[5] gave the known 1-methoxypentafluorocyclobutene.[6] However, tetrafluoro-1,2-cyclobutanedione (**10**)[5] underwent an addition reaction with trimethyl phosphite to give **11**. The structure of **11** was assigned on the basis of its n.m.r. and infrared spectra.[7]

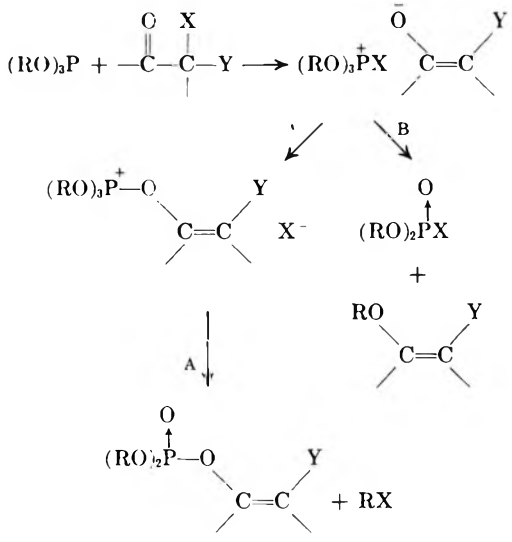


The enol ether **12** of perfluoro-4-heptanone could be hydrolyzed with fuming sulfuric acid to give α-hydroperfluoro-4-heptanone (**13**), thus giving an over-all reduction of an α-fluorine in a perfluoro ketone with trialkyl phosphite.



Although several mechanisms have been proposed for the reaction of α-chloro and α-bromo ketones with trialkyl phosphites, the recent studies of Hoffmann and Diehr[8] support path A in Scheme I.

SCHEME I



This scheme suggests initial attack on halogen forming a resonance-stabilized anion and $(RO)_3PX^+$, which has precedent in the formation of pentachlorocyclopentadienide ion from hexachlorocyclopentadiene and triethyl phosphite.[9] When X = Cl and Y = Cl or F, attack must occur preferentially at X, and reaction proceeds *via* path A. When X = Y = F, the cation in the initially formed enolate complex now possesses the stronger P–F bond, and displacement at carbon rather than phosphorus occurs (path B).

(5) D. C. England, *J. Am. Chem. Soc.*, **83**, 2205 (1961).

(6) J. T. Barr, K. E. Rapp, R. L. Pruett, C. T. Bahner, J. D. Gibson, and R. H. Lafferty, Jr., *ibid.*, **72**, 4480 (1950).

(7) However, see V. A. Kukhtin, K. M. Kirillova, R. R. Shagidullin, Y. Y. Samilov, N. A. Lyazina, and N. F. Rakova, *J. Gen. Chem. USSR* (Eng. Transl.), **32**, 2020 (1962).

(8) H. Hoffmann and H. J. Diehr, *Tetrahedron Letters*, 583 (1962).

(9) V. Mark, *ibid.*, 295 (1961).

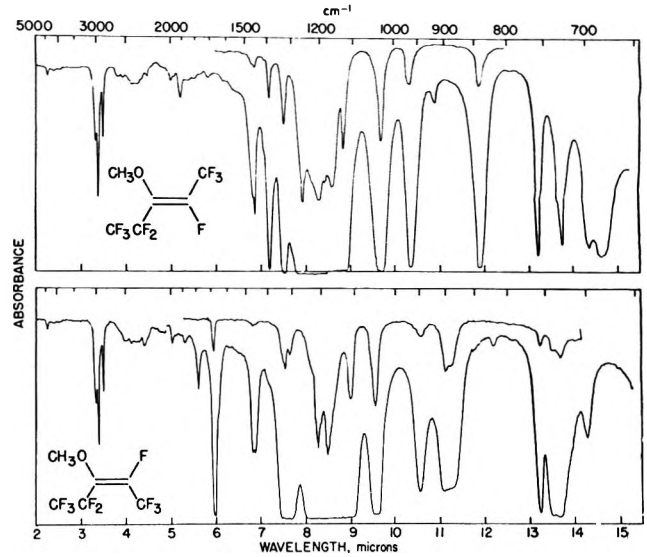


Fig. 1.—Infrared spectra of *cis*- and *trans*-3-methoxyperfluoro-2-pentene.

Experimental

sym-Difluorotetrachloroacetone and *sym*-dichlorotetrafluoroacetone were obtained from General Chemical Division, Allied Chemical and Dye Corp., Morristown, N. J., and were used without further purification. Perfluoro-4-heptanone and perfluoro-3-pentanone were prepared by the method of Wiley.[10] The phosphite esters were distilled just prior to use. *Caution. Many substituted vinyl phosphates are powerful cholinesterase inhibitors and are, therefore, highly toxic.*

3-Chloro-1,1,3,3-tetrafluoroisopropenyl Diethyl Phosphate (4).[11]—*sym*-Dichlorotetrafluoroacetone (50 g., 0.25 mole) was placed in a flask equipped with a reflux condenser, addition funnel, and magnetic stirrer. The flask was cooled with an ice–water bath, and 42 g. (0.25 mole) of triethyl phosphite was added dropwise with vigorous stirring. The rate of addition was adjusted to maintain gentle reflux, and ethyl chloride was evolved. The reaction mixture was allowed to stand overnight at room temperature and then was distilled directly. There was obtained 61.0 g. (81%) of **3-chloro-1,1,3,3-tetrafluoroisopropenyl diethyl phosphate** (**4**), b.p. 69–71° (4 mm.), $n^{25}D$ 1.3880.

Anal. Calcd. for $C_7H_{10}ClF_4O_4P$: C, 28.0; H, 3.4; F, 25.3. Found: C, 28.9; H, 3.8; F, 24.5.

The halogen-substituted isopropenyl phosphates are colorless oils, which produce marked respiratory effects on inhalation and should be considered toxic. Difficulties were encountered in securing acceptable analyses of the isopropenyl phosphates, which hydrolyzed readily with traces of moisture. The structures were assigned on the basis of the infrared and fluorine n.m.r. spectra. 3-Chloro-1,1,3,3-tetrafluoroisopropenyl diethyl phosphate showed bands in the infrared spectrum assignable to the terminal difluoromethylene (1767) and to the phosphate (1040 cm.$^{-1}$) groups.

In a similar manner, *sym*-difluorotetrachloroacetone and triethyl phosphite gave **1,3-difluoro-1,3,3-trichloroisopropenyl diethyl phosphate** (**5**), b.p. 81–82° (0.25 mm.), $n^{25}D$ 1.4437, in 80% yield. The infrared spectrum showed C=C at 1680 and phosphate at 1030 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_7H_{10}Cl_3F_2O_4P$: C, 25.2; H, 3.0; F, 11.4. Found: C, 25.3; H, 2.7; F, 12.1.

Hexachloroacetone and triethyl phosphite gave **1,1,3,3,3-pentachloroisopropenyl diethyl phosphate** (**3**), b.p. 131–132° (0.8 mm.), $n^{25}D$ 1.4954, in 60% yield. The infrared spectrum showed C=C at 1600 and phosphate at 1010 cm.$^{-1}$ (broad). Pentachloroisopropenyl trichloroacetate shows similar C=C absorption (1603 cm.$^{-1}$).[12]

(10) D. W. Wiley, U. S. Patent 3,091,643 (1963).

(11) The reactions of the chlorofluoro ketones with trialkyl phosphites were carried out in conjunction with Dr. J. J. Drysdale.

(12) W. M. Wagner, H. Kloosterziel, and A. F. Bickel, *Rec. trav. chim.*, **81**, 933 (1962).

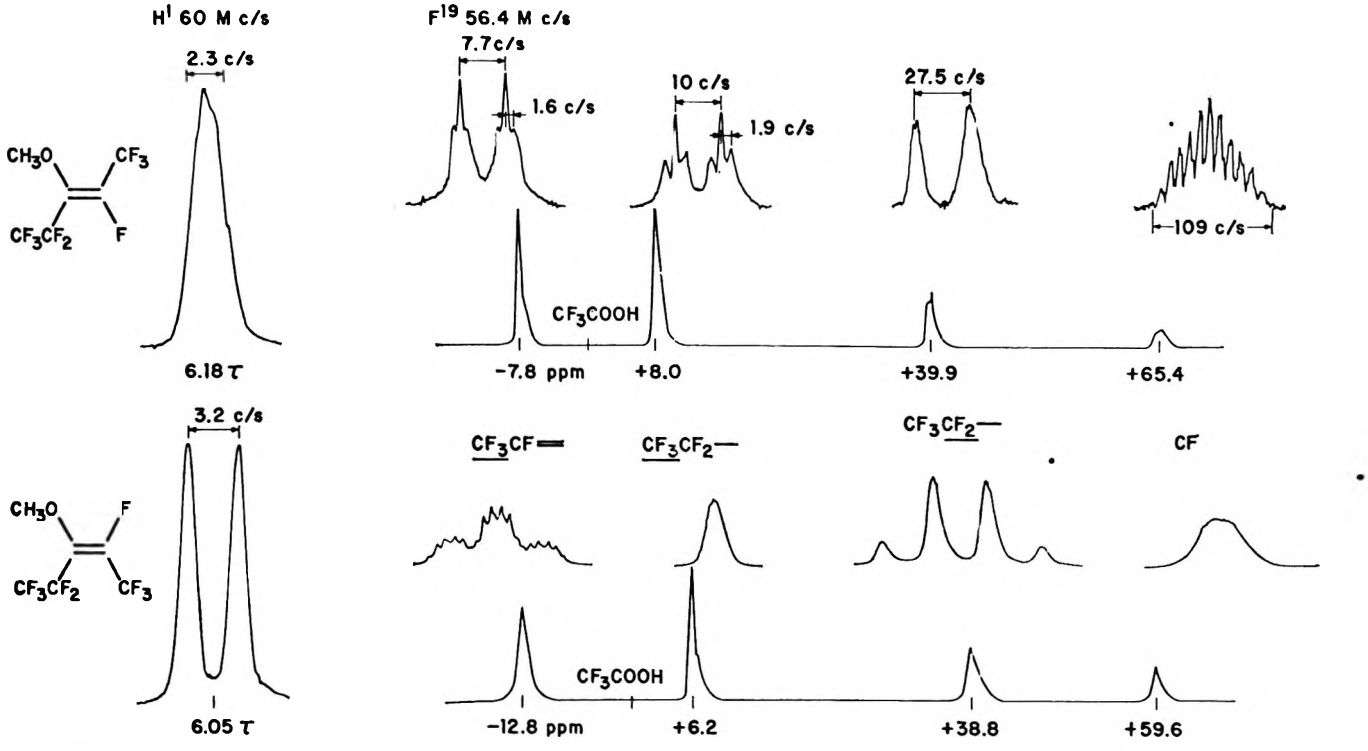


Fig. 2.—N.m.r. spectra of *cis*- (high boiling) and *trans*-3-methoxyperfluoro-2-pentene (low boiling). Enlarged regions are not drawn to same scale.

Anal. Calcd. for $C_7H_{10}Cl_3O_4P$: C, 22.9; H, 2.8. Found: C, 22.1; H, 2.8.

The fluorine and proton n.m.r. spectra of the isopropenyl phosphates were examined cursorily. The gross patterns were consistent with the assigned structures; however, no detailed analyses were attempted.

2,4,6-Trichlorophloroglucinoltris(dimethyl phosphate) (6).—2,2,4,4,6,6-Hexachloro-1,3,5-cyclohexanetrione, m.p. 48–49°, was prepared by the method of Zincke and Kegel.[4] The trione (20.0 g., 0.060 mole) was dissolved in anhydrous ether (50 ml.) in the apparatus described for the reactions of the chlorofluoro ketones. Trimethyl phosphite (22.3 g., 0.180 mole) was added over 1 hr., and after the exothermic reaction had subsided the mixture was allowed to stir at 25° for 48 hr. Evaporation of the ether gave a red crystalline mass, which was recrystallized from benzene to give 27.5 g. (83%) of the colorless **2,4,6-trichlorophloroglucinoltris(dimethyl phosphate)** (6), m.p. 155°.

Anal. Calcd. for $C_{12}H_{18}O_{12}Cl_3P_3$: C, 26.00; H, 3.28; Cl, 19.22. Found: C, 26.03; H, 3.37; Cl, 18.94.

The infrared spectrum of 6 showed aromatic C=C at 1565 and phosphate at 1050 cm.$^{-1}$ (broad). Hydrolysis of 6 with dilute base gave a good yield of trichlorophloroglucinol.

4-Methoxyperfluoro-3-heptene (12).—Trimethyl phosphite (5.58 g., 0.045 mole) was added to 18.30 g. (0.050 mole) of perfluoro-4-heptanone at a rate which maintained the vigorous reaction at reflux. After the addition was complete (30 min.), the colorless solution was heated to reflux (110°) for 15 min. The resulting liquid was then distilled to give 14.9 g. (91%) of 12, b.p. 104–109°, $n^{25}D$ 1.2989, and 5.4 g. (95%) of dimethyl phosphorofluoridate (9), b.p. 150°, $n^{25}D$ 1.3527 [lit.[13] b.p. 150.1° (759 mm.), $n^{23.8}D$ 1.3540]. (*Caution! Extremely toxic.*) Redistillation of the olefin 12 gave 12.1 g. of pure 4-methoxyperfluoro-3-heptene, b.p. 105–106°, $n^{25}D$ 1.2983.

Anal. Calcd. for $C_8H_3F_{13}O$: C, 26.5; H, 0.8; F, 68.2. Found: C, 26.7; H, 1.1; F, 68.2.

In a similar fashion using a Dry Ice condenser, 143 g. (0.537 mole) of perfluoropentanone was treated with 69 g. (0.556 mole) of trimethyl phosphite to give on distillation through a Heligrid column (736 mm.) a combined yield of 124 g. (88%) of *cis*- and ***trans*-3-methoxyperfluoro-2-pentene**. The lower boiling fractions, b.p. 69–71°, were predominantly (85%) one isomer, whereas the higher boiling fractions, b.p. 75–76°, were predominantly (95%) the other isomer. The ratio of the two isomers as determined by gas chromatography was essentially 1:1. Analytical samples were obtained by preparative gas chromatography using a column of 20% w./w. tetrakis(1H,1H,5H-octafluoropentyl and 1H,1H,7H-dodecafluoroheptyl) pyromellitate on 40–60-mesh firebrick at 50°: *trans* isomer, $n^{25}D$ 1.290, d_{25} 1.453; and *cis* isomer, $n^{24.5}D$ 1.298, d_{25} 1.504.

The infrared (Fig. 1) and Raman spectra of the higher boiling (*cis*) isomer showed strong absorption for C=C at 1690 and 1695 cm.$^{-1}$, respectively, whereas the corresponding spectra of the lower boiling (*trans*) isomer showed no absorption for C=C in the infrared (Raman, 1740 cm.$^{-1}$). The mass spectral analyses were consistent with both isomers having similar structures with identical parent mass peaks at 262. Also consistent with the assigned general structure was the presence of CF_3^+ and $C_2F_5^+$ fragments.

Anal. Calcd. for $C_6H_3F_9O$: C, 27.5; H, 1.2; F, 65.2. Found for *trans*: C, 27.8; H, 1.6; F, 65.3. Found for *cis*: C, 27.9; H, 1.6; F, 65.3.

The n.m.r. spectra are reproduced in Fig. 2. Assignments of each F multiplet are based on integrated intensities and on chemical shift comparisons with related compounds. The CF_3CF_2 multiplets are generally upfield from CF_3C=C multiplets.[14] Further, it is noted that, in the high-boiling isomer (not in the low-boiling isomer), there is strong coupling (J = 17.5 c.p.s.) between the CF_2 multiplet and the downfield CF_3 multiplet. Considering that *cis*-trifluoromethyl fluorine nuclei generally are coupled (at long range) more strongly than *trans*-trifluoromethyl groups[15] argues that (1) the high-boiling isomer (with C=C infrared absorption) has the structure where the two perfluoroalkyl groups are *cis* to each other and (2) the downfield CF_3 multiplet is that of the CF_3 on the double bond. Using this structural assignment, interpretation of the spectra gave the nuclear spin-coupling constants diagramed schematically below. The F multiplets in the *cis* isomer could only be resolved to give the coupling constants listed. It is noted that the vinyl fluorine is also coupled (at long range) more strongly with *cis* groups than with *trans*.

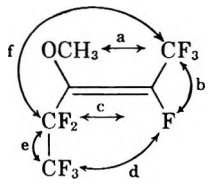
2-Ethoxyperfluoropropene.[16]—Triethyl phosphite (42 g., 0.25 mole) was added dropwise to 42 g. (0.25 mole) of hexafluoro-

(13) W. Lange and G. V. Krueger, *Ber.*, **65B**, 1598 (1932).

(14) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 323.

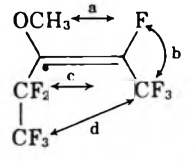
(15) S. Andreades, *J. Am. Chem. Soc.*, **84**, 864 (1962).

(16) This experiment was carried out by Dr. W. J. Middleton.



Low-boiling isomer (*trans*)

a, J_{HF} = ~0.6 c.p.s.
b, J_{FF} = 7.7 c.p.s.
c, J_{FF} = 27.5 c.p.s.
d, J_{FF} = 10.0 c.p.s.
e, J_{FF} = 1.9 c.p.s.
f, J_{FF} = 1.6 c.p.s.



High-boiling isomer (*cis*)

a, J_{HF} = 3.2 c.p.s.
b, J_{FF} = 4.9 c.p.s.
c, J_{FF} = 17.5 c.p.s.
d, J_{FF} = 2.8 c.p.s.

acetone contained in a flask equipped with a Dry Ice-cooled condenser. The rate of addition was adjusted so that a gentle reflux was maintained. The reaction mixture was distilled to give 22 g. (50%) of **2-ethoxy-1,1,3,3,3-pentafluoropropene** as a colorless liquid, b.p. 53–54°, $n^{25}D$ 1.3027. The infrared spectrum contained a band at 1760 cm.$^{-1}$ for C=C. The fluorine n.m.r. was consistent with an ABX_3 pattern for splitting.

Anal. Calcd. for $C_5H_5F_5O$: C, 34.1; H, 2.9; F, 53.9. Found: C, 34.7; H, 3.5; F, 53.8.

1-Ethoxy-2,3,3,4,4,4-hexafluoro-1-butene.—To 11.0 g. (0.066 mole) of triethyl phosphite, 20 g. (0.067 mole) of perfluorobutyraldehyde was added while cooling to 0°. The resulting semigelatinous (fluoroaldehyde polymer) mixture was then heated cautiously. Near 80°, a vigorous exothermic reaction occurred resulting in some loss of the volatile aldehyde. Distillation of the residue gave 8.2 g. (40%) of a mixture of the *cis* and *trans* isomers of **1-ethoxy-2,3,3,4,4,4-hexafluoro-1-butene,** b.p. 96.5–104°. An analytical sample of the pure *trans* isomer was obtained from a cut and had b.p. 103.5–104°, $n^{25}D$ 1.3282. The infrared spectrum contained a band at 1745 cm.$^{-1}$ for C=C. The fluorine n.m.r. (40 Mc.p.s., CF_3COOH ext.) spectrum consisted of three complex bands at +7.7 (CF_3), +43.0 (CF_2), and +86.0 p.p.m. (CF) in a ratio of 3:2:1; and the proton n.m.r. (40 Mc.p.s., tetramethylsilane ext.) spectrum consisted of three bands at τ 3.88 (—CF=C*H*O—, doublet, J_{HF} = 21 c.p.s.), 6.35 (—OCH_2CH$_3$, quadruplet, J = 7 c.p.s.), and 9.12 (CH$_2$CH_3, triplet, J = 7 c.p.s.) in a ratio of 1:2:3. The *trans* configuration was assigned on the basis of the observed 21-c.p.s. proton–fluorine coupling constant.[17]

(17) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959.

Anal. Calcd. for $C_6H_6F_6O$: C, 34.6; H, 2.9; F, 54.8. Found: C, 34.4; H, 2.8; F, 55.3.

1-Methoxyperfluorocyclobutene.[18]—Perfluorocyclobutanone (34 g., 0.2 mole) was bubbled into a solution of 12.4 g. (0.1 mole) of trimethyl phosphite in 50 ml. of dry ether at room temperature. There was recovered 8 g. of perfluorocyclobutanone and after removal of the ether distillation gave 9.5 g. (55%) of 1-methoxyperfluorocyclobutene, b.p. 85°, $n^{25}D$ 1.3292 (lit.[6] b.p. 87°, $n^{25}D$ 1.3300).

Dimethyl 2-Methoxy-3,3,4,4-tetrafluorocyclobuten-1-yl Phosphate.[18]—To a solution of 11 g. (0.09 mole) of trimethyl phosphite in 50 ml. of dry ether, was added dropwise 10 g. (0.06 mole) of perfluoro-1,2-cyclobutanedione with stirring and cooling in a Dry Ice–acetone bath at −70°. The blue diketone was rapidly decolorized. An additional 5 g. of trimethyl phosphite was then added, but no exothermic reaction occurred. The mixture was distilled to give 8.5 g. of dimethyl methylphosphonate, b.p. 69° (10 mm.), $n^{25}D$ 1.4069, and 6.5 g. (36%) of **dimethyl 2-methoxy-3,3,4,4-tetrafluorocyclobuten-1-yl phosphate,** b.p. 90° (1 mm.), $n^{25}D$ 1.3950. Proton n.m.r. indicated the presence of two different methoxyl groups in the ratio of 2:1, and the infrared spectrum contained an absorption band at 1750 cm.$^{-1}$ for the enol ether C=C stretch.[7]

Anal. Calcd. for $C_7H_9F_4O_5P$: C, 30.0; H, 3.2; P, 11.0; F, 28.6. Found: C, 30.5; H, 3.4; P, 11.0; F, 24.0.

3-Hydroperfluoro-4-heptanone.—A mixture of 23.3 g. (0.064 mole) of the 4-methoxyperfluoro-3-heptene and 35 ml. of 20% fuming sulfuric acid was heated at reflux for 22 hr. The reaction mixture was cooled to room temperature and carefully poured onto 300 g. of ice. Extraction of the solution with five 40-ml. portions of ether followed by careful distillation from phosphorus pentoxide gave 18 g. (81%) of **3-hydroperfluoro-4-heptanone,** b.p. 90°. An analytical sample was obtained by gas chromatography.

Anal. Calcd. for $C_7HF_{13}O$: C, 24.2; H, 0.3; F, 71.0. Found: C, 24.9, 24.6; H, 0.8, 0.7; F, 71.1, 71.4.

When dissolved in 1:1 ethanol–water, the ketone apparently formed a hemiketal, which titrated at 0° as a weak acid with pK_a 8.5 (neut. equiv.: calcd., 348; found, 329).

The proton n.m.r. showed a complex pattern centered at τ 4.80 consisting of a doublet with each component split further into two pairs of doublets (J's = 46, 15, and 5.6 c.p.s.). The fluorine n.m.r. (56.4 Mc.p.s., CF_3COOH, ext.) contained two CF_3 peaks at +5.0 (triplet, J = 9.3 c.p.s.) and +7.3 p.p.m. (doublet, J = 10 c.p.s.). The CF_2 region consisted of a peak at +43.5 (broad unresolved), a w,s,s,w quartet centered at +48.6 ($|w,s|$ = 290 c.p.s., $|s,s|$ = 143 c.p.s., individual peaks unresolved), and a peak at 50.0 p.p.m. (complex multiplet, partially overlapped by a portion of the w,s,s,w quartet). The CF absorption was at +132.4 p.p.m. (complex multiplet). The spectrum has been interpreted as being consistent with the CF_2, adjacent to the asymmetric —CFH–, having nonequivalent fluorine atoms.[19] Thus the proton n.m.r. is the X portion (quartet) of an ABX pattern, further split by the fluorine on the same carbon, with the AB portion being the w,s,s,w CF_2 absorption. The CF_3 splitting patterns are interpreted as long-range F–F coupling with the fluorines on the carbons β to the CF_3's.[20]

(18) This experiment was carried out by Dr. D. C. England.

(19) Ref. 14, pp. 377–381.

(20) N. Muller, P. C. Lauterbur, and G. F. Svatos, *J. Am. Chem. Soc.*, **79**, 1808 (1957).

The Stereochemistry of the Camphoketene Dimers[1]

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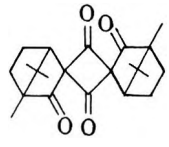
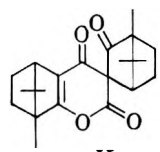
The stereochemistry of the camphoketene dimers has been deduced from optical rotatory dispersion and nuclear magnetic resonance data. The more dextrorotatory isomer has configuration S at C-3 of the pyronone ring as in formula III. This finding accords with theoretical assignments based on molecular rotation data for the dimers at 589 mμ.

Dehydrochlorination of *d*-camphor-3-carbonyl chloride with quinoline or triethylamine in ether gives two products of molecular formula $C_{22}H_{28}O_4$.[2] Staudinger and Schotz[2] assigned structure I to these isomers, but more recently Yates and Chandross[3] have shown that the two dimers should be represented by structure II.



I



II

The dimers were reported[2,3] to differ markedly in optical rotation; since they can differ in stereochemistry only at C-3 of the pyronone ring, it appeared likely that theoretical correspondences between optical rotation and stereochemistry could lead to an unambiguous prediction of configuration for the molecule. To check this prediction by degradation would be difficult, for the epimeric center is not very durable: both dimers give identical products upon acidic hydrolysis, basic hydrolysis, or thermal rearrangement.[3] Physical methods that would be sensitive to the stereochemical aspects of structure looked more promising.

Yates and Chandross[3] noted that the rates of alkaline hydrolysis of the dimers differed slightly, and that a tentative assignment of stereochemistry could be made on this basis.

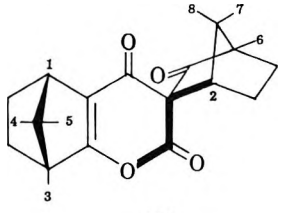
Results and Discussion

Preparation of the camphoketene dimers[2] gave materials having optical rotations in satisfactory agreement with the literature. Isomer A, the dimer which is less soluble in ether and forms compact crystals, had $[\alpha]_D$ +127° (lit.[2] +126.8°, lit.[3] +132°), while the second substance, which crystallizes in fine needles, had $[\alpha]_D$ +65° (lit.[2] +62.9°, lit.[3] +66.3°).

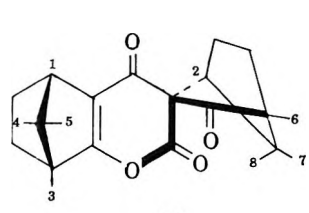
The nuclear magnetic resonance spectrum of the supposed second dimer, $[\alpha]_D$ +65°, was not comprehensible in terms of a single camphoketene dimer. For instance, the methyl region of the spectrum had peaks at 70, 63, and 54 c.p.s. (1.17, 1.05, and 0.90 p.p.m.) below tetramethylsilane with relative strengths in the ratios 1.1:3.3:1.5. Recrystallization of the material of $[\alpha]_D$ +65° from absolute methanol gave crystals having less positive rotations. The final recrystallization gave stout needles of m.p. 156–158°, $[\alpha]_D$ +23.7°. The n.m.r. spectrum of this resolved dimer, isomer B, was compatible with expectations for fully resolved material.

The crystals of $[\alpha]_D$ +62.9 to +66.3° are then a 1:1 mixture of the two diastereoisomeric camphoketene dimers. The slight discrepancy between the observed rotations and that calculated for an equimolar mixture of isomers A and B may be due either to incomplete resolution of isomer B, or to a small contamination of the 1:1 eutectic with isomer B.

The optical rotatory dispersion characteristics of dimers A and B are shown in Fig. 1. Both isomers have positive Cotton effects at the wave lengths corresponding to the K-bands for the α,β-unsaturated carbonyl moieties. Both of the α,β-unsaturated carbonyl systems, therefore, have the same chirality,[4] and are left-handed.[4] The dimers in question, then, are III and IV.



III



IV

The n.m.r. spectra of isomers A and B are strikingly different. In isomer A, $[\alpha]_D$ +127°, the two methine protons are centered at 172 and 166 c.p.s. (2.87 and 2.77 p.p.m.) and the methyl signals at 70, 63, and 54 c.p.s. (1.17, 1.05, and 0.90 p.p.m.) are of relative strength 1:4:1. For isomer B, $[\alpha]_D$ +23.7°, the two methine protons are found at 175 and 156 c.p.s. (2.82 and 2.60 p.p.m.), and the methyl absorptions at 70, 63, and 55 c.p.s. (1.17, 1.05, and 0.92 p.p.m.) are of relative strength 1:3:2. The two spectra are distinguishable by the chemical shift differences of one methine proton and of one methyl group. The stereochemistry of A results in substantial long-range deshielding of the methyl and methine protons in question, or that of B causes long-range shielding, or both influences may be operative.

The following assignments for the n.m.r. absorptions may be made at once. The tertiary methyl groups 3, 4, and 7 in each dimer appear at 63 c.p.s., and the methyl 6 is 7 c.p.s. lower, at 70 c.p.s. This chemical shift difference is close to that observed, 6.5 c.p.s., between the methyl group at C-1 and the two methyls at C-7 of camphor.[5] The methine proton at 172 or

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) H. Staudinger and S. Schotz, *Ber.*, **53**, 1105 (1920).

(3) P. Yates and E. A. Chandross, *Tetrahedron Letters*, No. **20**, 1 (1959).

(4) C. Djerassi, R. Records, E. Bunnenberg, K. Mislow, and A. Moscowitz, *J. Am. Chem. Soc.*, **84**, 870 (1962).

(5) G. V. D. Tiers, "Table of Characteristic N.M.R. Shielding Values," Central Research Department, Minnesota Mining and Manufacturing Co., Minneapolis, Minn., Organic Section Project 737602, March 28, 1958.

175 c.p.s. in the dimers is 1; it is shifted downfield by the adjacent carbonyl group.[6] The methyl group 5 at 54 or 55 c.p.s. is shifted upfield in both dimers by the carbon–carbon double bond below it. These assignments leave only the methine proton 2 and the methyl group 8 unaccounted for.

From examination of Dreiding[7] stereomodels of the dimers III and IV, it is apparent that methyl group 8 in isomer III is in close proximity to and to the side of the C-4 carbonyl group and, hence, is deshielded.[6] The methine proton 2 in dimer III is to the side of carbonyl groups at C-2 and C-4 and, accordingly, is deshielded.[6] The methyl group 8 in isomer IV is located below the C-2 carbonyl function, and is therefore shifted to higher field.[6] The n.m.r. chemical shift data indicate that dimer A, which has the methine proton 2 and methyl group 8 at lower field, is isomer III, and B is IV. The more dextrorotatory isomer has the S configuration[8] at C-3 of the pyronone ring.

The assignments for n.m.r. absorptions are summarized in Table I.

TABLE I

N.M.R. SPECTRAL ASSIGNMENTS FOR THE CAMPHOKETENE DIMERS

Dimer	Proton type	Number	Chemical shift, c.p.s.
III, A	Methine	1	172
	Methine	2	166
	Methyl	6	70
	Methyl	3, 4, 7, 8	63
	Methyl	5	54
IV, B	Methine	1	175
	Methine	2	156
	Methyl	6	70
	Methyl	3, 4, 7	63
	Methyl	5, 8	55

This stereochemical assignment is consistent with predictions based on Brewster's[9] correlations of configuration and optical activity. The total difference in molecular rotation between structures III and IV is expected to be $+k(2C_{11} - O)(Ca - C)$, where Ca represents a carbonyl group, C_{11} an olefinic carbon, and the other symbols have their usual[9] meanings. Then $\Delta M(\text{III} - \text{IV}) = +215°$. The calculation predicts that III is the more dextrorotatory isomer. In fact, $\Delta M(\text{A} - \text{B}) = +367°$, and the correspondence between theory and the observed molecular rotation difference is satisfactory when structure III represents isomer A, and IV, B.

New applications of Brewster's postulates are of particular interest when, as in the present instance, the skeletal system of the molecules is quite dissimilar to those of the compounds used in the development of the postulates. An earlier new application to norbornane derivatives[10] led to only partial success.

(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 119f.

(7) A. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(8) *Cf.*, R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); this designation requires comparison of the third set of substituents from C-3.

(9) J. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959).

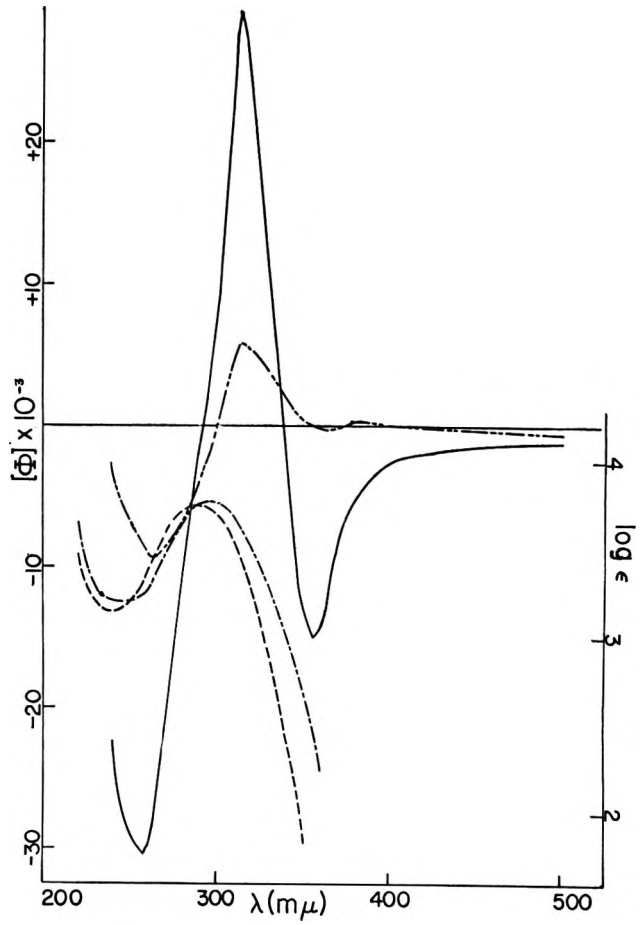


Fig. 1.—Optical rotatory dispersion and ultraviolet absorption curves for the camphoketene dimers A and B: o.r.d., A (— · · —), B (————); ultraviolet, A (- - - -), B (— - —).

Experimental[11]

Camphoketene Dimers.—Treatment of crude *d*-camphor-3-carbonyl chloride[2,12] with triethylamine in ether, followed by the usual work-up,[2] gave a mixture of the camphoketene dimers as yellow crystals (87% from *d*-camphor-3-carboxylic acid). Recrystallization from ether[2] gave dimer A as compact crystals, m.p. 151–152°, $[\alpha]_D$ +127° (c, 2.6); lit.[2] m.p. 152–153°, $[\alpha]_D$ +126.8°; lit.[3] m.p. 150–151.5°, $[\alpha]_D$ +132°.

The second solid was obtained after crystallization from methanol and had $[\alpha]_D$ + 65° (*c*, 2.3); lit.[2] $[\alpha]_D$ +62.9°, lit.[3] $[\alpha]_D$ +66.3°. The n.m.r. spectrum of this solid of $[\alpha]_D$ +65° showed methyl signals at 70, 63, and 54 c.p.s. below the internal standard, tetramethylsilane, with relative intensities 1.1:3.3:1.5. Repeated recrystallization from methanol led from the solid of $[\alpha]_D$ +65° to stout needles, m.p. 156–158°, $[\alpha]_D$ +23.7° (*c*, 1.2). The identity of this material as a camphoketene dimer (dimer B) was confirmed by infrared, n.m.r., and ultraviolet spectroscopic comparisons between the solid of $[\alpha]_D$ +65° and that of $[\alpha]_D$ +23.7°.

The n.m.r. data for methine and methyl protons of dimers A and B are shown in Table I. The o.r.d. data are given in Fig. 1.

(10) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *ibid.*, **83**, 3986 (1961).

(11) Melting points are reported as observed on a Kofler micro hot stage. The optical rotations at 589 mμ were determined in ethyl acetate at 26 ± 2°, l = 2, on a Zeiss polarimeter. The o.r.d. data were obtained in methanol with a Rudolph recording spectropolarimeter, Model 260-655-850. Ultraviolet spectra were determined in methanol with a Bausch and Lomb spectronic 505 spectrophotometer. The n.m.r. spectra were determined with deuteriochloroform solutions on a Varian A-60 instrument.

(12) N. Zelinsky, *Ber.*, **36**, 208 (1903).

The Stereochemistry of the Methylketene β-Lactone Dimer[1]

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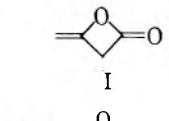
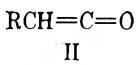
Received December 27, 1963

The stereochemistry of the methylketene β-lactone dimer has been deduced from dipole moment data. Carbon atoms 2 and 5 of the dimer are *trans*, as in formula VI. This assignment of stereochemistry has been confirmed by n.m.r. spectral comparisons between the methylketene β-lactone dimer and the intramolecular condensation product of tetramethylenediketene, 8-oxo-9-oxabicyclo[5.2.0]nonene-1.

Structure I for diketene is now generally accepted.[2] Aldoketenes (II) form both neutral dimers, having structures (III) analogous to that of diketene (I),[3-7] and acidic dimers that are derivatives (IV) of cyclobutane-1,3-dione.[8]



I



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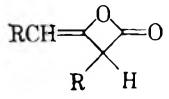
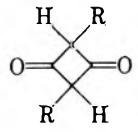


III



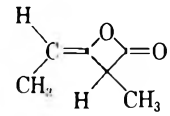
IV

The stereochemistry about the *exo*-cyclic double bond in the neutral aldoketene dimers (III) has not been established. That there may be two neutral methylketene dimers[8] and that two geometrical isomers are possible for structure III[7] have been recognized for some time, but no one has isolated two geometrical isomers of an aldoketene β-lactone dimer or suggested the geometrical disposition of substituents about the *exo*-cyclic double bond in the dimers III that can be prepared. The neutral methylketene dimer has been the subject of an electron diffraction study,[9] but the analysis did not afford an assignment of stereochemistry. Chemical approaches to the geometry of these dimers are rendered difficult by the lability of the lactone ring toward cleavage, which usually leads to stereochemically uninformative products.

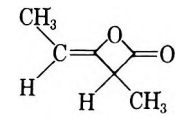
Investigation of the β-lactone dimers from methylketene and phenylketene by n.m.r. spectroscopy has shown that they are not mixtures of geometric isomers and probably have the same geometry.[10] No assignment of this stereochemistry, however, was possible.

Calculations and Results

The experimental data which make recognition of the stereochemistry of the methylketene β-lactone dimer possible are the electric dipole moments of diketene and the neutral methylketene dimer, 3.23 and 3.30 D., respectively.[3] To facilitate calculations based on the two possible geometrical isomers of the methylketene β-lactone dimer, V and VI, the following assumptions are made: V and VI have the same skeletal geometry as diketene[11]; they are planar; both C–C–H angles at C-4 are 120°; the C–C–H angle at C-2 is 114°; the methyl group at C-4 has a dipole moment of 0.35 ± 0.1 D.[12]; the methyl group at C-2 has a moment of 0.03 ± 0.03 D.[12]; and the dipole moments of the dimers may be approximated by a vector sum of bond and molecular electric dipole moments.[13]



V



VI

Let the oxygen and carbon atoms of the carbonyl groups of I, V, and VI define the positive x-axis, the lactone oxygen be on the plus y-axis, and θ designate the orientation of the dipole moment of diketene in this coordinant system. While θ is unknown, it should be small and positive; the carbonyl group must be the dominant polar influence in diketene.

Simple trigonometry and the assumptions set forth above lead to the equations

$$(3.30)^2 = [3.23\cos\theta_V + (0.35 \pm 0.1)\cos 42° + (0.03 \pm 0.03)\cos 57° \sin 13.5°]^2 + [3.23\sin\theta_V + (0.35 \pm 0.1)\sin 42° + (0.03 \pm 0.03)\cos 57°\cos 13.5°]^2 + [(0.03 \pm 0.03)\sin 57°]^2$$

$$(3.30)^2 = [3.23\cos\theta_{VI} + (0.35 \pm 0.1)\cos 78° + (0.03 \pm 0.03)\cos 57° \sin 13.5°]^2 + [3.23\sin\theta_{VI} - (0.35 \pm 0.1)\sin 78° + (0.03 \pm 0.03)\cos 57°\cos 13.5°]^2 + [(0.03 \pm 0.03)\sin 57°]^2$$

which have the solutions $\theta_V = 127 \pm 9°$ and $322 \pm 5°$, and $\theta_{VI} = 3 \pm 6°$ and $203 \pm 6°$. Only the calculation based on structure VI gives a plausible value for the orientation of the dipole moment of diketene. This result is sufficiently insensitive to reasonable variations in the initial assumptions and parameters for the group moments of the two methyl groups in the methylketene β-lactone dimer that the conclusion seems secure: the neutral methylketene dimer has the stereochemistry of formula VI, and in all probability, the other known aldoketene β-lactone dimers have the same geometry.

Independent evidence to corroborate this deduction of stereochemistry was sought.

Suberyl dichloride may be converted to cycloheptanone, presumably through the intermediates, tetramethylenediketene (VII) and the β,γ-unsaturated β-lac-

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) *Cf.*, V. V. Perekalin and T. A. Sokolva, *Usp. Khim.*, **25**, 1351 (1956).

(3) J. D. Roberts, R. Armstrong, R. F. Trimble, Jr., and M. Burg, *J. Am. Chem. Soc.*, **71**, 843 (1949).

(4) C. H. Hurd and C. A. Blanchard, *ibid.*, **72**, 1461 (1950).

(5) R. L. Wear, *ibid.*, **73**, 2390 (1951).

(6) A. S. Spriggs, C. M. Hill, and G. W. Senter, *ibid.*, **74**, 1555 (1952).

(7) J. R. Johnson and V. J. Shiner, Jr., *ibid.*, **75**, 1350 (1953).

(8) R. B. Woodward and G. Small, Jr., *ibid.*, **72**, 1297 (1950).

(9) J. Bregman and S. H. Bauer, *ibid.*, **77**, 1955 (1955).

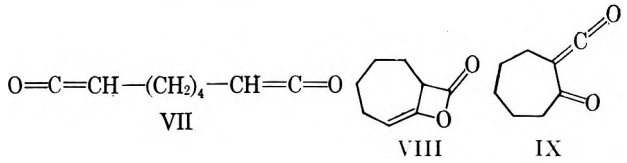
(10) J. E. Baldwin and J. D. Roberts, *ibid.*, **85**, 2444 (1963); and unpublished data.

(11) L. Katz and W. N. Lipscomb, *Acta Cryst.*, **5**, 313 (1952).

(12) *Cf.* C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, Chapter IX.

(13) Compare E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955); C. F. Wilcox, Jr., *ibid.*, **82**, 414 (1960).

tone VIII.[14] The postulated structure VIII would not be subject to undue steric strain and seems a reasonable conjecture. If this β,γ-unsaturated β-lactone of unambiguous stereochemistry could be isolated, it would be a valuable molecule for spectral comparisons with the methylene β-lactone dimer.



VII VIII IX

In the event, VIII was isolated and converted in 71% yield to cycloheptanone 2,4-dinitrophenylhydrazone. The infrared and the n.m.r. spectra [absorptions at 323 c.p.s., τ 4.62 (skewed triplet with some additional splitting, relative intensity 1); 238 c.p.s., τ 6.03 (complex multiplet, relative intensity 1); and 140–70 c.p.s., τ 7.7–8.8 (broad band, relative intensity 8)] of VIII clearly rule out any alternative formulation for the condensation product from VII, such as IX.[15]

The n.m.r. spectrum of VIII contains the desired information relevant to the stereochemistry of the methylketene β-lactone dimer. The α-hydrogen of the neutral methylketene dimer absorbs at 235.5 c.p.s., quite near to the α-hydrogen of VIII. But the chemical shift between the vinyl hydrogen of the neutral methylketene dimer (281.5 c.p.s.) and that of VIII is substantial—41.5 c.p.s. This fact suggests that the two vinyl hydrogens are in quite different magnetic environments, and therefore, that they have different stereochemistry.[16] The neutral methylketene dimer is thus VI, not V, in accord with the conclusions based on dipole moment data.

(14) A. T. Blomquist and R. D. Spencer, *J. Am. Chem. Soc.*, **69**, 472 (1947); **70**, 30 (1948).

(15) *Cf.* J. C. Sauer, *ibid.*, **69**, 2444 (1947); J. E. Baldwin, *J. Org. Chem.*, **28**, 3112 (1963).

Experimental[17]

8-Oxo-9-oxabicyclo[5.2.0]nonene-1 (VIII).—Suberyl dichloride was dehydrochlorinated with triethylamine in ether.[14] Flash distillation of the filtered reaction mixture at 1 mm. (bath temp., 135°) gave a colorless liquid having $\nu_{max}^{CCl_4}$ 1890 and 1725 cm.$^{-1}$, strong; 1925, 1855, 1820, 990, 935, 915, and 900 cm.$^{-1}$, medium. *Anal.* Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.93, 69.75; H, 7.77, 8.15.

The n.m.r. spectrum, described above, was determined with a solution 9.9% by weight in carbon tetrachloride on a Varian A-60 spectrometer. Tetramethylsilane was employed as the internal standard.

Cycloheptanone from VIII.—A 30.1-mg. sample of VIII was hydrolyzed with ethanolic potassium hydroxide,[14] cooled, neutralized with sulfuric acid, and diluted with a solution of 2,4-dinitrophenylhydrazine (83 mg.) in 5% ethanolic sulfuric acid. The solid which formed was collected and recrystallized from ethanol–ethyl acetate to give 45.4 mg. (71%) of cycloheptanone 2,4-dinitrophenylhydrazone, m.p. 140–143°, lit.[18] m.p. 147°. The crude derivative was purified by chromatography on Bentonite–kieselguhr[19] and identified by direct infrared spectral, thin layer chromatographic, and mixture melting point comparisons with authentic material (m.m.p. 145–147°).

(16) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 119f.

(17) Analyses are by J. Nemeth and associates, Urbana, Ill.

(18) The Merck Index, 7th Ed., Merck and Co., Inc., Rahway, N. J., 1960, p. 309.

(19) J. A. Elridge and M. Whalley, *Chem. Ind.* (London), 589 (1955).

The Acylation of Ketones with Methyl Dichlorofluoroacetate and Certain Related Reactions[1]

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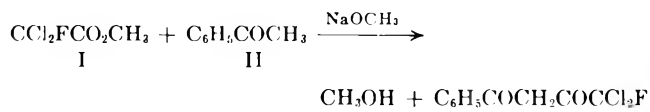
Received January 30, 1964

Several β-diketones of the type $RCOCH_2COCFCl_2$ have been prepared by the reaction of the appropriate ketones with methyl dichlorofluoroacetate in the presence of sodium methoxide. While 7-chloro-7-fluoronorcarane was obtained from the reaction of a mixture of cyclohexene and sodium methoxide with methyl dichlorofluoroacetate and *sym*-difluorotetrachloroacetone under appropriate conditions, a similar reaction with methyl dichlorofluoromethyl ketone gave a mixture of this chlorofluoronorcarane and methyl acetoacetate. A small amount of methyl oxalate and no 7,7-difluoronorcarane were obtained from a similar reaction with methyl chlorodifluoroacetate.

In a previous paper,[3] we reported the preparation of a series of β-diketones of the type $RCOCH_2COCF_2Cl$ in high yields by the acylation of a number of methyl ketones with methyl chlorodifluoroacetate. We now report the results of a study of the acylation of several methyl ketones with methyl dichlorofluoroacetate (I). Apparently there are no reported syntheses of β-diketones containing the dichlorofluoromethyl group.

The sodium methoxide-effected acylation of acetophenone (II) with I was studied first. When an ether solution of 1 equiv. of I was added rapidly (10 min.)



I II III

at room temperature to a suspension of 1 equiv. of sodium methoxide in ether followed by 1 equiv. of II (standard addition, the ester is added to the methoxide followed by the ketone), only a 14% yield of the β-diketone, benzoyldichlorofluoroacetylmethane (III), was obtained after a 20-hr. reaction time. It was felt that the low yield of III might be due to the possibility that some of I was decomposed by reaction with sodium methoxide. Accordingly, in an attempt to minimize the exposure of the ester to excess sodium

(1) This work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(2) This paper is based on part of a thesis presented by R. A. M. to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(3) R. A. Moore and R. Levine, *J. Org. Chem.*, **29**, 1439 (1964).

TABLE I

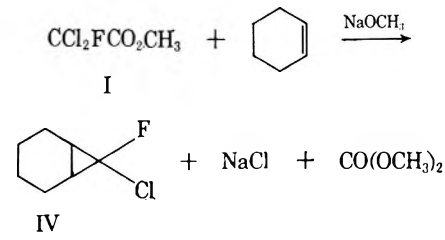
SYNTHESIS OF β-DIKETONES, $RCOCH_2COCFCl_2$, FROM METHYL KETONES AND METHYL DICHLOROFLUOROACETATE

R	Reaction time, hr. 0°	25°	Procedure	Yield, %	B.p., °C.	mm.	$n^{25}D$	Copper salt, m.p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
C_6H_5		20	S.A.[a]	14	129–131	4		265–266.5 dec.[g]	$C_{10}H_7Cl_2FO_2$	48.22	48.33	2.83	2.88
					34–35 (m.p.)[f]								
		24[b]	I.A.[a]	30									
		18[c]	I.A.	54									
	5[c]	18	I.A.	74									
CH_3	5[c]	18	I.A.	65	82.0–82.3	31	1.4810	181–182[f]	$C_5H_5Cl_2FO_2$	32.11	32.41	2.70	2.45
i-C_3H_7	5[c]	18	I.A.	18	102.0–103.0	33	1.4762	108–112 dec.[f]	$C_7H_9Cl_2FO_2$	39.09	39.21	4.22	4.19
	8[d]	16	S.A.	20									
Cyclopentanone	5[c]	18	I.A.	20	87.0–87.5	2.75	1.5080	175–179 dec.[f]	$C_7H_7Cl_2FO_2$	39.46	39.55	3.31	3.25
	8[d]	16	S.A.	48									
2-C_4H_3S[e]	8[d]	16	S.A.	71	100–102	0.4							
					57.6–58.6 (m.p.)[h]			238.5–239.5[f]	$C_8H_5Cl_2FO_2S$	37.66	37.30	1.98	2.07

[a] S.A. = standard addition; *i.e.*, the ester is added to sodium methoxide followed by the ketone. I.A. = inverse addition; *i.e.*, the ketone is added to sodium methoxide followed by the ester. [b] The ester is added over a 25-min. period. [c] The ester is added over a 2-hr. period. [d] The ester is added over a 15-min. period. [e] 2-C_4H_3S is the 2-thienyl radical. [f] Recrystallized from aqueous methanol. [g] Recrystallized from aqueous acetone. [h] Recrystallized from *n*-pentane.

methoxide, a reaction was effected in which the order of addition of the ester and ketone to sodium methoxide was reversed, the ester being added last (inverse addition, the ketone is added to the methoxide followed by the ester) over a more extended period of time, *i.e.*, 25 min. In this reaction the yield of III was increased to 30%. In addition, the hydrolysate (the reaction had been quenched with water) contained chloride ion, which indicates that the ester had been decomposed to some extent. When the last reaction was repeated except that the addition time of the ester was increased to 2 hr., the yield of III was raised to 53.5%.

Since the chlorine atoms of I appear to be labile and since Parham and Schweizer[4a] reported that dichlorocarbene is formed by the interaction of ethyl trichloroacetate with sodium methoxide, it was felt that a carbene might be formed in the methyl dichlorofluoroacetate–sodium methoxide system. Therefore, a reaction between I, sodium methoxide, and cyclohexene was performed using the procedure similar to that employed previously[4] in the analogous reaction with ethyl trichloroacetate. A mixture of equivalents of sodium methoxide and I in excess cyclohexene was stirred for 8 hr. at 0° in an ice bath. Then, the ice bath was removed with the intention of allowing the reaction mixture to stand overnight (16 hr.) at room temperature. However, after the reaction mixture had warmed to about 15°, an exothermic reaction ensued and the mixture refluxed without external heating for about 0.5 hr. After the mixture had cooled to room temperature it was allowed to stand for 16 hr. From the reaction mixture there was isolated a 35% yield of 7-chloro-7-fluoronorcarane (IV), whose properties are identical with those of the material prepared by Parham and Twelves[4b] by the reaction of dichlorofluoromethane with cyclohexene in the presence of potassium *t*-butoxide. A 43% yield of IV was obtained by maintaining the reaction mixture at 30–40° for 45 min. followed by 23 hr. at room temperature.



To show that chlorofluorocarbene is formed when the Claisen condensation is effected between I, II, and sodium methoxide at room temperature, this reaction was repeated under standard addition conditions except that cyclohexene was added as a chlorofluorocarbene trap. In this way, there was obtained IV (27%) and III (9%) in addition to recovered I (10%) and II (81%).

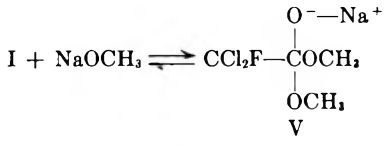
A method was devised for minimizing carbene formation when the reaction of the ester (I) with sodium methoxide in cyclohexene indicated that the formation of chlorofluorocarbene seems to be temperature-dependent. It appears that if, after exposing I to sodium methoxide for 8 hr. at 0°, enough of I remained so that when the temperature was raised to 15° an exothermic reaction developed (*vide supra*), then at 0° the rate of carbene formation is probably very slow. Thus, it seemed possible that by lowering the reaction temperature, better yields of the β-diketone (III) might be obtained by slowing down or eliminating the competing carbene-forming reaction. Some support for this argument was obtained by performing a reaction between I, II, and sodium methoxide at 0°. The ketone (II) was added to a suspension of sodium methoxide in ether and then the mixture was cooled to 0° in an ice bath. The ester (I) was then added at 0° over a 2-hr. period and stirring was continued for an additional 3 hr. at 0°. The ice bath was removed and

(4) (a) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24**, 1733 (1959); (b) W. E. Parham and R. R. Twelves, *ibid.*, **22**, 730 (1957).

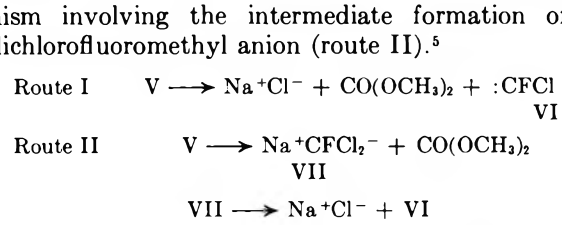
the mixture was allowed to stand for 18 hr. at room temperature and subsequently processed to give 73.5% yield of the β-diketone (III).

The same conditions were employed between I, acetone, and sodium methoxide to give a 65% yield of 1,1-dichloro-1-fluoroacetylacetone. However, when the same cooling period (5 hr.) was used in similar reactions between I and methyl isopropyl ketone, and between I and cyclopentanone, yields of only 18 and 20% of the respective β-diketones were obtained. When these last two reactions were repeated except that the standard addition method was used and the cooling period was extended to 8 hr. followed by 16 hr. at room temperature, there were obtained 20 and 48%, respectively, of dichlorofluoroacetylisobutyrylmethane and 2-dichlorofluoroacetylcyclopentanone. Similarly, 2-acetylthiophene gave a 71% yield of dichlorofluoroacetyl-2-thenoylmethane. The results of the experiments described above appear in Table I.

It is not known with certainty why the formation of chlorofluorocarbene in the methyl dichlorofluoroacetate–sodium methoxide system is temperature dependent. The intermediate involved in these reactions is undoubtedly the adduct V, which is formed by the addition of sodium methoxide across the carbonyl group of I. This adduct is similar to that which Perham and Schweizer[4a] suggest as an intermediate when dichlorocarbene is formed in the ethyl trichloroacetate–sodium methoxide system.



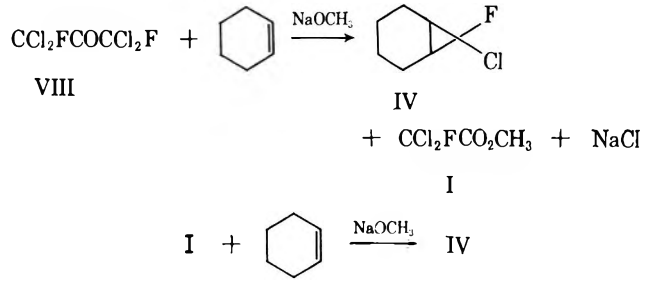
Then, chlorofluorocarbene (VI) could be formed from V by a concerted elimination of sodium chloride and methyl carbonate (route I) or by a two-step mechanism involving the intermediate formation of the dichlorofluoromethyl anion (route II).[5]



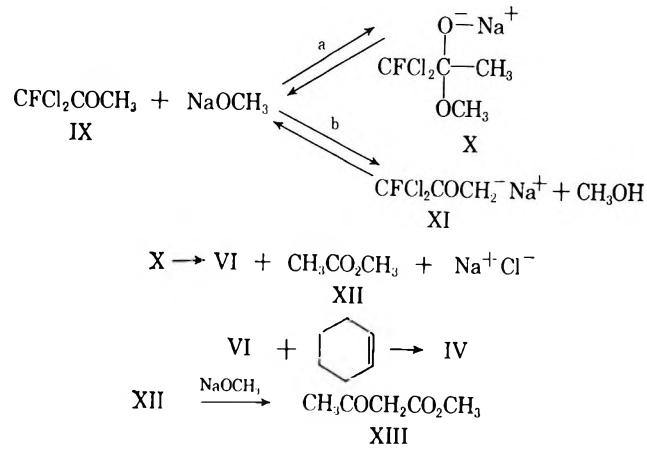
Regardless of whether route I or II operates in the methyl dichlorofluoroacetate–sodium methoxide system, the ease of carbene formation from V appears to be related to the ease of rupturing the carbon to carbon bond between the dichlorofluoromethyl group and the adjacent potential carbonyl carbon atom. Evidently the bond breaking step is thermally sensitive with the intermediate (V) being comparatively stable at 0° but unstable at room temperature. It is interesting to note that in the ethyl trichloroacetate–sodium methoxide system, the intermediate comparable to V must be unstable even at 0° since an 88% yield of 7,7-dichloronorcarane[4a] was obtained when ethyl trichloroacetate was treated at 0° with sodium methoxide in excess cyclohexene.

(5) Route II appears to be more reasonable than route I since it has been shown that VI is formed in a two-step process involving the prior formation of the dichlorofluoromethide ion in both the basic hydrolysis of dichlorofluoromethane [J. Hine and N. W. Burske, *J. Am. Chem. Soc.*, **78**, 337 (1956)] and in the decarboxylation of the dichlorofluoroacetate ion [J. Hine and D. C. Duffey, *ibid.*, **81**, 1129 (1959)].

Since methyl dichlorofluoroacetate (I) has been shown to be a carbene source when treated with sodium methoxide, it was of interest to see whether other systems containing the dichlorofluoroacetyl and also the chlorodifluoroacetyl groups could give rise to carbenes. Three additional reactions were studied which might give rise to chlorofluorocarbene. When *sym*-difluorotetrachloroacetone (VIII) was treated with sodium methoxide in cyclohexene, chlorofluorocarbene was formed as indicated by the isolation of IV in 38% yield.[6] It is suggested that the reaction takes place by the following scheme which suggests that part of IV may arise from the reaction of I with sodium methoxide and cyclohexene, a reaction which we have shown takes place.



However, when sodium dichlorofluoroacetate was treated with sodium methoxide in refluxing cyclohexene none of the norcarane was obtained. In addition, it was found that the reaction of methyl dichlorofluoromethyl ketone (IX), sodium methoxide, and cyclohexene gave a low yield (3.4%) of norcarane IV and a trace of methyl acetoacetate (XIII). The origin of IV and XIII can be rationalized according to the following scheme.



It is suggested that sodium methoxide can react with IX by (a) addition across the carbonyl group to give the adduct X and (b) by abstraction of an α-hydrogen atom to give the ketone anion XI, a reaction which apparently does not occur to an appreciable extent. Then, X may decompose to give VI, sodium chloride, and methyl acetate (XII). The carbene (VI) then reacts with cyclohexene to give IV and XII is self-condensed by sodium methoxide to give XIII.

Three reactions were also attempted as possible routes to difluorocarbene. Thus, methyl chlorodi-

(6) Recently a 36% yield of IV has been reported from the reaction of VII, potassium *t*-butoxide, and cyclohexene [B. Farah and S. Horensky, *J. Org. Chem.*, **28**, 2494 (1963)].

fluoroacetate (XIV) was treated with sodium methoxide in cyclohexene at 40–60° for 34 hr.[7a] However, no 7,7-difluoronorcarane (XVII) was isolated. Instead, there was obtained a small amount of methyl oxalate (XVI) which was probably formed by a nucleophilic displacement of chloride ion on carbon by methoxide followed by hydrolysis. This observation is of interest since Hine and Duffey[7b] noted that oxalic acid is formed

$$\underset{\text{XIV}}{CF_2ClCO_2CH_3} + OCH_3^- \longrightarrow \underset{\text{XV}}{CH_3OCFCO_2CH_3} + Cl^-$$

$$\text{XV} \xrightarrow{H_2O} \underset{\text{XVI}}{(CO_2CH_3)_2}$$

during the decarboxylation of chlorodifluoroacetate ion in aqueous solution.

Although Haszeldine, *et al.*,[8] have obtained an 11% yield of XVII when sodium difluorochloroacetate was thermally decomposed in a mixture of cyclohexene and diglyme, it has now been observed that heating a mixture of this salt and sodium methoxide in refluxing cyclohexene gave none of XVII. In addition, while Grant and Cassie[9] obtained a 59% yield of 7,7-dichloronorcarane from the reaction of hexachloroacetone with cyclohexene in the presence of sodium methoxide for 15 hr. (5 hr. at 0–5° and 10 hr. at 25°), none of XVI was obtained when a similar reaction was performed in the present study except that *sym*-dichlorotetrafluoroacetone was used with a reaction time of 25 hr. and a reaction temperature of 45–50°. A small amount of the starting ketone (20%) was isolated as its hydrate.

Experimental

Halogenated Intermediates. A. Methyl Dichlorofluoroacetate.—A mixture of dichlorofluoroacetic acid (147.0 g., 1.0 mole), absolute methanol (48.0 g., 1.5 moles), and 50 ml. of concentrated sulfuric acid was refluxed for 5 hr. and allowed to stand at room temperature for 17 hr. The crude ester was distilled from the reaction mixture and was washed successively with a saturated sodium carbonate solution, a saturated calcium chloride solution, and finally with water. It was distilled from phosphorus pentoxide to give 145 g. (90%) of methyl dichlorofluoroacetate, b.p. 114.5–115.5° at 732 mm., $n^{25}D$ 1.4024.[10]

B. Methyl Dichlorofluoromethyl Ketone.—Dichlorofluoroacetic acid (44.1 g., 0.3 mole) dissolved in 50 ml. of *n*-butyl ether was added, over a 2-hr. period at 0° to a rapidly stirred solution of methylmagnesium iodide (0.9 mole in 400 ml. of *n*-butyl ether). The mixture was stirred at 0° for 6 hr. more and then processed using the earlier procedure[11] for the preparation of ketones containing perhaloalkyl groups to give 16.5 g. (38.0%) of methyl dichlorofluoromethyl ketone, b.p. 94–95° at 744 mm., $n^{25}D$ 1.4025.

Anal. Calcd. for $C_3H_3Cl_2FO$: C, 24.85; H, 2.09. Found: C, 24.94; H, 2.03.

Acylation of Acetophenone with Methyl Dichlorofluoroacetate.—To commercial (Olin Mathieson) 95% sodium methoxide (6.0 g., 0.105 mole) suspended in 100 ml. of anhydrous ether, acetophenone (12.0 g., 0.100 mole) dissolved in 15 ml. of anhydrous ether was added in 10 min. To the rapidly stirred mixture which was maintained at 0° by an ice bath, methyl dichlorofluoroacetate (16.1 g., 0.100 mole) dissolved in 30 ml. of anhydrous ether was added over a 2-hr. period. After 3 additional hr. of stirring at 0°, the reaction mixture was allowed to stand at room temperature for 18 hr. The reaction was quenched and processed in the customary manner[3] to give 18.3 g. (73.5%) of benzoyldichlorofluoroacetylmethane, b.p. 129–131° at 4 mm.

Reactions Involving the Formation of Chlorofluorocarbene. A. From Methyl Dichlorofluoroacetate.—Methyl dichlorofluoroacetate (32.2 g., 0.20 mole) was added all at once to sodium methoxide (12.0 g., 0.21 mole) suspended in 140 ml. of dry cyclohexene and cooled to 0° in an ice bath. The reaction mixture was stirred for 8 hr. at 0° in a nitrogen atmosphere at which time the ice bath was removed. Upon warming to about 15° an exothermic reaction took place and the mixture refluxed for about 0.5 hr. without external heating and then cooled slowly to room temperature. The mixture was allowed to stand for 16 hr. at room temperature and then was quenched by the addition of 200 ml. of water. The phases were separated and the aqueous phase was extracted with two 100-ml. portions of *n*-pentane. The combined organic phases were dried over anhydrous magnesium sulfate. The solvent and the excess cyclohexene were removed at atmospheric pressure and the residue was distilled *in vacuo* to give 10.5 g. (35%) of 7-chloro-7-fluoronorcarane,[6] b.p. 69.5° at 34 mm., $n^{26}D$ 1.4576. The infrared spectrum of the product was superimposable on that of an authentic sample.

B. From the Reaction of Methyl Dichlorofluoroacetate with Sodium Methoxide, Acetophenone, and Cyclohexene.—Methyl dichlorofluoroacetate (48.3 g., 0.300 mole) in 45 ml. of anhydrous ethyl ether was added to a rapidly stirred slurry of 95% sodium methoxide (18.0 g., 0.315 mole), anhydrous ethyl ether (300 ml.), and cyclohexene (300 ml.). Acetophenone (36.0 g., 0.300 mole in 45 ml. of anhydrous ether) was added in 5 min.; the mixture was stirred for 18 hr. at room temperature and processed in the regular manner[3] to give, in addition to the excess cyclohexene solvent, acetophenone (29.0 g., 81%, b.p. 103–112° at 35 mm.), methyl dichlorofluoroacetate (4.8 g., 10%, b.p. 110–120° at 735 mm.), 7-chloro-7-fluoronorcarane (12.0 g., 27%, b.p. 69–75° at 35 mm.), and benzoyldichlorofluoroacetylmethane (8.3 g., 9%, b.p. 131–135° at 4 mm.).

C. From *sym*-Difluorotetrachloroacetone.—To a rapidly stirred suspension of 95% sodium methoxide (13.5 g., 0.25 mole) in cyclohexene (82.0 g., 1.0 mole), *sym*-difluorotetrachloroacetone (23.2 g., 0.1 mole) was added over a period of 1 hr. at such a rate that the reaction temperature remained at 35–40°. It was necessary to cool the reaction mixture intermittently for 2 hr. after the addition of the ketone to maintain the reaction temperature at 35–40°. The mixture was stirred for 6 hr. at room temperature and then was allowed to stand for 19 hr. The reaction was quenched as described above for A to give 7-chloro-7-fluoronorcarane (11.3 g., 38%, b.p. 50–54° at 14–16 mm.) in addition to recovered cyclohexene.

D. From Methyl Dichlorofluoromethyl Ketone.—To 95% sodium methoxide (13.5 g., 0.25 mole) suspended in cyclohexene (82.0 g., 1.0 mole), methyl dichlorofluoromethyl ketone (14.5 g., 0.10 mole) was added in 45 min. at such a rate that the reaction temperature did not exceed 40°. The mixture was stirred for 10 hr. at room temperature and hydrolyzed with 100 ml. of 10% sulfuric acid. The phases were separated and the aqueous phase was extracted with several portions of ether. The combined organic phases were dried over Drierite and the ether and unchanged cyclohexene were removed at atmospheric pressure. Distillation of the residue gave 1.0 g. of a liquid, b.p. 87–90° at 79 mm., which gave a positive test with alcoholic ferric chloride solution and suggested the presence of a β-keto ester. The mixture was dissolved in ether and was extracted with 2% sodium hydroxide solution to remove the β-keto ester. The ether layer was dried and distilled to give 0.5 g. (3.4%) of 7-chloro-7-fluoronorcarane (b.p. 62–62.5° at 24 mm., $n^{25}D$ 1.4572) whose infrared spectrum was superimposable on that of an authentic sample. The basic extract was acidified with dilute sulfuric acid and extracted with ether. The ether extracts were concentrated to give methyl acetoacetate (0.1 g.) which gave a semicarbazone, m.p. 151–152° alone and when mixed with an authentic sample,[12] and whose infrared spectrum was superimposable on that of an authentic sample.

Reaction of Methyl Difluorochloroacetate, Cyclohexene, and Sodium Methoxide.—Methyl difluorochloroacetate (36.0 g., 0.25 mole) was added in 10 min. to a rapidly stirred suspension of 95%

(7) (a) A higher temperature was used than in the analogous reaction with I which gave a 35–43% (*vide supra*) yield of 7-chloro-7 fluoronorcarane, since it was believed that XIV would be more stable than I to cleavage by sodium methoxide; (b) J. Hine and D. C. Duffey, *J. Am. Chem. Soc.*, **81**, 1131 (1959).

(8) J. M. Birchall, G. W. Gross, and R. N. Haszeldine, *Proc. Chem. Soc.*, 81 (1960).

(9) F. W. Grant and W. B. Cassie, *J. Org. Chem.*, **25**, 1433 (1960).

(10) E. Gryszkewiez-Trochimowski, A. Sporzynski, and J. Wnuk, *Rec. trav. chim.*, **66**, 419 (1947).

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(12) H. Staudinger and H. Becker, *Ber.*, **50**, 1021 (1917).

sodium methoxide (17.3 g., 0.32 mole) in 250 ml. of cyclohexene under a nitrogen atmosphere. During the course of the addition of the ester, the reaction temperature rose to 45° and subsequently the reaction mixture assumed a gel-like consistency. The reaction mixture was warmed to about 65° when an exothermic reaction occurred and the mixture refluxed without external heating for about 30 min. After the reaction temperature had dropped to 40°, the reaction was maintained at 40° for 10 hr. by external heating and then the mixture was heated to and maintained at 60° for 24 hr. The reaction was quenched by the addition of 200 ml. of water, the phases were separated, and the organic phase was extracted with three 100-ml. portions of *n*-pentane. The combined organic phases were dried over Drierite. After removing the *n*-pentane and the cyclohexene, a small residue remained, which on distillation gave 0.6 g. (2.4%) of methyl oxalate, b.p. 159–161° at 735 mm., m.p. 53–54°. The infrared spectrum of this ester was superimposable on that of an authentic sample of methyl oxalate.

Polymeric Peroxide of 2,5-Dimethyl-2,4-hexadiene and a New Selective Reduction of Its Peroxide Linkage

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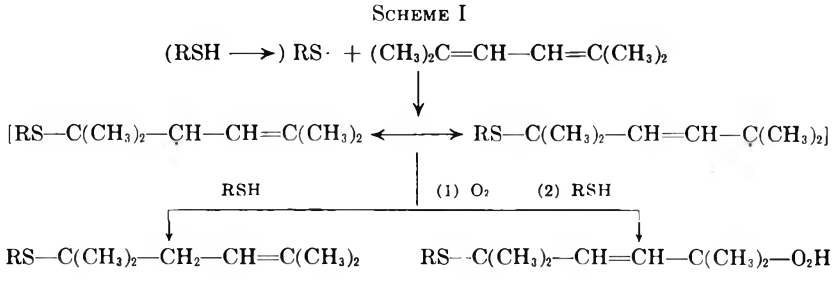
The autoxidation of 2,5-dimethyl-2,4-hexadiene affords in good yield the corresponding *trans*-1,4-polyperoxide as the only detectable product. This appears to be the first completely selective autoxidation of an acyclic conjugated diene. The *trans*-1,4 structure of the polyperoxide was established by infrared and n.m.r. analysis and by the results of reduction reactions. Catalytic hydrogenation of the polyperoxide produced 2,5-dimethylhexane-2,5-diol in high yield. During base-catalyzed reduction with an aromatic thiol, on the other hand, only the peroxide linkages were cleaved to yield *trans*-2,5-dimethyl-3-hexene-2,5-diol in 75% yield. The latter reaction represents a new method for the selective reduction of the O–O bond in polyperoxides containing olefinic linkages.

Previous reports from this laboratory have indicated that there is a correlation between the structure of a conjugated diene and the course of its free-radical reactions.[3] If the initial allylic-radical intermediate enters into a reaction requiring significant activation energy, the thermodynamically more stable products are formed.[4-6] If, on the other hand, the allylic radical undergoes a reaction requiring little or no activation energy, the thermodynamically less stable products are produced.[4,7] Typical examples of this principle are thiol addition and thiol co-oxidation reactions[4] (see Scheme I).

SCHEME I



The autoxidation of conjugated dienes to form polymeric peroxides resembles the above-mentioned co-oxidation reaction in its second propagation step. In both cases, an allylic radical intermediate combines with the oxygen diradical in a step of negligible activation energy. One might therefore anticipate similar product orientations for the two reactions. However, to the best of our knowledge, completely selective autoxidation reactions of acyclic conjugated dienes have never been observed.

In studying the autoxidation of 1,3-butadiene, Handy and Rothrock[8] showed that both 1,2- and 1,4-addition of oxygen occurred. In a series of papers, Kern and co-workers reported the autoxidation of chloroprene,[9,10] isoprene,[11] and 2,3-dimethyl-1,3-butadiene.[11-13] They arrived at the conclusion that isoprene and 2,3-dimethyl-1,3-butadiene each form 1,2-polyperoxides. However, their published data do not prove that these were the sole reaction products. In a later study Kawahara[14] indeed found that the autoxidation of 2,3-dimethyl-1,3-butadiene is a more complex reaction and specifically mentioned that 1,4-addition may also occur.

A polymeric peroxide of 2,5-dimethyl-2,4-hexadiene had also been reported previously by Harper and coworkers.[15] Although these workers suggested a 1,4-

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(3) For a summarized treatment of this subject see A. A. Oswald and K. Griesbaum, "Free Radical Addition of Thiols to Diolefins and Acetylenes," in "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., in press.

(4) A. A. Oswald, B. E. Hudson, Jr., G. Rodgers, and F. Noel, *J. Org. Chem.*, **27**, 2439 (1962).

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(10) See also A. L. Klebanskii and R. M. Sorokina, *Zh. Prikl. Khim.*, **35**, 2735 (1962).

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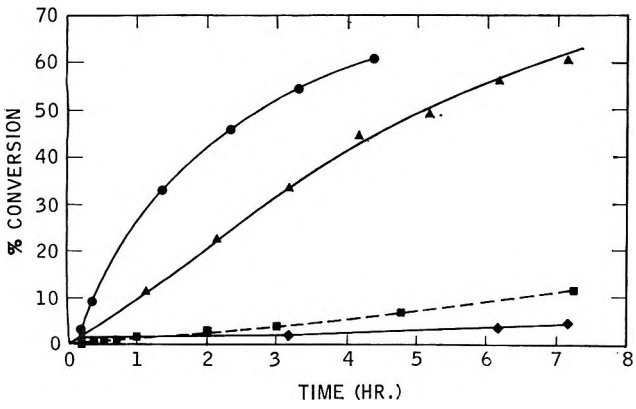


Fig. 1.—Autoxidation of 2,5-dimethyl-2,4-hexadiene under different conditions: ●, no solvent, ultraviolet irradiation; ▲, 0.35 *M* benzene solution, ultraviolet irradiation; ■, no solvent, no irradiation; ◆, 0.35 *M* benzene solution, 10 min. of ultraviolet irradiation.

structure for their polyperoxide, they did not produce any experimental evidence for it. Furthermore, they did not report any yields, so that no conclusions could be drawn as to the selectivity of their autoxidation reaction. Since it was found recently in this laboratory that 2,5-dimethyl-2,4-hexadiene could be co-oxidized in an exclusively *trans*-1,4 manner,[4] it seemed probable that the autoxidation of this same diene might indeed exhibit a similar selectivity. Therefore, we examined the latter reaction in more detail.

Selective reduction of O–O bonds in polyperoxides containing olefinic unsaturation have been achieved in moderate yields, using lithium aluminum hydride[8,14] as reducing agent. Catalytic hydrogenation with Adams catalyst,[15] on the other hand, has been claimed to attack the C=C– rather than the O–O bonds. Mayo and Miller[16] found that hydrogen sulfide or mercaptans under weakly basic conditions are good reducing agents for styrene polyperoxide. However, similar reactions with polyperoxides containing olefinic bonds have apparently remained unexamined. Recently we found that thiols in the presence of catalytic amounts of amines can be used for the selective reduction of unsaturated hydroperoxides.[17] This prompted us to try a similar thiol method for the reduction of unsaturated dialkyl polyperoxides.

Results

Autoxidation of the Diene.—The autoxidation of 2,5-dimethyl-2,4-hexadiene (I) was carried out on the neat liquid and in benzene solution. The degree of conversion was followed by quantitative n.m.r. analyses of the reaction mixtures. This method allowed us at the same time to check the selectivity of the reaction towards the formation of a uniform product.

The fastest rates were observed for the ultraviolet-catalyzed autoxidation of the undiluted diene. Within 3 hr., 52% of the diene had reacted to form the polyperoxide II with essentially complete selectivity (Fig. 1). The rate of this reaction dropped continually with increasing conversion. This might be explained by a gradual decrease of the oxygen diffusion due to the increasing viscosity of the reaction mixture. At a conversion level of 60%, the reaction mixture became heterogeneous as the polyperoxide began to separate as a colorless semisolid.

Autoxidation of the undiluted diene in the absence of ultraviolet initiation proceeded at a much slower rate. The reaction had a pronounced induction period of 10–15 min. and reached a conversion of only 4% after 3 hr. (*cf.* 52% conversion in the former case).

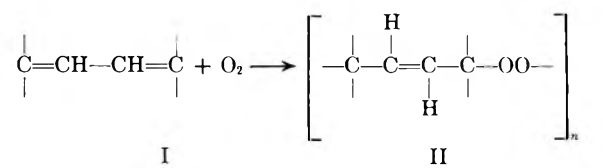
Autoxidation of the diene in a 0.35 *M* benzene solution showed some marked differences. The ultraviolet-catalyzed reaction proceeded at a slower, but more constant rate than that of the undiluted diene. Both these effects may be due to the dilution of the reaction mixture. When the ultraviolet irradiation was discontinued, on the other hand, the autoxidation rate decreased abruptly. The noninitiated oxidation in benzene solution, did not show any detectable conversion even after 20 hr.

Polyperoxide of the Diene.—The peroxide was usually prepared by ultraviolet light catalyzed autoxidation of the undiluted diene. The pure polyperoxide could be isolated from the reaction mixtures in up to 84% yield, the remainder being the unchanged diene.

After recrystallization from methanol, the polyperoxide II, m.p. 62–65°, had an average molecular weight of 1520, corresponding to 10–11 repeating units. It was very insensitive towards shock, flashed quite moderately when heated over an open flame, and was only slowly reduced by sodium iodide in acetic acid at room temperature. However, on heating in sodium iodide–acetic acid, about 90% of the calculated active oxygen could be detected.

The n.m.r. spectrum of the polyperoxide (Table I) showed only two signals with the relative intensities of 1:6, thus demonstrating the presence of only one compound, the 1,4-autoxidation product. The shift of the double bond during the reaction from the α- to the β-position relative to the methyl groups changed the spectrum characteristically. While the methyl groups in the diene appeared as two separate signals resulting from the *cis* and *trans* position relative to the olefinic protons, they were all equivalent in the polyperoxide due to free rotation around the C–C single bonds and gave rise to a sharp singlet, shifted to higher field by about 0.45 p.p.m. The olefinic protons appeared as a sharp singlet also shifted to higher field compared to the corresponding signal in the conjugated diene. These changes are in full agreement with results obtained on analogous olefinic compounds.[18]

The *trans* configuration of the polyperoxide was indicated by a strong infrared absorption band at 10.2 μ[19a] and a very weak absorption at 5.95 μ[19b] (Table II). This assignment was further supported by reduction experiments and by n.m.r. studies as discussed below.



I II

(16) F. R. Mayo and A. A. Miller, *J. Am. Chem. Soc.*, **78**, 1023 (1956).

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(19) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, (a) p. 45, (b) p. 36, (c) p. 96.

TABLE I

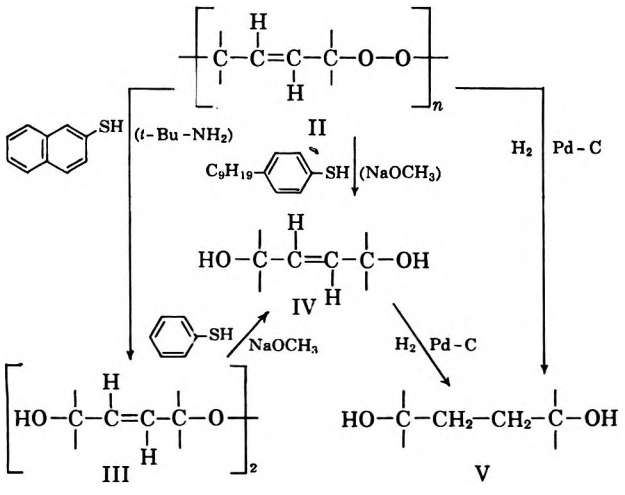
PARAMETERS OF N.M.R. SPECTRA OF 2,5-DIMETHYL-2,4-HEXADIENE AND ITS OXIDATION PRODUCTS[a]

Compound	Chemical shifts of structural units[b]			
	$-\overset{CH_3}{\underset{CH_3}{C}}-$	$=\overset{H}{C}-$	$-CH_2-CH_2-$	$O-H^c$
A CH_3 ... CH_3 A B CH_3 ... CH_3 B	A: 1.73[d] B: s 1.78	s 5.97[e]		
$\left[-(CH_3)_2C-\overset{H}{\underset{|}{C}}=C-C(CH_3)_2-OO-\right]_n$	s 1.30	s 5.70		
$\left[HO-(CH_3)_2C-\overset{H}{\underset{|}{C}}=C-C(CH_3)_2-O-\right]_2$	s 1.30	s 5.68		3.50
$HO-(CH_3)_2C-\overset{H}{\underset{|}{C}}=C-C(CH_3)_2-OH$	s 1.32	s 5.80		s 2.82
$HO-(CH_3)_2C-\overset{H}{\underset{|}{C}}=\overset{H}{\underset{|}{C}}-C(CH_3)_2-OH$	s 1.40	s 5.35		s 1.50
$HO-(CH_3)_2C-CH_2-CH_2-C(CH_3)_2OH$	s 1.23		s 1.58	s 2.20

[a] $CDCl_3$ as a solvent. [b] Downfield from tetramethylsilane, internal reference; p.p.m.; s = singlet. [c] The positions of these signals may vary with the nature of the solvent and the concentration. [d] Unresolved doublet, assigned the *trans*-methyl group since it shows a remote splitting ($J \sim 0.5$ c.p.s.) by the *trans*-vinyl protons (L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p. 85); the *cis*-methyl group signal shows no coupling and appears as a sharp singlet. [e] Broadened owing to coupling to the *trans*-methyl groups.

All these data suggested that the autoxidation of 2,5-dimethyl-2,4-hexadiene occurred in a selective *trans*-1,4 manner.[20]

Reduction of the Polyperoxide.—The proposed *trans*-1,4 structure of the polyperoxide II was further proven by the following series of reduction reactions.



Catalytic hydrogenation on palladium–charcoal under pressure reduced both the C=C– and the O–O bonds to give 2,5-dimethylhexane-2,5-diol (V) in almost quantitative yield.

t-Butylamine-catalyzed reduction with 2-naphthalenethiol attacked the O–O bonds selectively. This reaction, however, did not produce the anticipated unsaturated diol IV, but instead only the partially reduced product III as evidenced from its positive peroxide test with sodium iodide in acetic acid. The infrared spectrum of this compound (m.p. 58–59°) had a strong OH absorption at 3.0 μ.[19c] The n.m.r. spectrum showed three singlets with the relative intensities of approximately 1:2:12, corresponding to the hydroxy, vinyl, and methyl protons, respectively. The presence of a strong infrared band (in carbon tetrachloride solution) at 9.68 μ that was not present in the spectrum of either II or IV convinced us that III was not an eutectic mixture of the diol IV and the starting polyperoxide II. Furthermore, a synthetic mixture of the polyperoxide II and the diol IV exhibited an n.m.r. spectrum in which all signals characteristic of the individual components clearly were separated. On the basis of this evidence and the relative intensities of the n.m.r. signals, structure III is suggested for this partially reduced product. The successful further reduction of III with thiophenol in the presence of a base to form *trans*-2,5-dimethyl-3-hexene-2,5-diol furnished additional proof for this structure.

Complete reduction of the peroxy linkages of the polyperoxide II was achieved by using a stronger base as catalyst and higher reaction temperatures. When a mixture of the polyperoxide, 4-nonylthiophenol, and catalytic amounts of sodium methylate was heated under vacuum, a rapid exothermic reaction occurred at 130–140°. This reaction yielded 75% of *trans*-2,5-dimethyl-3-hexene-2,5-diol (IV). The residue contained 4-nonylphenyl disulfide, indicating that the following reaction took place.

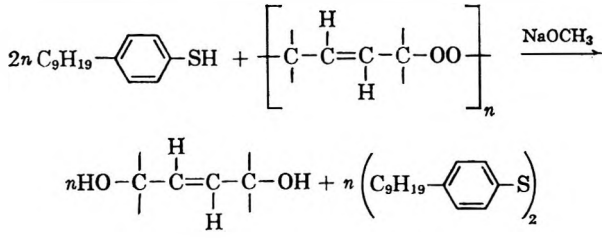
(20) From here on, methyl groups are represented by unsatisfied bonds in the formula.

TABLE II

INFRARED SPECTRA OF 2,5-DIMETHYL-2,4-HEXADIENE AND ITS OXIDATION PRODUCTS[a]

Compound	Stretching region: OH	Stretching region: =C—H	Stretching region: C=C	—C(CH₃)₂— deformation	Other				
$(CH_3)_2C{=}CH{-}CH{=}C(CH_3)_2$[b]	...	3.30 m	6.15 m	7.22 s 7.27 s				8.54 m	
$\left[-(CH_3)_2C{-}\underset{H}{C}{=}C{-}C(CH_3)_2{-}OO-\right]_n$	...	3.31 i	5.95 w	7.27 s 7.36 s	7.75 m	7.97 s		8.55 s	8.82 vs
$HO{-}\left[(CH_3)_2C{-}\underset{H}{C}{=}C{-}C(CH_3)_2{-}O\right]_2$	3.00 vs	3.31 i		7.26 s 7.35 s	7.75 m	7.95 s		8.55 i	8.80 vs
$HO{-}(CH_3)_2C{-}\underset{H}{C}{=}C{-}C(CH_3)_2OH$[c]	3.00 vs	3.31 w	6.12 w	7.30 s 7.37 s	7.83 s			8.14 s	8.85 vs
$HO{-}(CH_3)_2C{-}\underset{H}{C}{=}\underset{H}{C}{-}C(CH_3)_2OH$[c]	3.00 vs	3.30 i 3.30	6.05 w	7.25 s 7.35 s	7.68 m	7.99 w	8.32 m	8.45 s	8.64 vs
$HO{-}(CH_3)_2C{-}CH_2{-}CH_2{-}C(CH_3)_2OH$[c]	3.05 vs	...	...	7.27 s 7.33 s	7.64 m	7.77 s	8.00 s	8.30 s	8.70 vs

[a] Characteristic absorption peaks: vs, very strong; s, strong; m, medium; w, weak; i, inflection. [b] No solvent. [c] KBr pellet.



The structure of the diol (IV) was established by subsequent catalytic hydrogenation to form 2,5-dimethylhexane-2,5-diol (V), and by its n.m.r. spectrum (Table I). Its *trans* configuration[21] was confirmed by agreement of its melting point[22,23] and the position of typical infrared bands[23] with those reported for authentic samples.

We realized that the exclusive formation of a *trans*-diol in the selective reduction reaction did not necessarily prove the proposed *trans* configuration of the polyperoxide II, since isomerization could occur under the conditions of the reduction reaction. To exclude the possible intermediacy of a *cis*-diol, we prepared the corresponding *cis*-2,5-dimethyl-3-hexene-2,5-diol and treated it under the same conditions. No isomerization was observed. Since there is no apparent reason to assume that *cis–trans* isomerization of a *cis*-polyperoxide would occur more easily than that of a *cis*-diol, we feel that this experiment adds strong support to the proposed *trans* configuration of the polyperoxide II.

This was further substantiated by a comparison of the n.m.r. spectra of all of our products with that of the *cis*-diol (Table I). From the fact that both the methyl and the vinyl proton signals of the dimeric peroxide III appeared as singlets, it was evident that the change from the structural unit of a $(CH_3)_2C{-}O{-}O$ to that of a $(CH_3)_2C{-}OH$ group does not exert a noticeable chemical shift of these signals (the same is true for *t*-butyl alcohol and *t*-butyl hydroperoxide). A change of the configuration at the double bond, however, does give rise to a significant chemical shift, as can be seen by a comparison of the spectra of *cis*- and *trans*-2,5-dimethyl-3-hexene-2,5-diol (Table I). The perfect correspondence of the signals of the polyperoxide II with those of the *trans*- rather than those of the *cis*-2,5-dimethyl-3-hexene-2,5-diol supports, therefore, anew the *trans* configuration of the polyperoxide II.

Infrared studies demonstrated that the OH absorption bands of both *trans*- and *cis*-2,5-dimethyl-3-hexene-2,5-diol shifted to lower wave lengths upon dilution (Table III). This would indicate that the hydroxyl groups of the *cis*-diol do not form strong intramolecular hydrogen bridges. Molecular models showed that steric crowding of the methyl groups might well prevent the hydroxyl groups from assuming a conformation that would allow strong intramolecular hydrogen bonding.

TABLE III

RESULTS OF HYDROGEN BONDING STUDIES BY INFRARED SPECTROSCOPY OF THE STEREOISOMERIC 2,5-DIMETHYL-3-HEXENE-2,5-DIOLS

Concentration, mole/l.	Cell size, mm.	Wave length (μ) of OH stretching band[a]: *cis*-Diol[b]	*trans*-Diol[c]
1.0	0.096	3.0 vs	2.93 vs and 2.77 m
0.1	0.98	3.08 vs	2.89 m and 2.76 s
0.01	10.0	3.08 m and 2.90 s	2.87 w and 2.76 s
0.005	10.0	... 2.90 w	

[a] vs, very strong; s, strong; m, medium; w, weak. [b] Due to the limited solubility in CCl_4 the 1 *M* solution was prepared in $CHCl_3$ and subsequently diluted with CCl_4. [c] The 1.0 and 0.1 *M* solutions were run in $CHCl_3$; the 0.01 *M* solution was obtained by diluting the former with CCl_4.

(21) The configuration of this diol has been a controversial issue in the literature for a long time. See, *e.g.*, (a) R. Johnson and O. H. Johnson, *J. Am. Chem. Soc.*, **62**, 2615 (1940); (b) I. Zalkind, *ibid.*, **63**, 2282 (1941); (c) R. Johnson, *ibid.*, **63**, 2282 (1941).

(22) K. Alder and H. V. Brachel, *Ann.*, **608**, 195 (1957).

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characteristic peaks above 7.5 μ, including C—O stretching and =C—H deformation absorption peaks[d]									
	9.47 s	10.13 m				11.88 vs	12.25 m	15.05 m
		10.20 s				11.38 s	12.98 m	
	9.68 vs		10.35 s			11.35 m		
	9.91 m	10.20 vs	10.39 vs	10.73 m		10.98 m	11.98 w	12.94 s	14.85 m
		10.28 s	10.44 s	10.76 m		11.36 m	11.98 m	12.15 m	13.59 m
9.09 vs	9.72 w	10.14 w	10.34 m	10.74 s	10.82 s	10.96 vs		12.73 m	13.23 m

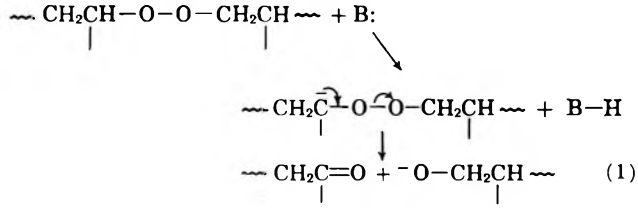
[d] In CCl_4 solution.

Discussion

The formation of an exclusively 1,4-polyperoxide is the first example of an entirely selective copolymerization of oxygen and an acyclic conjugated diene. It extends the scope of our previous hypothesis[7] concerning the course of conjugated diene-free radical reactions, *i.e.*, the intermediate allylic radical combines with the oxygen diradical at the more substituted allylic position.

The selective reduction method described above represents a new synthetic tool for the conversion of an unsaturated dialkyl polyperoxide to the corresponding unsaturated diol. The high yields and the lack of *cis–trans* isomerization under these conditions suggest that this method may also be useful as an analytical tool for the structural elucidation of similar unsaturated autoxidation products. An inherent advantage of this method over others is the fact that the reduction products can in any given case be removed from the reaction mixture as soon as they are formed. This is possible since the starting polyperoxides are higher boiling materials than their reduction products and because the reducing thiol is converted to its higher boiling disulfide. The only essential criterion is, therefore, to select a thiol that is higher boiling than the anticipated reduction product(s).

There are several obvious reaction paths that may be generally envisaged for the cleavage of peroxide linkages under the conditions employed.[24a,b] Mayo and Miller[16] proposed that the first step in base-catalyzed cleavage reactions may involve the abstraction of a proton at the α-carbon atom. Subsequent cleavage would then lead to a carbonyl compound and an alcohol, *e.g.*, see eq. 1.



(1)

Since all the α-carbon atoms in the polyperoxide II are substituted by methyl groups, this reaction path can be precluded in our case.

A second possibility is the homolytic cleavage of the peroxy bond and subsequent hydrogen abstraction from a thiol to form alcohol and disulfide. Since our reduction reactions occurred at rather high temperatures, such a homolytic cleavage of the peroxide cannot be excluded. However, it is hard to recognize the role of the base in a reaction of this type. Therefore, we would like to advance another proposal for the course of our base-catalyzed peroxide reduction, shown below.

$$\text{RO—OR} \longrightarrow 2\text{RO}\cdot \xrightarrow{2\text{R'SH}} 2\text{ROH} + \text{R'SSR'}$$

$$\begin{aligned} \text{R'S}^- + \text{RO—OR} &\longrightarrow \text{R'S—OR} + \text{RO}^- \\ \text{R'S}^- + \text{R'S—OR} &\longrightarrow \text{R'S—SR'} + \text{RO}^- \\ \hline 2\text{R'S}^- + \text{RO—OR} &\longrightarrow \text{R'S—SR'} + 2\text{RO}^- \end{aligned}$$

The first step in this reaction course involves a nucleophilic substitution at oxygen by the thiolate ion to form an alkoxide ion and a sulfenate ester. Subsequent displacement of a second alkoxide ion—this time at sulfur—by another thiolate ion leads to the observed reaction products, *viz.*, alcohol and disulfide. The latter step would be analogous to the well-known reduction of hypoiodite to iodine by the iodide ion.

Experimental

Materials.—2,5-Dimethyl-2,4-hexadiene from Matheson was practical grade. It was redistilled before use. 2,5-Dimethyl-3-hexyne-2,5-diol and 2,5-dimethylhexane-2,5-diol from Matheson were recrystallized before use. The "4-nonylthiophenol" from Pitt-Consol was a mixture of isomeric 4-nonylthiophenols.

(24) A. G. Davies, "Organic Peroxides," Butterworth and Co. (Publishers) Ltd., London, 1961: (a) p. 128, (b) p. 165.

Methods of Analyses.—The infrared spectra were recorded on a Baird spectrophotometer, Model B. The hydrogen bonding studies were made using a calcium fluoride prism. The nuclear magnetic resonance spectra were recorded on a Varian Model A-60 proton resonance spectrometer.

Method of Autoxidation.—The autoxidation was generally carried out in a round-bottom flask, equipped with a condenser, a magnetic stirrer, and a sintered glass inductor. The reaction flask in each case was placed into a temperature controlled (15 ± 1°) water bath. For the ultraviolet-initiated reactions, quartz flasks were used, while the uncatalyzed reactions were carried out in darkened Pyrex flasks. In cases where only intermittent irradiation was used, the quartz flask was darkened and the ultraviolet lamp was removed while the oxygenation was continued. As a source for the ultraviolet light, a 100-w. Hanovia utility lamp was used. The oxygen flow rate was in each case adjusted so that one bubble of gas left the reaction mixture per second.

For a comparison of the relative autoxidation rates under different conditions, samples were taken from the reaction mixtures at regular time intervals and analyzed by n.m.r. spectroscopy. The results of these experiments are summarized in Fig. 1.

Preparation of the Polyperoxide II.—The freshly distilled diene I (122 g., 0.1 mole) was autoxidized under ultraviolet irradiation. After 2–5 min. the mixture in the reaction flask exhibited a faint yellow color which disappeared within the next hour. After 4–5 hr. 60% of the diene was converted and the peroxide began to precipitate as a white semisolid. The oxygenation was continued overnight without further ultraviolet irradiation to yield a sticky, colorless mass. Infrared and n.m.r. analysis of this crude mixture demonstrated that it consisted only of the polyperoxide and the unreacted diene. The crude mixture was recrystallized from methanol and *n*-heptane to yield 133.3 g (84%) of the polyperoxide II, m.p. 62–65°.

Anal. Calcd. for $(C_8H_{14}O_2)_n$: C, 67.57; H, 9.92. Found: C, 67.42; H, 10.56; mol. wt. (cryoscopic in *p*-bromotoluene), 1520, *i.e.*, $n = 10$–11.

The active oxygen content was determined by reduction of the polyperoxide by a saturated solution of sodium iodide in glacial acetic acid at 60° under nitrogen atmosphere, and subsequent titration of the iodine liberated. The titration value was corrected by running a blank sample under the same conditions.

Anal. Calcd. for active oxygen: 11.25. Found: 10.0 (89% of the theory).

Catalytic Hydrogenation of the Polyperoxide II.—A mixture containing 10 g. (0.07 mole) of the polyperoxide and 0.5 g. of a 10% palladium-on-charcoal catalyst in 70 ml. of tetrahydrofuran reacted for 22 hr. under approximately 10 atm. of hydrogen pressure at 24°. The catalyst was removed by filtration and the solvent was evaporated to yield 8.9 g. (90%) of the essentially pure (according to its infrared spectrum) saturated diol V. It was recrystallized from a mixture of ether and *n*-pentane to yield colorless crystals, m.p. 87–88°. Mixture melting point (86–87°) and comparison of the infrared and n.m.r. spectra with those of an authentic sample established identity.

Partial Reduction of the Polyperoxide II.—A solution containing 12.8 g. (0.08 mole) of 2-naphthalenethiol, 5.68 g. (0.04 mole) of the polyperoxide II, and 0.28 g. (0.004 mole) of *t*-butylamine in 100 ml. of tetrahydrofuran was heated to reflux overnight. The reaction mixture was poured into twice its volume of methanol and kept in the refrigerator for a day. The di(2-naphthyl) disulfide by-product was filtered and the mother liquor cooled to −70°. The dimeric peroxide III precipitated as a colorless solid, m.p. 58–59°.

Selective Reduction of the Dimeric Peroxide III.—A mixture of 10 g. (0.35 mole) of the dimeric peroxide III, 38.5 g. (0.35 mole) of benzenethiol, and 5.9 g. (0.1 mole) of sodium methoxide was placed into a flask, equipped with a 10-cm. Vigreux column. The mixture was heated under vacuum (1 mm.) while it was stirred. At a bath temperature of 120°, an exothermic reaction occurred. The reduction product distilled together with some benzenethiol. After recrystallization from ether, 8 g. (80%) of *trans*-2,5-dimethyl-3-hexene-2,5-diol (IV) was obtained, m.p. 93–94°.

Selective Reduction of the Polyperoxide II.—A mixture of 20 g. (0.14 mole) of the polyperoxide and 1.35 g. (0.025 mole) of sodium methoxide in an excess (95 g., 0.4 mole) of isomeric 4-nonylthiophenol was treated as in the previous case. A vigorous reaction occurred at a bath temperature of 140°. The product distilled between 95–97° at 2 mm. Recrystallization from ether afforded 15 g. (75%) of the diol IV, m.p. 93–94°.

The residue in the distillation flask was a dark brown oil. The unchanged 4-nonylthiophenol was removed from it by methanol extraction. The residue thereof was a mixture of isomeric di(4-nonylphenyl) disulfides, as shown by the comparison of its infrared and n.m.r. spectra with those of an authentic sample.

Preparation of Isomeric Di(4-nonylphenyl) Disulfides.—To a solution of 45.2 g. (0.2 mole) of the isomeric 4-nonylthiophenol and 0.73 g. (0.01 mole) of *t*-butylamine in 100 ml. of methanol, 9 g. (0.01 mole) of *t*-butyl hydroperoxide was added dropwise with stirring. The temperature was kept below 20° by an ice bath. The disulfide separated from the methanol solution as a slightly yellow oil. It was washed three times with 25-ml. portions of methanol to remove the unchanged hydroperoxide. Then the oil was separated and the methanol traces were removed by vacuum distillation to yield 38 g. (84%) of the crude disulfide. A sample of the isomeric disulfide was distilled, b.p. 210–220° (0.3 mm.). A narrow boiling fraction of the distillate (b.p. 215–216° at 0.3 mm.) was used for its characterization. N.m.r. analysis established that the signals of the aliphatic *vs.* aromatic protons were in the correct ratio. The ratio of the CH_3 *vs.* CH_2 proton signals, on the other hand, was higher than expected, thus indicating that the side chains consisted of isomeric nonyl groups. This probably explains why the disulfide did not crystallize.

Anal. Calcd. for $C_{30}H_{46}S_2$: C, 76.53; H, 9.84; S, 13.62. Found: C, 76.54; H, 9.58; S, 13.78.

Catalytic Hydrogenation of the Unsaturated Diol IV.—A mixture of 0.9 g. of IV and 0.2 g. of a 10% palladium-on-charcoal catalyst in 50 ml. of methanol reacted for 24 hr. under 100 atm. of hydrogen pressure at room temperature. The catalyst was removed by filtration and the solvent was evaporated to yield 0.7 g. (77%) of the saturated diol V, m.p. 87–88°. Mixture melting point (86–87°) and comparison of the infrared and n.m.r. spectra established identity with an authentic sample and with the product, derived from catalytic reduction of the polyperoxide.

Preparation of *cis*-2,5-Dimethyl-3-hexene-2,5-diol.—A mixture of 29 g. (0.2 mole) of 2,5-dimethyl-3-hexyne-2,5-diol and 0.5 g. of a 10% palladium-on-charcoal catalyst in 100 ml. of ethanol reacted for 3 min. under 85 atm. of hydrogen pressure at room temperature. The catalyst was removed by filtration, and the solvent was evaporated to yield 28.8 g. (95%) of the crude reduction product that was recrystallized from ether, m.p. 65–68° (*cf.* 69° in the literature[23]). N.m.r. analysis showed that besides the expected *cis*-2,5-dimethyl-3-hexene-2,5-diol, 6% of the *trans*-diol IV, and 5–6% of the saturated diol V were present in the reaction product.

Attempts at Isomerizing *cis*-2,5-Dimethyl-3-hexene-2,5-diol.—A mixture of 5 g. of the diol and 2.7 g. of sodium methoxide in 47 g. of 4-nonylthiophenol was heated to 140°. To assure that the diol had appropriate contact time, the reaction mixture was kept at 50 mm. pressure for 15 min. and it was vigorously stirred. Then the vacuum was increased and 4.5 g. (90%) of the diol was recovered. N.m.r. analysis showed that the configuration of the diol had not changed.

Acknowledgment.—The authors wish to thank Dr. D. N. Hall for very helpful discussions, A. M. Palmer and T. Vicai for valuable technical help, and D. E. Bachert and J. J. Waters for recording the infrared and n.m.r. spectra. The supply of a sample of 4-nonylthiophenol by the Pitt-Consol Chemical Company, Newark, New Jersey, is gratefully acknowledged.

The Synthesis and Some Reactions of 1-Amino-4-methylestra-1,3,5(10)-trien-17-one

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The sodium salt of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one was condensed with 4-chloro-2-phenylquinazoline to give 4-methyl-1-(2-phenyl-4-quinazolinyloxy)estra-1,3,5(10)-trien-17-one (IV). Thermal rearrangement of IV gave 4-methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one (V), which was hydrolyzed to 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII). Replacement of the diazotized amino group afforded the 1-bromo (VIII) and 1-fluoro (IX) derivatives.

A series of substituted 1-chloro-4-methylestra-1,3,5-(10)-trienes (*e.g.*, I) was recently prepared in these laboratories by the reaction of androsta-1,4-dien-3-ones with oxalyl chloride.[1] The synthesis of 4-methylestra-1,3,5(10)-trienes with other substituents in the 1-position has now been investigated. The parent 1-unsubstituted[2-4] as well as the 1-methyl,[2] 1-hydroxy,[5,6] 1-acetoxy,[5] 1-methoxy,[5-7] and 1-(β-hydroxyethoxy)[7] substituted 4-methylestra-1,3,5(10)-trienes have already been reported in the literature.

We wish to describe the synthesis of 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII). The presence of the amino function makes possible the introduction of a variety of groups at position 1 by replacement reactions of the corresponding diazonium derivative. In this manner we have synthesized 1-bromo- and 1-fluoro-4-methylestra-1,3,5(10)-trien-17-one (VIII, IX). Hecker has previously prepared a series of 3-substituted estratrienes from 17β-acetoxy-3-aminoestra-1,3,5(10)-triene by replacement of the corresponding diazonium ion.[8]

The general procedure developed by Scherrer[9] for the conversion of phenols into anilines was adapted to the synthesis of the 1-amino steroid VII. Although Scherrer was able to condense salts of hindered phenols, such as 2,3,6-trimethylphenol with 4-chloro-2-phenylquinazoline (III)[10] in boiling diglyme, the sodium salt of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II)[5,6] was recovered unchanged under these conditions. However, when these reactants were heated under nitrogen pressure at 200°, the condensation proceeded readily to give 4-methyl-1-(2-phenyl-4-quinazolinyloxy)estra-1,3,5(10)-trien-17-one (IV) in good yield. Thermal rearrangement[9] of this intermediate afforded 4-methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one (V). This rearrangement gave an optimum yield in 5 hr. at 330°, and the course of the reaction was easily followed by spectroscopic techniques. As the reaction progressed, the strong infrared absorption peaks at 1622, 1492, 1385, 1224, and 1070 cm.$^{-1}$ of the quinazoline IV diminished in intensity as absorption peaks at 1689, 1604, and 1269 cm.$^{-1}$ due to the quinazolinone V appeared and increased in intensity. The ultraviolet absorption maximum at 257 mμ due to IV diminished in intensity as the rearrangement proceeded, and the spectrum of the final quinazolinone V exhibited a minimum at 260 and a maximum at 282 mμ.

The hydrolysis of the quinazolinone V was carried out essentially according to the method used by Scherrer[9] for the synthesis of simpler anilines. Treatment of crude V with ethanolic sodium hydroxide gave an intermediate assumed to be the substituted amidine VI. Further treatment of VI with dilute hydrochloric acid yielded 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII) and a large quantity of neutral material which appeared to be mostly quinazolinone V, resulting from recyclization of the amidine intermediate VI. Further hydrolyses of this material gave additional amounts of the desired product. The over-all yield of crude amino steroid VII from 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II) was 67%.

Scherrer[9] has shown that his procedure introduces the amino group on the same carbon atom to which the phenolic hydroxyl was originally attached, with no additional rearrangement of substituents. In accord with this, the infrared spectrum of VII exhibited a strong sharp absorption peak at 814 cm.$^{-1}$, characteristic of a 1,2,3,4-tetrasubstituted benzene.

The diazonium ion formed from 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII) was very unstable. Evolution of nitrogen with concurrent formation of an acid-insoluble precipitate, presumably the corresponding phenol II, was evident soon after the addition of sodium nitrite to a cooled solution of VII in acetic acid. Although only an 11% yield of 1-bromo-4-methylestra-1,3,5(10)-trien-17-one (VIII) could be obtained following diazotization at 0°,[8,11] lowering the temperature of the diazotization reaction to −15° slowed the decomposition of the diazonium ion sufficiently that a 27% yield of the bromo compound VIII was obtained. Further evidence for the unusual instability of the diazonium ion was found during its conversion to 1-fluoro-4-methylestra-1,3,5(10)-trien-17-one (IX). Whereas aromatic diazonium fluoborate salts normally are sufficiently stable to be isolated from the diazotization reaction and decompose to the aromatic fluorides generally at temperatures above 100°,[12] the diazotization of 1-amino-4-methylestra-1,3,5(10)-trien-

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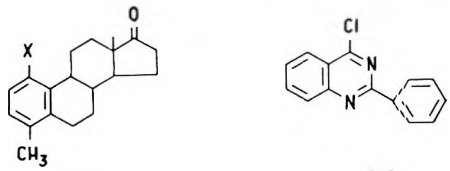
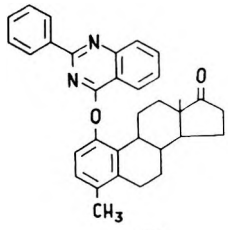
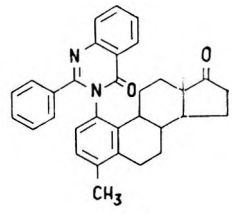


I X = Cl
II X = OH
VII X = NH_2
VIII X = Br
IX X = F

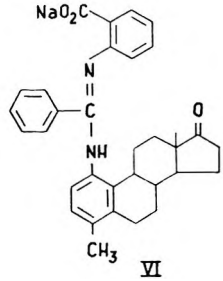
III



IV



V



VI

17-one (VII) in fluoroboric acid solution proceeded with spontaneous evolution of nitrogen at 0° to give IX directly in 29% yield. In both of these reactions, the primary by-product was 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II).

The biological activity of these compounds and their derivatives will be discussed in a later paper.

Experimental[13]

4-Methyl-1-(2-phenyl-4-quinazolinyloxy)estra-1,3,5(10)-trien-17-one (IV).—A solution of 5.47 g. of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II)[5] in 200 ml. of pure dry diglyme was stirred under nitrogen and treated with 0.94 g. of a 53% dispersion of sodium hydride in mineral oil. When the reaction ceased and no more hydrogen was evolved, 4.40 g. of 4-chloro-2-phenylquinazoline (III)[10] was added. The mixture was covered with a pressurized nitrogen atmosphere (50 p.s.i.) and heated at 200° for 10 hr. The mixture then was cooled to room temperature, poured into concentrated sodium chloride solution, and filtered. The precipitate was washed well with water and dried in air. The crude 4-methyl-1-(2-phenyl-4-quinazolinyloxy)-estra-1,3,5(10)-trien-17-one, 10.0 g., was sufficiently pure to be used directly for the next step.

An analytical sample recrystallized from ether had m.p. 213–214.5°; $[\alpha]^{24}D$ +243° (*c* 1.0, $CHCl_3$); λ_{max} 286 mμ (ε 16,900) and 257 mμ (ε 34,100); ν_{max} 1739, 1622, 1560, 1492, 1385, 1224, 1070, 782, and 711 $cm.^{-1}$.

Anal. Calcd. for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73. Found: C, 80.98; H, 6.56; N, 5.80.

4-Methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one (V).—A suspension of 10.3 g. of crude 4-methyl-1-(2-phenyl-4-quinazolinyloxy)estra-1,3,5(10)-trien-17-one (IV) in 100 ml. of heavy mineral oil was covered with an atmosphere of nitrogen and stirred and heated at 330° for 5 hr. The homogeneous mixture then was cooled to room temperature, diluted with 100 ml. of petroleum ether (b.p. 35–60°), cooled in ice, and filtered. The precipitate was washed with petroleum ether and dried in air, yielding 8.25 g. (80%) of crude 4-methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one. The filtrate was concentrated on a steam bath, cooled, and extracted with methanol. The washings were concentrated to dryness on a steam bath, and the residue again was extracted with methanol. The extract was poured into water, and the precipitate was collected and dried in air, yielding an additional 1.28 g. (12%) of crude product. This material was sufficiently pure to be used directly for the next step.

An analytical sample recrystallized from ether had m.p. 231–232.5°; $[\alpha]^{24}D$ +147° (*c* 1.0); λ_{max} 282 mμ (ε 14,100), λ_{min} 260 mμ (ε 11,300); ν_{max} 1742, 1689, 1604, 1560, 1474, 1269, 773, and 701 $cm.^{-1}$.

Anal. Calcd. for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73. Found: C, 81.03; H, 6.46; N, 5.80.

1-Amino-4-methylestra-1,3,5(10)-trien-17-one (VII).—A solution of 18.25 g. of crude 4-methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one (V) in 1300 ml. of absolute ethanol was treated with 150 g. of sodium hydroxide in 300 ml. of water. The resulting solution was refluxed for 7 hr., cooled in ice, treated with 525 ml. of 12 *N* hydrochloric acid, and allowed to stand overnight at room temperature. The mixture then was stirred and refluxed for 1.5 hr., cooled, and filtered. The sodium chloride precipitate was washed well with ethanol and discarded. The filtrate and washings were concentrated under reduced pressure, poured into water, and filtered. The filtrate was made alkaline with concentrated sodium hydroxide solution, saturated with potassium carbonate, and filtered. The precipitate was washed well with water and dried under reduced pressure at 60°, affording 3.8 g. of 1-amino-4-methylestra-1,3,5(10)-trien-17-one.

The acid-insoluble precipitate appeared to consist mainly of quinazoline V, and rehydrolysis of this following the above procedure gave 1.11 g. of product. A third hydrolysis of the insoluble precipitate yielded an additional 0.61 g. of crude product. The total crude yield was 7.21 g., a 67% yield based on the starting 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II). This amino steroid was used directly for the next steps without further purification.

An analytical sample recrystallized from hexane had m.p. 216–218°; $[\alpha]^{23}D$ +315° (c 0.6); λ_{max} 241 mμ (ε 7400) and 293 mμ (ε 2200); ν_{max} 3425, 3355, 1733, 1628, 1590, and 814 $cm.^{-1}$.

Anal. Calcd. for $C_{19}H_{25}NO$: C, 80.51; H, 8.89; N, 4.94. Found: C, 80.33; H, 8.81; N, 4.95.

1-Bromo-4-methylestra-1,3,5(10)-trien-17-one (VIII).—A solution of 283 mg. of crude 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII) in 6 ml. of acetic acid, 2 ml. of propionic acid, 7 ml. of water, and 1 ml. of concentrated sulfuric acid was cooled to −15° in an ice–salt bath. A solution of 76 mg. of sodium nitrite in 2 ml. of water was added over a period of 10 min., keeping the temperature at −15 ± 1°. The reaction was stirred an additional 20 min. at −15°, during which time a slow evolution of gas commenced and a precipitate began to form. A cooled solution (−10°) of 500 mg. of cuprous bromide in 2 ml. of water and 3 ml. of 48% hydrobromic acid then was added, and the mixture was allowed to warm to 0° and was stirred for 1 hr. It then was warmed to room temperature over a 30-min. period and heated on a steam bath for 30 min. The solution was poured into very dilute hydrobromic acid (*ca.* 0.1%) and filtered. The precipitate was dried under reduced pressure at 60° to give 329 mg. of crude material, which was chromatographed on alumina (Woelm, neutral, activity grade I). Elution with 10% ether in benzene yielded 95 mg. (27%) of 1-bromo-4-methylestra-1,3,5(10)-trien-17-one, m.p. 172–174°. An analytical sample recrystallized from methanol had m.p. 175–176°; $[\alpha]^{23}D$ +292° (*c* 0.4); λ_{max} 271 mμ (ε 278); ν_{max} 1739 and 810 $cm.^{-1}$.

Anal. Calcd. for $C_{19}H_{23}BrO$: C, 65.71; H, 6.68; Br, 23.01. Found: C, 65.97; H, 6.81; Br, 23.01.

This compound was identical with the 1-bromo-4-methylestra-1,3,5(10)-trien-17-one, m.p. 171–173°, prepared in low yield from androsta-1,4-diene-3,17-dione by treatment with oxalyl bromide and oxalic acid.[1]

Elution with pure ether afforded 91 mg. of crude phenolic material, shown to be mostly 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one by thin-layer chromatography and by comparison of infrared spectra.

(13) The melting points were determined on a Fisher-Johns block and are corrected. The infrared spectra were recorded on a Beckman IR-7 in KBr disks. The ultraviolet spectra and the optical rotations were run in methanol solution unless otherwise noted.

1-Fluoro-4-methylestra-1,3,5(10)-trien-17-one (IX).—A solution of 283 mg. of crude 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII) in 2.5 ml. of acetic acid, 3 ml. of water, and 7 ml. of 48% fluoroboric acid was cooled and treated with 0.7 g. of solid sodium hydroxide. The resulting solution was cooled to 2°, and a solution of 76 mg. of sodium nitrite in 2 ml. of water was added over a 5-min. period. Evolution of a gas was soon evident. The mixture was stirred at 0° for 30 min. and then warmed to room temperature over a 30-min. period. The mixture was poured into 400 ml. of water, and the precipitate was filtered and dried in air, yielding 274 mg. of crude material. This was chromatographed on alumina (Woelm, neutral, activity grade I). Elution with 10% ether in benzene afforded 83 mg. (29%) of 1-fluoro-4-methylestra-1,3,5-(10)-trien-17-one, m.p. 192–196°. An analytical sample recrystallized from methanol had m.p. 196–197°; $[\alpha]^{23}D$ +196° (*c* 0.6, $CHCl_3$); ν_{max} 1737, 1604, 1419, 1237, and 819 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{23}FO$: C, 79.69; H, 8.10; F, 6.63. Found: C, 79.42; H, 8.23; F, 6.74.

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Base-Catalyzed Aromatization of *p*-Quinone Disulfonimide–Cyclopentadiene Adducts

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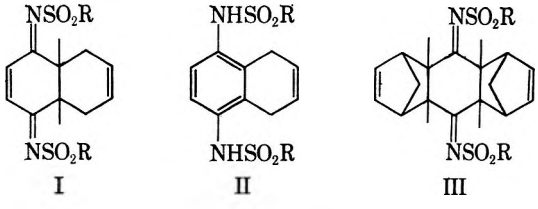
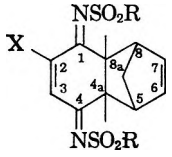
Simple monoadducts (IV) of *p*-quinone disulfonimides and cyclopentadiene were isomerized to their aromatic forms (V) by base catalysis. Structures of several quinone imide–cyclopentadiene adducts were thus confirmed. The alleged 4a-chloro-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-bis(dimethylaminosulfonimide) (VI) of Adams and Shafer was shown to be the isomeric 6-chloro compound (IVg). Treatment of ring-unsubstituted *p*-quinone disulfonimides with equimolar amounts of cyclopentadiene has previously been shown to result only in the formation of the diadducts (III). When *p*-quinonedimethanesulfonimide was treated with an excess of cyclopentadiene in the presence of triethylamine catalyst, the aromatized monoadduct (VII) was obtained exclusively.

Quinone disulfonimides have been shown to undergo the Diels–Alder reaction with dienes to give either the simple adducts (I) or the aromatized adducts (II).[1-6]



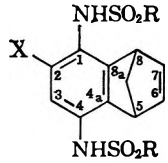
Simple adducts of dienes, other than cyclopentadiene, were caused to isomerize to the corresponding aromatized forms by treatment with catalytic amounts of hydrobromic acid.[1-3,5] Cyclopentadiene was shown to react with ring-unsubstituted *p*-quinone disulfonimides to give diadducts (III) exclusively[1] and with ring-substituted imides to give simple monoadducts (IV) which resisted isomerization to the aromatic forms upon treatment with acid catalyst.[2,5] Our initial interest in adducts of type IV was related to certain fungicidal activities of this series.

We have found that cyclopentadiene adducts of type IV can be isomerized to the aromatic forms (V) by treatment with a catalytic amount of amine base in an inert solvent. Thus, 2-chloro-4a,5,8,8a-tetrahydro-5,8-methano-1,4-naphthoquinonedimethanesulfonimide (IVa) was converted instantaneously to the corresponding 2-chloro-5,8-dihydro-5,8-methano-1,4-naphthalenedimethanesulfonamide (Va) by a catalytic amount of triethylamine in benzene solution. Similar aromatized adducts prepared in this way are 2-chloro-5,8-dihydro-5,8-methano-1,4-naphthalenebis(*p*-chlorobenzenesulfonamide) (Vb), 2-chloro-5,8-dihydro-5,8-methano-1,4-



IV

Compound	R	X	Yield, %
IVa	CH_3	Cl	84
b	*p*-ClC_6H_4	Cl	88
c	C_6H_5	Cl	96[5]
d	*n*-C_4H_9	Cl	86
e	CH_3	SCH_3	80
f	CH_3	SC_6H_{11}	...
g	$N(CH_3)_2$	Cl	34[4]



V

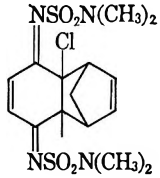
Compound	R	X	Yield, %
Va	CH_3	Cl	74
b	*p*-ClC_6H_4	Cl	89
c	C_6H_5	Cl	94
d	*n*-C_4H_9	Cl	46
e	CH_3	SCH_3	87
f	CH_3	SC_6H_{11}	58
g	$N(CH_3)_2$	Cl	55

(1) R. Adams and C. R. Walter, Jr., *J. Am. Chem. Soc.*, **73**, 1152 (1951).
(2) R. Adams and W. Moje, *ibid.*, **74**, 2593 (1952).
(3) R. Adams and J. D. Edwards, Jr., *ibid.*, **74**, 2603 (1952).
(4) R. Adams and P. R. Shafer, *ibid.*, **75**, 667 (1953).
(5) R. Adams and R. W. P. Short, *ibid.*, **76**, 2408 (1954).
(6) R. Adams and W. P. Samuels, *ibid.*, **77**, 5383 (1955).

naphthalenedibenzenesulfonamide (Vc), and 2-chloro-5,8-dihydro-5,8-methano-1,4-naphthalenedi-*n*-butanesulfonamide (Vd). Adduct IVa was also aromatized to Va in 70% yield by the exposure of a benzene solution of IVa to ultraviolet light for a period of 48 hr.

Adducts of 2-alkylthio-*p*-benzoquinonedimethanesulfonimides and cyclopentadiene were found to undergo reverse Diels–Alder reaction in the absence of excess cyclopentadiene. The base-catalyzed aromatization was used to characterize the unstable 2-methylthio-4a,5,8,8a-tetrahydro-5,8-methano-1,4-naphthoquinonedimethanesulfonimide (IVe) and 2-cyclohexylthio-4a,5,8,8a-tetrahydro-5,8-methano-1,4-naphthoquinonedimethanesulfonimide (IVf), giving 2-methylthio-5,8-dihydro-5,8-methano-1,4-naphthalenedimethanesulfonamide (Ve) and 2-cyclohexylthio-5,8-dihydro-5,8-methano-1,4-naphthalenedimethanesulfonamide (Vf), respectively. These reactions were accomplished in 60 and 90% yields by treatment of the alkylthioquinonedimethanesulfonimides with an excess of cyclopentadiene and a catalytic amount of triethylamine in benzene or chloroform solution.

Adams and Shafer[4] obtained two products by the treatment of 2-chloro-*p*-quinonebis(dimethylaminosulfonimide) with an excess of cyclopentadiene: a white solid, which proved to be the aromatized adduct (Vg), and a yellow isomer which did not aromatize upon treatment with acid. They suggested that the yellow isomer was the adduct VI formed by the addition of the



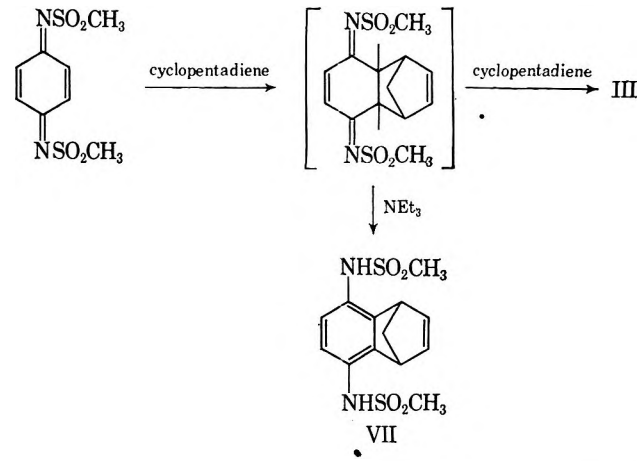
VI

cyclopentadiene molecule to the side of the quinone imide nucleus containing the chlorine atom. Upon repetition of the experiment, we also obtained the two products. However, when the yellow material was treated with base catalyst, a white crystalline substance identical with Vg was produced. The yellow isomer, therefore, was assigned structure IVg. Its failure to isomerize to the aromatic form on treatment with hydrobromic acid was merely the characteristic behavior of the simple cyclopentadiene adducts.

Although ring-unsubstituted *p*-quinone disulfonimides normally react with equimolar amounts of cyclopentadiene to give diadducts[1] (III) exclusively, we obtained a monoadduct, in aromatized form (VII), in 87% yield when either an equimolar amount or an excess of cyclopentadiene was added to *p*-quinonedimethanesulfonimide in an inert solvent in the presence of triethylamine catalyst.

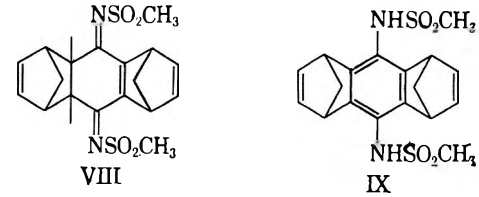
Thus, the rate of the base-catalyzed aromatization of the monoadduct is greater than that of the addition of the second molecule of cyclopentadiene to the monoadduct, and the addition of the first cyclopentadiene molecule is the rate-determining step. Cyclopentadiene monoadducts of ring-unsubstituted *p*-quinone disulfonimides have been otherwise inaccessible.

Oxidation of VII to the corresponding diimide with lead tetraacetate permitted the addition of a second



VII

molecule of cyclopentadiene to give the simple adduct (VIII) in the absence of base or the aromatized adduct (IX) when the addition was made in the presence of triethylamine catalyst.



VIII IX

Experimental[7]

2-Chloro-4a,5,8,8a-tetrahydro-5,8-methano-1,4-naphthoquinonedimethanesulfonimide (IVa).—To a solution of 131.5 g. (0.443 mole) of 2-chloro-*p*-quinonedimethanesulfonimide[6] in 2.5 l. of chloroform was added 72 g. (1.1 moles) of cyclopentadiene. A transient dark red color was formed, and after 15 min. the color became pale yellow. The solution was then concentrated *in vacuo* to about 200 ml., diluted with carbon tetrachloride, and cooled to give 134.2 g. (84%) of light yellow crystals, m.p. 139–140° dec. Recrystallization from aqueous acetic acid gave the pure substance as light yellow crystals, m.p. 140–141° dec.

Anal. Calcd. for $C_{13}H_{15}ClN_2O_4S_2$: C, 43.03; H, 4.17; N, 7.72. Found: C, 43.11; H, 4.13 N, 7.57.

2-Chloro-5,8-dihydro-5,8-methano-1,4-naphthalenedimethanesulfonamide (Va). A.—To a boiling solution of 18.1 g. (0.0500 mole) of IVa in 250 ml. of benzene was added 5.60 g. (0.0553 mole) of triethylamine. The color of the solution changed immediately from pale yellow to amber. The gray solid, which crystallized as the solution cooled to room temperature, was collected on a filter and recrystallized from aqueous acetic acid (Norit) to give 10.9 g. (60%) of light tan crystalline solid, m.p. 210–212°. Three further recrystallizations from aqueous methanol gave the pure product as colorless crystals, m.p. 216.5–217.5°.

Anal. Calcd. for $C_{13}H_{15}ClN_2O_4S_2$: C, 43.03; H, 4.17; Cl, 9.77; N, 7.72; S, 17.67. Found: C, 43.33; H, 3.93; Cl, 9.65; N, 7.52; S, 17.58.

The infrared spectrum showed the presence of the –NH– linkage (3220–3270 cm.$^{-1}$).

B.—A solution of 5.00 g. (0.0138 mole) of IVa in 250 ml. of benzene was placed in a Pyrex flask and irradiated with a 275-w. G. E. sunlamp over a distance of 15 cm. for 48 hr. Upon standing at room temperature for several days thereafter, the solution yielded 3.72 g. (74%) of white solid. Recrystallization from glacial acetic acid gave a white solid, m.p. 216–218°.

The infrared spectrum of this substance and that of the substance prepared by procedure A were identical.

2-Chloro-*p*-phenylenebis(*p*-chlorobenzenesulfonamide).—To a stirred, ice-cold solution of 40.0 g. (0.186 mole) of chloro-*p*-phenylenediamine dihydrochloride in 400 ml. of pyridine was added a solution of 78.6 g. (0.372 mole) of *p*-chlorobenzene-

(7) All melting points are uncorrected. All cyclopentadiene was freshly prepared before use.

sulfonyl chloride in 80 ml. of pyridine. The mixture was allowed to stand at room temperature for 15 hr. and was then poured into ice and concentrated hydrochloric acid. The resulting crude substance was dissolved in a solution of 60 g. of sodium hydroxide in 1140 ml. of water and stirred for 30 min. with 30 g. of Norit at room temperature and filtered. The filtrate was acidified with dilute hydrochloric acid to give a white precipitate, which was recrystallized from glacial acetic acid to give 56.7 g. (62%) of the pure product as colorless crystals, m.p. 211–212°.

Anal. Calcd. for $C_{18}H_{13}Cl_3N_2O_4S_2$: C, 43.96; H, 2.66; N, 5.70. Found: C, 44.10; H, 2.76; N, 5.60.

2-Chloro-*p*-quinonebis(*p*-chlorobenzenesulfonimide).—This procedure exemplifies the general method used for the preparation of all of the diimides described in this paper.

To a well-stirred suspension of 56.3 g. (0.114 mole) of 2-chloro-*p*-phenylenebis(*p*-chlorobenzenesulfonamide) in 850 ml. of glacial acetic acid was added 65.8 g. (0.149 mole) of lead tetraacetate. A yellow color was apparent almost immediately. After the mixture had been stirred for 1 hr. at room temperature, 10 ml. of ethylene glycol was added to destroy excess lead tetraacetate, and the mixture was stirred for an additional 25 min. Water (850 ml.) was then added to precipitate 55.0 g. (98%) of yellow, crystalline solid. Recrystallization from glacial acetic acid gave the pure product as yellow crystals, m.p. 178–179° dec.

Anal. Calcd. for $C_{18}H_{11}Cl_3N_2O_4S_2$: C, 44.14; H, 2.26; N, 5.72. Found: C, 43.98; H, 2.33; N, 5.72.

2-Chloro-4a,5,8,8a-tetrahydro-5,8-methano-1,4-naphthoquinonebis(*p*-chlorobenzenesulfonimide) (IVb).—Cyclopentadiene (20 ml.) was added to a warm solution of 20.0 g. (0.0408 mole) of 2-chloro-*p*-quinonebis(*p*-chlorobenzenesulfonimide) in 200 ml. of chloroform. After the disappearance of the transient violet color, the solvent was removed by evaporation *in vacuo*, and the yellow, gummy residue was crystallized from cyclohexane–ethyl acetate to give 19.9 g. (88%) of yellow crystals, m.p. 153°.

Anal. Calcd. for $C_{23}H_{17}Cl_3N_2O_4S_2$: C, 49.69; H, 3.08; Cl, 19.14. Found: C, 49.59; H, 3.19; Cl, 18.82.

2-Chloro-5,8-dihydro-5,8-methano-1,4-naphthalenebis(*p*-chlorobenzenesulfonamide) (Vb).—Triethylamine (6 drops) was added to a well-stirred, boiling solution of 3.95 g. (0.00710 mole) of IVb in 80 ml. of benzene. The color of the solution changed immediately from yellow to amber. The reaction mixture was then allowed to cool to room temperature, and 3.53 g. (89%) of light tan solid was obtained. Recrystallization from glacial acetic acid (Norit) afforded colorless crystals, m.p. 242–243° dec.

Anal. Calcd. for $C_{23}H_{17}Cl_3N_2O_4S_2$: C, 49.69; H, 3.08; N, 5.04. Found: C, 49.83; H, 3.31; N, 4.63.

The infrared spectrum showed the presence of the –NH– linkage (3240 cm.$^{-1}$).

2-Chloro-5,8-dihydro-5,8-methano-1,4-naphthalenedibenzenesulfonamide (Vc). A.—Triethylamine (2 drops) was added to a solution of 1.35 g. (0.00278 mole) of IVc[6] in 25 ml. of chloroform. A dark brown coloration was immediately apparent. The mixture was allowed to stand at room temperature for 22 hr., during which time 0.68 g. (50%) of brown solid crystallized. Recrystallization from ethanol (Norit) gave light tan crystals, m.p. 246° dec.

Anal. Calcd. for $C_{23}H_{19}ClN_2O_4S_2$: C, 56.72; H, 3.93; N, 5.75. Found: C, 56.64; H, 3.86; N, 5.67.

The infrared spectrum showed the presence of the –NH– linkage (3240 cm.$^{-1}$).

B.—Cyclopentadiene (2 ml.) was added to a warm solution of 1.6 g. (0.0038 mole) of 2-chloro-*p*-quinonedibenzenesulfonimide[8] and 2 drops of triethylamine in 25 ml. of chloroform. A brown color was immediately apparent, and the reaction mixture was allowed to stand at room temperature for 22 hr., during which time 1.50 g. (94%) of brown crystals formed. Recrystallization from ethanol (Norit) gave colorless crystals, m.p. 247° dec.

Anal. Calcd. for $C_{23}H_{19}ClN_2O_4S_2$: C, 56.72; H, 3.93; N, 5.75. Found: C, 56.86; H, 3.77; N, 5.68.

The infrared spectrum was identical with that of the product obtained by procedure A.

***p*-Phenylenedi-*n*-butanesulfonamide.**—*n*-Butanesulfonyl chloride (69.7 g., 0.445 mole) was added over a period of 10 min. to a well-stirred, ice-cold solution of 24.1 g. (0.223 mole) of *p*-phenylenediamine in 230 ml. of pyridine. The mixture was then stirred at room temperature for 3 hr. and was poured into a mixture of ice and excess concentrated hydrochloric acid. The dark purple solid, thus obtained, was dissolved in a solution of 72 g. of sodium hydroxide in 1370 ml. of water. The solution was stirred with 36 g. of Norit for 20 min. at room temperature, filtered, and acidified with dilute hydrochloric acid to yield 64.0 g. (82.5%) of light tan solid. Recrystallization from glacial acetic acid (Norit) gave colorless platelets, m.p. 178–179°.

Anal. Calcd. for $C_{14}H_{24}N_2O_4S_2$: C, 48.25; H, 6.94; N, 8.04. Found: C, 48.94; H, 6.94; N, 7.96.

***p*-Quinonedi-*n*-butanesulfonimide.**—Lead tetraacetate oxidation of *p*-phenylenedi-*n*-butanesulfonamide afforded a 94% yield of the pure diimide as yellow platelets, m.p. 135–136° dec.

Anal. Calcd. for $C_{14}H_{22}N_2O_4S_2$: C, 48.53; H, 6.40; N, 8.09. Found: C, 48.96; H, 6.43; N, 8.16.

2-Chloro-*p*-phenylenedi-*n*-butanesulfonamide.—Concentrated hydrochloric acid (80 ml.) was added in one portion to a well-stirred suspension of 30.7 g. (0.0915 mole) of *p*-quinonedi-*n*-butanesulfonimide in 250 ml. of ethanol. The color disappeared after 1 min., and the white product began to crystallize. The mixture was diluted with 150 ml. of water to give 32.3 g. (95%) of white solid. Recrystallization from ethanol gave colorless needles, m.p. 134–135°.

Anal. Calcd. for $C_{14}H_{23}ClN_2O_4S_2$: C, 43.91; H, 6.05; N, 7.32. Found: C, 43.81; H, 5.78; N, 7.28.

2-Chloro-*p*-quinonedi-*n*-butanesulfonimide.—Lead tetraacetate oxidation of 2-chloro-*p*-phenylenedi-*n*-butanesulfonamide gave a quantitative yield of the diimide as a yellow solid, crystallizing from cyclohexane–carbon tetrachloride in yellow needles, m.p. 69–70°.

Anal. Calcd. for $C_{14}H_{21}ClN_2O_4S_2$: C, 44.14; H, 5.56; N, 7.36. Found: C, 44.37; H, 5.46; N, 7.17.

2-Chloro-4a,5,8,8a-tetrahydro-5,8-methano-1,4-naphthoquinonedi-*n*-butanesulfonimide (IVd).—Cyclopentadiene (15.2 g., 0.230 mole) was added to a solution of 11.0 g. (0.0289 mole) of 2-chloro-*p*-quinonedi-*n*-butanesulfonimide in 80 ml. of chloroform. The reaction was moderately exothermic and was accompanied by a transient violet color. The solvent was removed by evaporation *in vacuo*, and the residue solidified upon being triturated with ether to give 11.1 g. (86%) of pale yellow crystals, m.p. 110–111°. Two recrystallizations from benzene–ether gave pale yellow crystals, m.p. 112–113°.

Anal. Calcd. for $C_{19}H_{27}ClN_2O_4S_2$: C, 51.05; H, 6.09; N, 6.27. Found: C, 51.14; H, 5.99; N, 6.21.

2-Chloro-5,8-dihydro-5,8-methano-1,4-naphthalenedi-*n*-butanesulfonamide (Vd).—Triethylamine (6 drops) was added to a warm solution of 2.87 g. (0.00641 mole) of IVd in 25 ml. of benzene. A green color formed immediately, and after standing at room temperature for 1 hr., the solution exhibited an amber-red color. The benzene was removed by evaporation *in vacuo*, and the oily residue was crystallized from a minimum of hot, aqueous acetic acid (Norit) to give 1.32 g. (46%) of light tan crystals. Recrystallization from aqueous acetic acid gave colorless crystals, m.p. 138–139.5°.

Anal. Calcd. for $C_{19}H_{27}ClN_2O_4S_2$: C, 51.05; H, 6.09; N, 6.27. Found: C, 51.26; H, 6.08; N, 6.26.

The infrared spectrum showed the presence of the –NH– linkage (3245 cm.$^{-1}$).

2-Methylthio-*p*-phenylenedimethanesulfonamide.—To a cold (6°) solution of 26.2 g. (0.100 mole) of *p*-quinonedimethanesulfonimide[8] and 1 ml. of triethylamine in 3.5 l. of chloroform was added 12.0 g. (0.250 mole) of methanethiol. The yellow color of the solution became lighter immediately, and a white solid precipitated. Carbon tetrachloride (1 l.) was added, and 28.7 g. (92%) of white solid was obtained. Recrystallization from glacial acetic acid gave colorless needles, m.p. 166–167°.

Anal. Calcd. for $C_9H_{14}N_2O_4S_3$: C, 34.82; H, 4.55; N, 9.03. Found: C, 34.82; H, 4.38; N, 8.88.

2-Methylthio-*p*-quinonedimethanesulfonimide.—Lead tetraacetate oxidation converted 2-methylthio-*p*-phenylenedimethanesulfonamide to the diimide in 88% yield. Recrystallization from chloroform–carbon tetrachloride gave bright red crystals, m.p. 171° dec.

Anal. Calcd. for $C_9H_{12}N_2O_4S_3$: C, 35.05; H, 3.92; N, 9.09. Found: C, 34.95; H, 3.87; N, 8.85.

2-Methylthio-4a,5,8,8a-tetrahydro-5,8-methano-1,4-naphthoquinonedimethanesulfonimide (IVe).—Cyclopentadiene (30 ml.) was added to a solution of 6.20 g. (0.0200 mole) of 2-methylthio-*p*-quinonedimethanesulfonimide in 250 ml. of chloroform at room temperature. The color of the solution changed within 1 min.

(8) R. Adams and A. S. Nagarkatti, *J. Am. Chem. Soc.*, **72**, 4601 (1950).

from dark red to light orange. The chloroform was then removed by evaporation *in vacuo*, and the yellow, gummy residue was crystallized from nitromethane to give 6.03 g. (80%) of yellow solid. Attempts to recrystallize the substance from various solvents always resulted in the formation of a red color as the solutions were heated. This apparent reverse Diels–Alder reaction was finally avoided by the recrystallization of the crude material from ethanol containing a slight excess of cyclopentadiene to give a yellow solid, m.p. 159° dec. (with rapid decoloration from about 145°).

Anal. Calcd. for $C_{14}H_{18}N_2O_4S_3$: C, 44.90; H, 4.84; S, 25.68. Found: C, 45.50; H, 4.77; S, 24.95.

The infrared spectrum showed the ethylenic double bond stretching band at 1582 cm.$^{-1}$.

The solid product on standing a few hours underwent a spontaneous reverse Diels–Alder reaction as evidenced by its acquisition of a red color and by the presence of the characteristic odor of cyclopentadiene.

2-Methylthio-5,8-dihydro-5,8-methano-1,4-naphthalenedimethanesulfonamide (Ve).—Cyclopentadiene (40 ml.) was added to a solution of 9.25 g. (0.0300 mole) of 2-methylthio-*p*-quinonedimethanesulfonimide in 800 ml. of benzene. The color of the solution changed from a deep red to yellow over a period of 3 min. Triethylamine (5 ml.) was then added, and the solution was boiled under reflux for 20 min., during which time some crystalline product separated. After the mixture had been concentrated to 400 ml. and cooled, there was obtained 9.83 g. (87%) of light tan solid. Recrystallization from glacial acetic acid (Norit) gave colorless crystals, m.p. 243.5–244° dec.

Anal. Calcd. for $C_{14}H_{18}N_2O_4S_3$: C, 44.90; H, 4.84; N, 7.48. Found: C, 44.71; H, 4.79; N, 7.76.

The infrared spectrum showed the presence of the –NH– linkage (3245 cm.$^{-1}$).

2-Cyclohexylthio-*p*-phenylenedimethanesulfonamide.—A solution of 11.6 g. (0.100 mole) of cyclohexanethiol and 6 drops of triethylamine in 50 ml. of chloroform was added in one portion to a warm solution of 26.2 g. (0.100 mole) of *p*-quinonedimethanesulfonimide[8] in 1250 ml. of chloroform. A violet color formed immediately and persisted. After the solution had been allowed to stand at room temperature for 30 min., the solvent was removed by evaporation *in vacuo*, leaving a light tan solid residue. Recrystallization from ethanol (Norit) yielded 35.0 g. (93%) of tan crystals. Further recrystallization from glacial acetic acid (Norit) gave colorless crystals, m.p. 131–132°.

Anal. Calcd. for $C_{14}H_{22}N_2O_4S_3$: C, 44.42; H, 5.86; N, 7.40. Found: C, 44.42; H, 5.64; N, 7.63.

2-Cyclohexylthio-*p*-quinonedimethanesulfonimide.—Lead tetraacetate oxidation of 2-cyclohexylthio-*p*-phenylenedimethanesulfonamide afforded a 90% yield of the diimide as a red solid, crystallizing from carbon tetrachloride as red crystals, m.p. 149–150°.

Anal. Calcd. for $C_{14}H_{20}N_2O_4S_3$: C, 44.66; H, 5.35; N, 7.44. Found: C, 44.31; H, 5.11; N, 7.71.

2-Cyclohexylthio-5,8-dihydro-5,8-methano-1,4-naphthalenedimethanesulfonamide (Vf).—Cyclopentadiene (8.2 ml.) was added to a solution of 6.79 g. (0.0180 mole) of 2-cyclohexylthio-*p*-quinonedimethanesulfonimide in 100 ml. of chloroform. The addition resulted in a color change from violet to amber within 2 min.[9] Triethylamine (3 ml.) was added, and the mixture was allowed to remain at room temperature for 2 hr. The solvent was then removed by evaporation *in vacuo*, and the semisolid residue was crystallized from a minimum of hot, glacial acetic acid (Norit) to give 4.63 g. (58%) of light tan solid. Recrystallization from glacial acetic acid gave colorless crystals, m.p. 183.5–184°.

Anal. Calcd. for $C_{15}H_{26}N_2O_4S_3$: C, 51.57; H, 5.92; N, 6.33. Found: C, 51.33; H, 5.65; N, 6.56.

The infrared spectrum showed the presence of the –NH– linkage (3280 cm.$^{-1}$).

Characterization of Alleged 4a-Chloro-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-bis(dimethylaminosulfonimide) (VI).—Treatment of 2-chloro-*p*-quinonebis(dimethylaminosulfonimide) with cyclopentadiene was repeated after the experiment of Adams and Shafer[4] with similar results. Two products were obtained: 2-chloro-5,8-dihydro-5,8-methano-1,4-naphthalenebis(dimethylaminosulfonamide) (Vg), m.p. 208.5–209.5° dec. (lit. 209.6–210.6° dec.), and a yellow crystalline isomer, m.p. 140–141° dec. (lit. 140–141° dec.). The infrared spectrum showed the same band at 1590 cm.$^{-1}$ attributed by the other authors to the carbon–nitrogen double bond.

To a warm, stirred solution of 3.00 g. (0.00712 mole) of the yellow isomer in 60 ml. of benzene was added 5 drops of triethylamine. The color of the solution changed from bright yellow to dark brown over a period of 3 min. The mixture was then boiled for 5 min., and upon cooling it yielded 0.65 g. of white solid. The filtrate was concentrated *in vacuo* to a dark brown, oily residue which was crystallized from nitromethane (Norit) to give 1.00 g. more of product, making the total yield 1.65 g. (55%). The combined portions were twice recrystallized from nitromethane (Norit) to give colorless crystals, m.p. 209.5–210.5° dec.

Anal. Calcd. for $C_{15}H_{21}ClN_4O_4S_2$: C, 42.80; H, 5.03; S, 15.23. Found: C, 42.75; H, 5.04; S, 15.35.

The infrared spectrum of this substance was identical with that of Vg.

5,8-Dihydro-5,8-methano-1,4-naphthalenedimethanesulfonamide (VII).—Cyclopentadiene (20 ml.) was added to a warm solution of 52.4 g. (0.200 mole) of *p*-quinonedimethanesulfonimide[8] and 1.7 ml. of triethylamine in 3 l. of chloroform. A dark brown color formed immediately, and the solution boiled spontaneously. After the reaction mixture had been allowed to stand at room temperature for 63 hr., a white solid had precipitated, and the supernatant liquid exhibited a cherry-red color. The solid was collected on a filter, washed with chloroform, and air-dried. The product (57.5 g., 88%), m.p. 211–212°, did not require further purification.

Anal. Calcd. for $C_{13}H_{16}N_2O_4S_2$: C, 47.54; H, 4.91; N, 8.53. Found: C, 47.79; H, 4.87; N, 8.35.

The infrared spectrum showed the presence of the –NH– linkage (3245 cm.$^{-1}$).

5,8-Dihydro-5,8-methano-1,4-naphthoquinonedimethanesulfonimide.—Lead tetraacetate oxidation of VII gave the diimide in 88% yield as a red solid, crystallizing from nitromethane as red crystals which decomposed without melting at 208°.

Anal. Calcd. for $C_{13}H_{14}N_2O_4S_2$: C, 47.84; H, 4.32; S, 19.65. Found: C, 47.83; H, 4.22; S, 19.65.

1,4,4a,5,8,9a-Hexahydro-1,4:5,8-dimethano-9,10-anthraquinonedimethanesulfonimide (VIII).—Cyclopentadiene (7 ml.) was added to a stirred suspension of 12.0 g. (0.0368 mole) of 5,8-dihydro-5,8-methano-1,4-naphthoquinonedimethanesulfonimide in 300 ml. of chloroform at room temperature. The color changed from dark red to light yellow over a period of about 2 min. The chloroform and excess cyclopentadiene were then removed by evaporation *in vacuo*, leaving 14.4 g. (100%) of product as a light yellow solid, which was twice recrystallized from ethanol to give light yellow crystals, m.p. *ca.* 182° dec.

Anal. Calcd. for $C_{18}H_{20}N_2O_4S_2$: C, 55.08; H, 5.14; S, 16.34. Found: C, 55.19; H, 5.16; S, 15.90.

1,4,5,8-Tetrahydro-1,4:5,8-dimethano-9,10-anthracenedimethanesulfonamide (IX). A.—Triethylamine (6 drops) was added to a boiling solution of 7.00 g. (0.0178 mole) of VIII in 100 ml. of chloroform. The solution was boiled under reflux for 32 hr., and upon cooling yielded 4.38 g. (63%) of light tan solid. Recrystallization from dimethylformamide gave a white solid which decomposed without melting from 300 to 320°.

Anal. Calcd. for $C_{18}H_{20}N_2O_4S_2$: C, 55.08; H, 5.14; S, 16.34. Found: C, 54.89; H, 5.20; S, 15.9.

The infrared spectrum showed the presence of the –NH– linkage (3240 cm.$^{-1}$).

B.—Cyclopentadiene (1.1 g., 0.017 mole) was added to a solution of 5.0 g. (0.016 mole) of 5,8-dihydro-5,8-methano-1,4-naphthoquinonedimethanesulfonimide and 6 drops of triethylamine in 200 ml. of chloroform with stirring. The solution was allowed to stand at room temperature for 20 min. during which time the color changed from red to yellow. The solution was then concentrated to yield 4.5 g. (72%) of tan crystals. Recrystallization from nitromethane gave a light tan solid which decomposed above 300°.

The infrared spectrum of this substance and that of the product prepared by procedure A were identical.

Acknowledgment.—The author is grateful to Mr. R. A. Nyquist of the Chemical Physics Research Laboratory, The Dow Chemical Company, for determination of the infrared spectra.

(9) Attempts to isolate the simple adduct (IVf) resulted in reversal of the Diels–Alder reaction to give the red 2-cyclohexylthio-*p*-quinonedimethanesulfonimide and cyclopentadiene.

Synthesis and Reactions of 2,6-Dimethyl-7,7-dicyanoquinonemethide

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The preparation of 2,6-dimethyl-7,7-dicyanoquinonemethide by the reaction of 2,6-dimethylphenol with thionyl chloride followed by treatment with malononitrile is described. This quinonemethide was treated with phenols, anthrone, N,N-dimethylaniline, and malononitrile to yield 1,6-addition products.

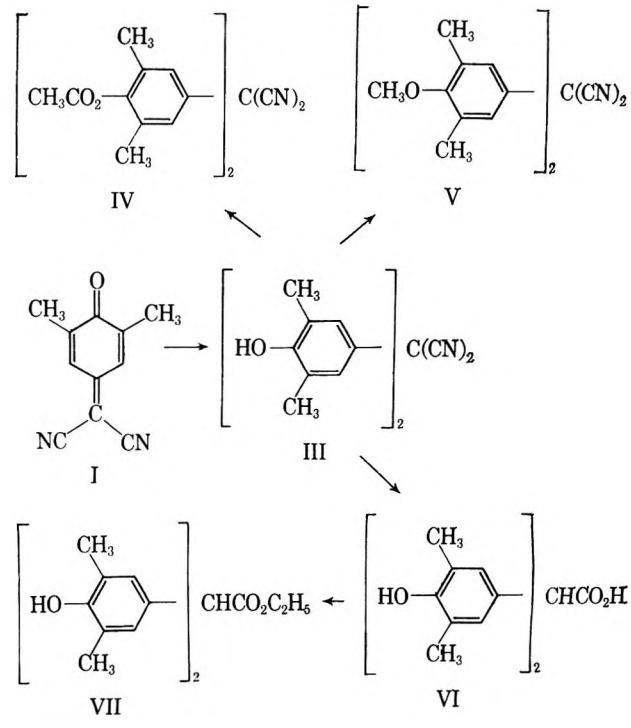
In this report the preparation and some reactions of 2,6-dimethyl-7,7-dicyanoquinonemethide (I) are described. Comparatively few compounds possessing the *p*-benzoquinonemethide structure have been reported[1] in the literature. Although 2,6-dialkylquinonemethides[1c,d] have been prepared in solution either by the dehydrohalogenation of the corresponding 4-halomethylphenols or by the oxidation of the 4-alkylphenols, the extreme instability of these compounds did not permit their isolation and characterization. The attempted isolation of these compounds lacking substituents on the methylene carbon generally resulted in dimerization. On the other hand the oxidation of 2,6-di-*t*-butyl-4-(2-propyl)phenol with potassium ferricyanide has been reported[1a] to yield a stable 2,6-di-*t*-butyl-7,7-dimethylquinonemethide. Similarly, the corresponding quinonemethides[1a,c] have been prepared from 2,6-di-*t*-butyl-4-(2-butyl)phenol and 2,6-di-*t*-butyl-4-ethylphenol. Apparently the replacement of the hydrogens on C-7 of the quinonemethide with other substituents inhibits the dimerization reaction. In the case of I, the presence of highly electronegative cyano groups imparts considerable stability to the quinonemethide structure.

The reaction of anthrone with thionyl chloride followed by treatment with malononitrile in *p*-dioxane has been reported[2] to produce 10-dicyanomethyleneanthrone (II). In view of the facile interconversion of anthrone and 9-anthrol, it appeared to us that this reaction, if applicable to simple phenols, would lead to a synthesis of 7,7-dicyanoquinonemethides. Thus, I was obtained by the reaction of 2,6-dimethylphenol, thionyl chloride, and malononitrile.

In contrast to the high yield (88%) of II obtained with anthrone, the use of 2,6-dimethylphenol *via* a similar sequence of reactions resulted in a low yield of the quinonemethide I. This compound was isolated from the reaction of the above phenol with thionyl chloride and malononitrile as a dark red complex formed between the quinonemethide I and 2,6-dimethyl-4-chlorophenol. The chlorophenol was formed by the action of thionyl chloride on 2,6-dimethylphenol. Considerable difficulty was encountered in consistently obtaining the product. The reaction was always accompanied by considerable tar formation. In addition to the quinonemethide, one or more of the following compounds were isolated from different runs: 2,6-dimethyl-4-chlorophenol, sulfur, tetracyanoethylene, 2,6-dimethyl-4-tricyanovinylphenol, bis(3,5-dimethyl-4-hydroxyphenyl)malononitrile, and 3,5-dimethyl-4-hydroxyphenyl 3,5-dimethyl-4-hydroxybenzenethiolsulfonate.[3]

In view of the high reactivity of *p*-benzoquinonemethides, perhaps the low yield of I is not unreasonable. In fact it is somewhat surprising that it was isolated from the reaction mixture which at one time contained thionyl chloride, hydrogen chloride, malononitrile, etc. The addition of 2,6-dimethyl-4-chlorophenol to the initial mixture to increase the chlorophenol available for complexing failed to result in a higher yield of I. Neither this chlorophenol nor tetracyanoethylene appeared to be an intermediate in the reactions leading to the synthesis of I. Although we feel that the quinonemethide formation is proceeding *via* the same mechanism as for 10-dicyanomethyleneanthrone synthesis involving a sulfur-containing intermediate, the two paths need not be the same.

The quinonemethide I was readily separated as golden yellow needles by trituration of the red complex with ethanol to remove 2,6-dimethyl-4-chlorophenol. The complex was readily re-formed by the addition of the chlorophenol. In the infrared, I exhibited a sharp absorption band at 2240 and a strong band at 1640 cm.$^{-1}$ characteristic for a conjugated nitrile group and a quinone CO group,[4] respectively. The CO absorption band of I in comparison to the same band in *p*-



(1) (a) C. D. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, **78**, 3797 (1956); (b) C. D. Cook and B. E. Norcross, *ibid.*, **81**, 1176 (1959); (c) L. Filar and S. Winstein, *Tetrahedron Letters*, **25**, 9 (1960); (d) J. D. McClure, *J. Org. Chem.*, **27**, 2365 (1962); (e) A. Huebele, H. Suhr, and U. Heilmann, *Ber.*, **95**, 639 (1962).

(2) H. H. Takimoto and L. O. Krbechek, *J. Org. Chem.*, **27**, 4688 (1962).

(3) H. H. Takimoto and G. C. Denault, *ibid.*, **29**, 759 (1964).

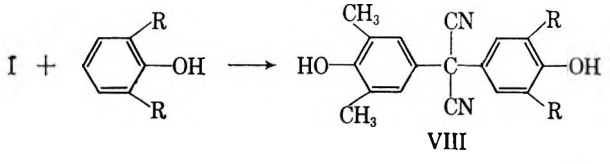
(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, Chapters 9 and 15.

benzoquinone had undergone a shift to a lower frequency. An ultraviolet absorption band at 334 mμ (ε 36,300) taken in ethanol was also observed. The proton n.m.r. spectrum of I in deuteriochloroform showed peaks at 2.52 and 7.71 p.p.m. from tetramethylsilane in the ratio of 3:1.

The quinonemethide I readily underwent a 1,6-addition with 2,6-dimethylphenol in the presence of an acid to yield bis(3,5-dimethyl-4-hydroxyphenyl)malononitrile (III). This compound was also obtained in some runs during the synthesis of I presumably from the reaction of I with 2,6-dimethylphenyl chlorosulfinate in the reaction mixture or from the free phenol formed during the work-up. III was converted to the diacetate IV with acetic anhydride or to the dimethyl ether V with dimethyl sulfate. Hydrolysis and decarboxylation of III gave bis(3,5-dimethyl-4-hydroxyphenyl)-acetic acid (VI). The latter compound was further converted to the ethyl ester VII by ethanolysis. VI was found to be identical with the compound[5] prepared from 2,6-dimethylphenol and diethyl ketomalonate followed by hydrolysis and decarboxylation.

Compound I appears to be similar in its chemical behavior with 7,7,8,8-tetracyanoquinonedimethide.[6] I was reduced to 2,6-dimethyl-4-dicyanomethylphenol in high yield either by catalytic hydrogenation or with thiophenol. Although 10-dicyanomethyleneanthrone, a structural analog of I, was catalytically hydrogenated, attempted reduction using thiophenol failed to yield 10-dicyanomethylanthrone. These results represent another case in which the *p*-benzoquinoid compound was more readily reduced to the aromatic structure than the corresponding anthraquinoid compound. The reduction of I with mercaptoacetic acid gave a low yield of 2,6-dimethyl-4-dicyanomethylphenol, the major product being a sulfur- and a nitrile-containing compound, whose structure as yet has not been identified.

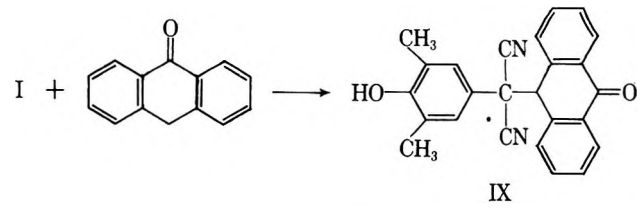
The acid-catalyzed 1,6-addition of phenols to I appears to be a general reaction. In addition to 2,6-dimethylphenol mentioned earlier, I reacted with both phenol, itself, and 2,6-di-*t*-butylphenol to yield the corresponding 3,5-dimethyl-4-hydroxyphenyl malononitrile derivatives VIII where R = H, CH_3, or *t*-C_4H_9.



VIII

In the absence of an acid, I formed a bright red complex with phenol or 2,6-dimethylphenol, whereas with 2,6-di-*t*-butylphenol, complex formation appeared not to take place. This is probably due to the bulkiness of *t*-butyl groups of the latter compound and may also account for the fact that the di-*t*-butylphenol underwent the addition to I with some reluctance in comparison to other phenols.

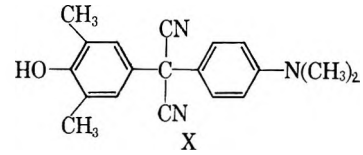
Similar to the reactions with phenols, I also reacted with anthrone to yield the 10-anthronylmalononitrile derivative IX. However, the reaction of 10-dicyanomethyleneanthrone (II) with 2,6-dimethylphenol cat-



IX

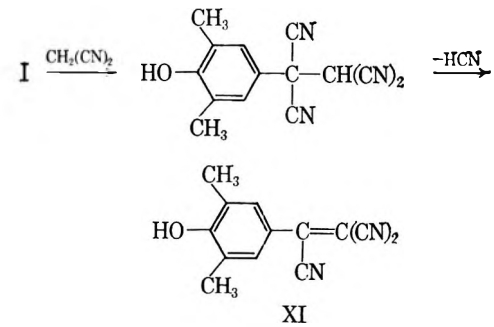
alyzed by boron trifluoride etherate or hydrogen chloride failed to yield IX under the conditions tried.

The reaction of I with N,N-dimethylaniline yielded an addition product (X). A structure isomeric to X involving a nuclear substitution of the 4-dimethylanilino group on the quinonemethide ring, although possible, has been ruled out by its nuclear magnetic resonance spectrum.



X

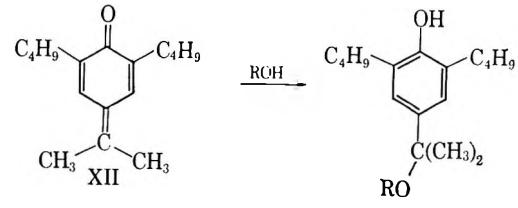
In contrast to the above reaction, the treatment of I with malononitrile in either acid or base yielded 2,6-dimethyl-4-tricyanovinylphenol (XI) which had previously been prepared[7] from 2,6-dimethylphenol and tetracyanoethylene. In the present case XI presumably resulted from the initial addition of malononitrile to I, followed by the elimination of hydrogen cyanide. It can readily be seen that XI found in the synthesis of I probably resulted from this reaction since malononitrile was used in excess.



XI

The treatment of the quinonemethide I with amines such as aniline, piperidine, and pyrrolidine appeared to result in initial formation of intensely colored complexes which reacted further to yield displacement and/or addition products. These products with amines have not been characterized as yet, although with aniline an addition product has been isolated.

The 1,6-addition of alcohol to 2,6-di-*t*-butyl-7,7-dimethylquinonemethide (XII) has been reported[1a] to proceed at room temperature when catalyzed by sulfuric acid. However, a solution of I in methanol con-



XII

(5) R. V. Smith and M. D. Bealor, *J. Org. Chem.*, **27**, 3092 (1962).

(6) (a) D. S. Acker and W. R. Hertler, *J. Am. Chem. Soc.*, **84**, 3370 (1962); (b) W. R. Hertler, H. D. Hartzler, D. S. Acker, and R. E. Benson, *ibid.*, **84**, 3387 (1962).

(7) G. N. Sauesen, V. A. Engelhardt, and W. J. Middleton, *ibid.*, **80**, 2815 (1958).

taining sulfuric acid yielded the unchanged quinonemethide, even after heating for 0.5 hr. I appears to be considerably less reactive than XII.

Experimental[8,9]

2,6-Dimethyl-7,7-dicyanoquinonemethide (I).—2,6-Dimethylphenol (9.76 g.) was added to 40 ml. of thionyl chloride and the resultant yellow solution was refluxed for 45 min. A vigorous evolution of hydrogen chloride was observed during this heating period. Malononitrile (10.56 g.) dissolved in 120 ml. of *p*-dioxane (distilled from sodium) was then added to the hot solution. Approximately 60 ml. of distillate was then removed from the system under reduced pressure and the remaining solution was refluxed for 1 hr. The solution, which was initially yellow, changed in color to amber, cherry red, and finally dark red to almost black. The remaining thionyl chloride and dioxane were then removed under reduced pressure leaving a black, viscous material. This material was poured out into a beaker and allowed to stand in the open for 2 days. During this time the material had hardened somewhat to a black tarry mass. The black mass was repeatedly extracted with hot petroleum ether (b.p. 60–90°). The dark red petroleum ether extracts were combined and concentrated to yield 4.5 g. of a dark red solid. This red solid was contaminated with free sulfur and 2,6-dimethyl-4-chlorophenol. Repeated recrystallizations from petroleum ether using decolorizing carbon yielded 3.0 g. (22%) of dark red needles melting at 94–96°. This solid proved to be a complex between 2,6-dimethyl-7,7-dicyanoquinonemethide (I) and 2,6-dimethyl-4-chlorophenol.

Anal. Calcd. for $C_{19}H_{17}N_2ClO_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 67.01; H, 5.01; N, 8.21.

The red complex of 2,6-dimethyl-7,7-dicyanoquinonemethide and 2,6-dimethyl-4-chlorophenol was triturated with small portions of ethanol until a gold colored solid was obtained. This solid was recrystallized from cyclohexane to yield 2,6-dimethyl-7,7-dicyanoquinonemethide as golden needles melting at 134–135°. A molecular weight determination by freezing point depression in benzene gave values of 177 and 172.

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.22. Found: C, 71.91; H, 4.52; N, 15.22.

The black residue from above, after the petroleum ether extraction of the quinonemethide–chlorophenol complex, was extracted further with several portions of hot benzene. The benzene solutions were combined, treated with decolorizing carbon, and concentrated. From this solution in different runs, there were obtained one or several of the following compounds in varying amounts: 2,6-dimethyl-4-chlorophenol, tetracyanoethylene, 2,6-dimethyl-4-tricyanovinylphenol, sulfur, bis(3,5-dimethyl-4-hydroxyphenyl)malononitrile, and 3,5-dimethyl-4-hydroxyphenyl 3,5-dimethyl-4-hydroxybenzenethiolsulfonate.[3]

The above procedure describes a run in which one of the best yields of I was obtained. Even when the apparent identical procedure was followed, the yields varied from 0 to 25%. We have been unable to determine the optimum conditions necessary for consistently obtaining a significant yield. However, the reaction carried out as described above has been satisfactory in providing the quinonemethide for the present study.

Bis(3,5-dimethyl-4-hydroxyphenyl)malononitrile (III).—A gold colored solution of the quinonemethide (0.18 g.) and 2,6-dimethylphenol (0.15 g.) dissolved in 25 ml. of benzene was saturated with gaseous hydrogen chloride, stoppered, and then allowed to stand overnight. The golden solution had turned water white during this time. The benzene solution was concentrated down to give a quantitative yield of a white crystalline solid (III) melting at 196–198°. This product was recrystallized from benzene. The infrared spectrum of the product showed an absorption band at 2530 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.22; H, 5.72; N, 9.16.

Bis(3,5-dimethyl-4-acetoxyphenyl)malononitrile (IV).—A mixture of bis(3,5-dimethyl-4-hydroxyphenyl)malononitrile (1.0 g.), pyridine (20 ml.), and acetic anhydride (8 ml.) was refluxed for 2 hr. The reaction mixture was cooled to room temperature and then poured onto crushed ice. The white solid, which precipitated, was separated, washed first with cold 2% hydrochloric acid and then with water, and dried to yield 1.25 g. (98%) of IV. Recrystallizations from ethanol gave white crystals, m.p. 211–214°. The infrared spectrum of the product exhibited absorption bands at 2260 (CN) and 1757 cm.$^{-1}$ (CO_2R).

Anal. Calcd. for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.70; H, 5.65; N, 7.31.

Bis(3,5-dimethyl-4-methoxyphenyl)malononitrile (V).—A mixture of bis(3,5-dimethyl-4-hydroxyphenyl)malononitrile (3.06 g.), dimethyl sulfate (5 ml.), and potassium carbonate (5.0 g.) in 100 ml. of acetone was refluxed for 19 hr. The mixture was allowed to cool and then filtered. The white solid, obtained after the removal of the solvent, was washed with water and then recrystallized from cyclohexane to yield 3.11 g. (93%) of bis(3,5-dimethyl-4-methoxyphenyl)malononitrile, m.p. 139–142°. Further recrystallizations from cyclohexane yielded an analytical sample, m.p. 142–144°. The infrared spectrum of the product exhibited a nitrile absorption band at 2260 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.37; H, 6.68; N, 8.40.

Bis(3,5-dimethyl-4-hydroxyphenyl)acetic Acid (VI).—A solution of bis(3,5-dimethyl-4-hydroxyphenyl)malononitrile (1.5 g.) and sodium hydroxide (25.0 g.) dissolved in dioxane (30 ml.) and water (75 ml.) was refluxed for 3.5 hr. The color of the solution turned from an initial purple to dark green. An evolution of ammonia was detected during this heating period. The solution was cooled, poured onto crushed ice, and then acidified by a dropwise addition of concentrated hydrochloric acid to the well-stirred cold mixture. The copious precipitate which separated was collected yielding 1.45 g. (98%) of V melting at 209–215°. Recrystallizations from a mixture of toluene and methanol gave white crystals melting at 215–217°. This compound showed no melting point depression when mixed with a sample of bis(3,5-dimethyl-4-hydroxyphenyl)acetic acid (m.p. 214–216°) prepared by the method of Smith and Bealor[5] and their infrared spectra were identical.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.07; H, 6.76.

Ethyl Bis(3,5-dimethyl-4-hydroxyphenyl)acetate (VII).—A solution of bis(3,5-dimethyl-4-hydroxyphenyl)acetic acid (0.8 g.) in 25 ml. of ethanol and 5 ml. of concentrated hydrochloric acid was refluxed for 24 hr. A quantitative yield of VII separated from the reaction mixture upon cooling to room temperature. An analytical sample, m.p. 164–165°, was prepared by three recrystallizations from benzene. The infrared spectrum of the product showed absorption bands at 3580 (OH) and 1720 cm.$^{-1}$ (CO_2R).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.17; H, 7.25.

2,6-Dimethyl-4-dicyanomethylphenol. A.—A solution of the quinonemethide I (0.40 g.) dissolved in 75 ml. of benzene was hydrogenated for 2 hr. using 0.05 g. of 5% palladium on charcoal. The mixture was filtered and the filtrate was concentrated to about 20 ml. Cyclohexane (20 ml.) was then added and the solution was placed in the cold for 10 min. White crystals which appeared were separated by filtration to yield 0.39 g. (96.5%) of 2,6-dimethyl-4-dicyanomethylphenol melting at 141–143°. Two recrystallizations from benzene–cyclohexane mixture yielded an analytical sample, m.p. 142–144°. The infrared spectrum of the product exhibited absorption bands at 3580 (OH) and 2265 cm.$^{-1}$ (CN). The proton n.m.r. spectrum in deuteriochloroform showed peaks at 2.70 (methyl), 5.15 (hydroxyl), 5.25 (methine), and 7.25 p.p.m. (aromatic) from tetramethylsilane in the ratio of 6:1:1:2, respectively. The hydrogen absorption at 5.15 p.p.m. appeared as an extremely broad peak.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.3; H, 5.46; N, 14.81.

B.—Thiophenol (3 ml.) was added to a solution of the quinonemethide (0.18 g.) in 10 ml. of acetic acid. The gold colored solution turned orange red. After standing overnight at room temperature, the color of the solution had changed to yellow. The volatile materials were then allowed to evaporate leaving a yellow crystalline residue. This residue was only partially soluble in cyclohexane. The white solid insoluble in cold cyclohexane was separated to yield 0.17 g. (93.5%) of 2,6-dimethyl-4-dicyanomethylphenol melting at 139–141°. Mixture

(8) All melting points are uncorrected.

(9) Analysis were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., Micro-Tech Laboratories, Skokie, Ill., and by Mr. S. Hotta of Aerospace Corp. The infrared and ultraviolet spectra were obtained on a Perkin-Elmer Model 21 and a Beckman DK-2 spectrophotometer. A Varian HR-60 n.m.r. spectrometer was used for the proton n.m.r. spectra.

melting point with the catalytic hydrogenation product of the quinonemethide showed no depression and their infrared spectra were identical.

Reaction of the Quinonemethide with Phenol.—A gold colored solution of the quinonemethide (0.18 g.) and phenol (0.15 g.) dissolved in 20 ml. of tetrahydrofuran containing 5 drops of concentrated hydrochloric acid was allowed to stand at room temperature for 2 days. The volatile materials were then removed from the pale yellow solution leaving a light brown residue. This residue was dissolved in hot benzene. On cooling 3,5-dimethyl-4-hydroxyphenyl-(4-hydroxyphenyl)malononitrile (0.26 g., 96%) separated as light brown needles which melted at 190–194°. Recrystallizations from benzene yielded an analytical sample, m.p. 196–198°. This compound when mixed with bis-(3,5-dimethyl-4-hydroxyphenyl)malononitrile (III) melted at 170–185°. The infrared spectrum of the product exhibited absorption bands at 3460, 3350 (OH), and 2275 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.6; H, 5.14; N, 10.08.

Reaction of the Quinonemethide with 2,6-Di-*t*-butylphenol.—Concentrated hydrochloric acid (5 drops) was added to a solution of the quinonemethide (0.18 g.) and 2,6-di-*t*-butylphenol (0.25 g.) in 25 ml. of tetrahydrofuran. The gold colored solution was allowed to stand at room temperature for 24 hr. No color change was observed. The removed of the volatile constituents gave impure starting materials as the residue. Tetrahydrofuran (25 ml.) and concentrated hydrochloric acid (5 drops) were again added. Refluxing the golden solution for 3 hr. effected no change in color. Five more drops of concentrated hydrochloric acid were added and the stoppered flask was set aside. After 3 days the golden color had disappeared. The removal of the volatiles yielded 0.26 g. (66.5%) of 3,5-dimethyl-4-hydroxyphenyl-(3,5-di-*t*-butyl-4-hydroxyphenyl)malononitrile melting at 171–175°. Recrystallizations from cyclohexane yielded an analytical sample, m.p. 176.5–178°. The infrared spectrum of the product showed absorption bands at 3570 (OH) and 2270 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.18. Found: C, 76.6; H, 8.00; N, 7.33.

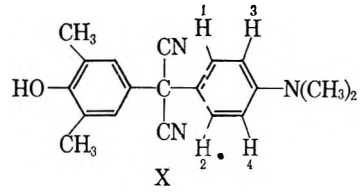
Reaction of the Quinonemethide with Anthrone.—A solution of the quinonemethide (0.18 g.) and anthrone (0.20 g.) in 20 ml. of tetrahydrofuran containing 5 drops of concentrated hydrochloric acid was allowed to stand for 3 hr. During this time the gold colored solution gradually turned yellow and white crystals separated out from the reaction mixture. The mixture was concentrated and then cooled to yield 0.36 g. (95%) of 3,5-dimethyl-4-hydroxyphenyl(10-anthronyl)malononitrile. Two recrystallizations from acetonitrile gave 0.32 g. of a white solid melting at 258–261°. The infrared spectrum of the product showed absorption bands at 3360 (OH), 2265 (CN), and 1670 cm.$^{-1}$ (quinone CO).

Anal. Calcd. for $C_{25}H_{18}N_2O_2$: C, 79.35; H, 4.80; N, 7.40. Found: C, 79.5; H, 4.81; N, 7.17.

Reaction of the Quinonemethide with N,N-Dimethylaniline.—Acetic acid (1 ml.) was added to a dark blue solution of the quinonemethide (0.18 g.) and N,N-dimethylaniline (1 ml.) dissolved in 10 ml. of tetrahydrofuran and the resultant solution was gently warmed for 1 hr. The dark solution was cooled and 25 ml. of water was added. White needles (0.30 g.) which separated were collected. An analytical sample (m.p. 157–158°) of 3,5-dimethyl-4-hydroxyphenyl-(4-N,N-dimethylanilino)malononitrile (X) was prepared by recrystallizations from cyclohexane. Infrared spectrum of the product showed absorption bands at 3600 (OH) and 2260 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{19}H_{19}N_3O$: C, 74.71; H, 6.27; N, 13.76. Found: C, 74.90; H, 6.35; N, 13.89.

The proton n.m.r. spectrum in deuteriochloroform showed peaks at 2.56 (methyl), 3.26 (methyl), 4.95 (hydroxyl), and 7.22 p.p.m. (aromatic) from tetramethylsilane in the ratio of 6:6:1:2, respectively. In addition the protons at positions 1, 2, 3, and 4



X

gave rise to a set of four lines at 6.74, 7.00, 7.34, and 7.39 p.p.m. corresponding to an AB-type spectrum. This indicated that positions 1 and 2 are equivalent but chemically shifted from the other equivalent protons at positions 3 and 4. The sum of the areas under each pair of lines corresponded to two protons.

In the absence of an acid catalyst, the quinonemethide and N,N-dimethylaniline yielded a complex which was isolated as dark blue shiny crystals. The complex was decomposed readily giving back the original quinonemethide on standing in the open at room temperature or on a melting point block at about 60°.

Reaction of the Quinonemethide with Malononitrile.—A solution of the quinonemethide (0.18 g.) and malononitrile (0.07 g.) dissolved in 10 ml. of tetrahydrofuran containing 5 drops of concentrated hydrochloric acid was allowed to stand at room temperature for 16 hr. Upon removal of the solvent, a quantitative yield of 2,6-dimethyl-4-tricyanovinylphenol, m.p. 178–181°, was obtained. Several recrystallizations from benzene gave a sample melting at 182–183° dec. This compound showed no melting point depression when mixed with an authentic sample of 2,6-dimethyl-4-tricyanovinylphenol[6] prepared by the reaction of 2,6-dimethylphenol with tetracyanoethylene. The infrared spectra were identical.

Anal. Calcd. for $C_{13}H_9N_3O$: C, 69.94; H, 4.07; N, 18.82. Found: C, 70.2; H, 4.16; N, 18.92.

The same product, 2,6-dimethyl-4-tricyanovinylphenol, was obtained from the reaction between the quinonemethide and malononitrile with pyridine and also in the absence of any catalyst.

Acknowledgment.—The authors are grateful to Dr. A. G. Whittaker for measurements and interpretations of nuclear magnetic resonance spectra. The authors are also indebted to Dr. L. Schieler for the helpful interest in this work and to Mr. S. Hotta for infrared and ultraviolet spectral measurements and assistance in the laboratory.

The Silver and Molybdenum Metal Complexes of *cis,cis,cis*-1,4,7-Cyclononatriene

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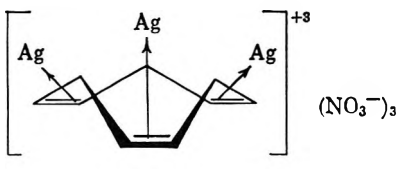
The preparations and properties of the silver nitrate–*cis,cis,cis*-1,4,7-cyclononatriene adduct and *cis,cis,cis*-1,4,7-cyclononatriene molybdenum tricarbonyl are described. The data for making the structural assignments of the two metal complexes are presented. In these assigned structures, the silver nitrate adduct of the title hydrocarbon has the silver ions associated with the outer (divergent) π-orbital lobes; the molybdenum tricarbonyl complex has the molybdenum bonded to the inner (convergent) π-orbital lobes of the title hydrocarbon.

Recently we reported the synthesis of *cis,cis,cis*-1,4,7-cyclononatriene (I).[1] Our isolation and purification procedure employed the formation of its silver nitrate complex (II). The silver nitrate complex of I forms with extreme ease. Either pure I or a solution of I (carbon tetrachloride, cyclohexane, isooctane) gives a quantitative yield of the salt when shaken with excess aqueous silver nitrate. The ligand does not rearrange during the complex formation since I is quantitatively regenerated from II with ammonium hydroxide. The complex II is an air-stable, white crystalline solid (m.p. 248° dec.) and is only slowly changed (days) when exposed to light. It exhibits a high degree of crystal stability, since it decomposes at a temperature significantly higher than silver nitrate itself (m.p. 212°). It is also noteworthy that ligand I can be recovered after thermal decomposition of II.

The elemental analyses and molecular weight determination of the complex show it has the formula C_9H_{12}-$(AgNO_3)_3$. The infrared spectrum of II exhibits major absorptions at 7.14, 7.20 sh, 7.69, 7.74 sh, and 7.97 μ. The proton n.m.r. spectrum shows clearly that the ligand I is present in the salt. The typical nine-lined pattern of the olefinic hydrogens of I[1] is seen at τ 4.08 (area = 2) and two separate multiplets for the methylene hydrogens at *ca.* τ 6.3 and 7.5 (area = 1), respectively. The conformation of ligand I has already been indicated to be the crown[2] and preliminary results of an X-ray structural determination of II show that the required C_{3v} symmetry is present. In addition, the conformation of I has been proven to be the crown by proton–proton spin decoupling experiments (this laboratory).[3]

From the above data, we assign the following structure to the complex II.



II

In this structure, the silver ions are bicoordinate and associated with the outer, or divergent, π-bond lobes. The symmetrical structure which has the silver ions bonded to the inner, or convergent, π-orbital lobes, we believe, is ruled out, since it would be sterically impossible to accommodate three silver ions in the space necessary for bonding along these directed π-lobes. Also, the silver ions would be as far apart as possible, due to the repulsion of their residual like charge. Our assigned structure (II) satisfies this requirement as well. This complex is the most stable cyclic triene–silver nitrate adduct thus far reported,[4] based on its ease of formation, high decomposition temperature, stability to oxygen and light, and its low dissociation constant (a sample of II, when subjected to a pressure of 0.1 mm. for 14 hr., showed no weight loss).

Because of the unique geometry of I, which results in half of the π-orbital lobes converging on one side of the plane of the double bonds, it was thought that metal complexes would easily form utilizing these converging lobes. Attempts to form such metal complexes were made with both molybdenum and chromium hexacarbonyls. It was thought that little change in the metal–ligand bonding angles would be necessary in order to form such complexes since both the molybdenum and chromium hexacarbonyls are bipyramidal with CO–M–CO angles of 90°. Aside from many other possible products, two likely pairs are *cis,cis,cis*-1,4,7-cyclononatrienemolybdenum or chromium tricarbonyl and di-*cis,cis,cis*-1,4,7-cyclononatrienemolybdenum or -chromium.

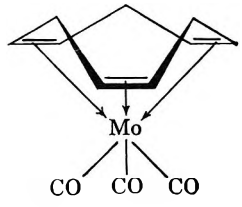
Despite this expected favorable situation, our attemps to complex I with chromium hexacarbonyl were unsuccessful. However, I readily forms a single product with molybdenum hexacarbonyl in refluxing isooctane or cyclohexane. The crude product precipitates out of solution in approximately 40% yield. Nearly all of the unchanged I can be recovered as II by treating the filtrate with aqueous silver nitrate. The molybdenum complex (III) is a lemon yellow, air-stable, crystalline solid which can be recrystallized from methylene chloride–cyclohexane or sublimed with accompanying decomposition at 140° (0.01 mm.). The compound does not exhibit a discrete melting point, but rather decomposes at various temperatures dependent upon the conditions employed, *e.g.*, slow decomposition beginning at 155° in a capillary open to the atmosphere, 185° in a sealed evacuated capillary. The complex is unstable in polar solvents (acetonitrile). Even acetone displaces the ligand from the molybdenum complex.

The elemental analysis of III gives it an empirical formula of $C_{12}H_{12}O_3Mo$. Its molecular weight was determined to be 310 (theory, 300). The infrared spectrum (KBr) exhibits strong absorptions at 5.14 and 5.44 μ and weak absorptions at *ca.* 3.4, 6.38, 6.66, 6.96, 7.74, 8.05, 8.11, and 13.02 μ. The ultraviolet spectrum shows

(1) K. G. Untch, *J. Am. Chem. Soc.*, **85**, 345 (1963).
(2) K. G. Untch and R. J. Kurland, *ibid.*, **85**, 346 (1963).
(3) K. G. Untch and R. J. Kurland, unpublished results.
(4) (a) For cyclooctatrienes see, A. C. Cope and F. A. Hochstein, *J. Am. Chem. Soc.*, **72**, 2515 (1950); W. O. Jones, *J. Chem. Soc.*, 1808 (1954); (b) for cyclododecatrienes, see L. I. Zakharkin and V. V. Korneva, *Dokl. Akad. Nauk SSSR*, **132**, 1078 (1960).

absorptions at λ_{max} 257 mμ (ε 18,000) and 352 (14,000) in cyclohexane at 5.3×10^{-5} mole/l.

The new molybdenum carbonyl complex is assigned structure III based on the above data. The structure



III

of III was proved when its proton n.m.r. spectrum was obtained. Despite the compound's low solubility in chloroform, enough did dissolve to provide a satisfactory spectrum using a Varian 100-Mc. spectrometer. The proton n.m.r. absorption patterns of III were somewhat unexpected. It was thought that the molybdenum tricarbonyl complex would display an n.m.r. spectrum quite similar to that of the "frozen" hydrocarbon (except for chemical shift differences).[2] The same nine-lined pattern of the parent triene is observed for the olefinic hydrogens of the metal complex (τ 6.09), thus showing the ligand to be intact and unrearranged. However, the methylene hydrogens absorb at nearly the same magnetic field (multiplet centered at *ca.* τ 6.95), unlike the two absorptions of the inner and outer methylene hydrogens of the "frozen" parent triene, which are separated by nearly 100 c.p.s. (60 Mc.).[2] In order to verify that the conformation of the ligand is a fixed crown, the olefinic protons were irradiated and the methylene hydrogen multiplet was observed. A typical AB quartet is observed for them which demonstrates the magnetic equivalence of the three inner and that of the three outer methylene hydrogens.

It is interesting that the proton n.m.r. absorptions of the inner and outer methylene hydrogens of III appear as one multiplet. Either the two types of methylene hydrogens are chemically shifted to approximately the same value accidentally, or the hydrocarbon portion of the metal complex is more nearly planar than the parent I. X-Ray structural determinations of I and III would decide between these alternatives and both are currently being undertaken.

Experimental

Infrared spectra were obtained from Nujol and halocarbon mulls and recorded with Beckman spectrophotometers, Models IR-4 and IR-9. Ultraviolet spectra were obtained on a Cary spectrophotometer, Model 15. Proton n.m.r. spectra were obtained on either a Varian Associates Model A-60 or HR-100 n.m.r. spectrometer.[5] Chemical shifts are given in p.p.m. downfield from tetramethylsilane. Melting and decomposition points were determined in capillary tubes and are uncorrected.

***cis,cis,cis*-1,4,7-Cyclononatriene–Silver Nitrate Complex (II).**—A solution of 24 mg. (0.2 mmole) of *cis,cis,cis*-1,4,7-cyclononatriene and 3.0 ml. of carbon tetrachloride was shaken with a solution of 159 mg. (0.9 mmole) of silver nitrate and 1.0 ml. of water. The resulting white precipitate was collected by suction filtration. Recrystallization of the crude salt from acetonitrile and diethyl ether at room temperature gave 126 mg. (quantitative yield) of II as white needles, m.p. 248° dec.

Anal. Calcd. for $C_9H_{12}O_9N_3Ag_3$: C, 17.16; H, 1.92; Ag, 51.38; mol. wt., 629.8. Found: C, 17.46; H, 2.06; Ag, 51.40; mol. wt., 146 × 4 = 584 (H_2O) and 162 × 4 = 648 (CH_3CN) (Mechrolab Model 301A osmometer).

A saturated deuterium oxide solution of II containing sodium 2,2-dimethyl-2-silapentane-5,5-sulfonate as an internal reference was used to obtain its proton n.m.r. spectrum.

A solution of 126 mg. (0.2 mmole) of II and 5.0 ml. of water was treated with 3.0 ml. of *ca.* 8 *N* ammonium hydroxide solution. The resulting suspended precipitate was extracted into carbon tetrachloride, which was washed with water until neutral. The carbon tetrachloride layer was treated with 159 mg. (0.9 mmole) of silver nitrate dissolved in 1.0 ml. of water. The resulting precipitate was collected and recrystallized as above to yield 125 mg. of white needles, m.p. 248° dec.

***cis,cis,cis*-1,4,7-Cyclononatrienemolybdenum Tricarbonyl.**—A solution of 76.2 mg. (0.635 mmole) of I (obtained from 400 mg. of purified II treated with ammonium hydroxide solution) and 15.0 ml. of isooctane was placed in a 50-ml. three-necked flask equipped with a magnetic stirrer, condenser, and gas inlet. After purging the system with nitrogen[6] 370 mg. (0.70 mmole) of molybdenum hexacarbonyl was added. The flask was immersed into a preheated (110°) oil bath and refluxed under a nitrogen atmosphere for 20 hr. During the course of this period a yellow solid precipitated from solution. The reaction mixture was cooled and the crude solid (90 mg., 47% yield) was collected by suction filtration. Recrystallization from methylene chloride–cyclohexane gave 63 mg. of yellow platelets. Melting point determinations were carried out on a sample that had been sublimed at 140° (0.01 mm.). Slow decompositions beginning at 155° in an open capillary tube and 185° in a sealed evacuated capillary tube were observed.

Anal. Calcd. for $C_{12}H_{12}O_3Mo$: C, 48.03; H, 4.00; O, 16.00; mol. wt., 300.1. Found: C, 48.22; H, 4.37; O, 16.14; mol. wt., 310 (benzene) (Mechrolab Model 301A osmometer).

The proton n.m.r. spectra were obtained from a saturated chloroform-*d* solution of III containing tetramethylsilane as the internal reference.

Acknowledgment.—The authors are pleased to acknowledge the assistance of Mrs. Margaret Sanville in obtaining the infrared spectra and that of Mrs. M. Y. Flynn in the molecular weight determinations.

(5) We thank Mr. L. F. Johnson of Varian Associates for the undecoupled and decoupled spectra obtained on the 100-Mc. spectrometer.

(6) Complete elimination of oxygen is necessary for the reaction to proceed. We have had several experiments fail to give any product due to traces of oxygen.

The Reaction of Sulfamide with α- and β-Diketones. The Preparation of 1,2,5-Thiadiazole 1,1-Dioxides and 1,2,6-Thiadiazine 1,1-Dioxides

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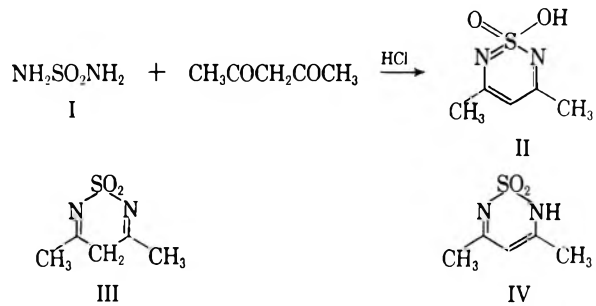
Reaction of sulfamide with a variety of β-diketones gave (2H)-1,2,6-thiadiazine 1,1-dioxides (V). The use of N-monosubstituted sulfamides gave 2-substituted 1,2,6-thiadiazine 1,1-dioxides (VI). The use of ethyl acylpyruvates as the β-diketones led to the 3-carbethoxy derivatives (VII), which reacted readily with amines to give amides and with hydrazine to give a hydrazide. The use of 2-acylcyclohexanones in the reaction with sulfamide gave 5,6,7,8-tetrahydro-(1H)-2,1,3-benzothiadiazine 2,2-dioxides (VIII). Catalytic hydrogenation of 3,5-dimethyl-(2H)-1,2,6-thiadiazine 1,1-dioxide gave the completely saturated tetrahydro-3,5-dimethyl-(2H)-1,2,6-thiadiazine 1,1-dioxide. Reaction of sulfamide with α-diketones led to 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides (IX). Reaction of sulfamide with α-hydroxy ketones gave 3,4-disubstituted 1,2,5-Δ²-thiadiazoline 1,1-dioxides (X). Catalytic reduction of either IX or X (where $R_1 = R_2 = C_6H_5$) led to the corresponding 3,4-disubstituted 1,2,5-thiadiazolidine 1,1-dioxide (XIII).

As part of a study underway in these laboratories aimed at the synthesis of new and unique heterocyclic systems we were interested in investigating the chemistry of sulfamide (I), a substance which has recently become commercially available.[1]

The use of sulfamide and N-substituted sulfamides in the preparation of heterocyclic compounds has been studied to a certain extent by Paquin,[2] and by others.[3] We were interested especially in investigating the reactions of sulfamide and substituted sulfamides with α- and β-diketones of various kinds.

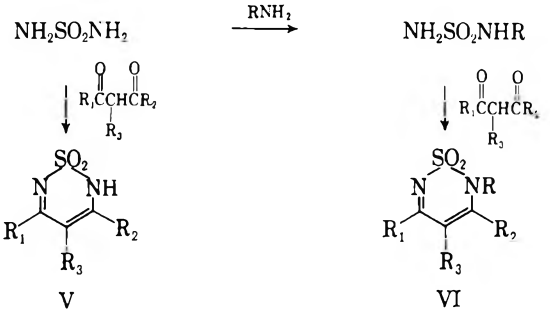
One report appears in the literature by Degering and Wilson[4] on the reaction between sulfamide and 2,4-pentanedione in the presence of gaseous hydrogen chloride. Structures II, III, and IV were considered by these authors for the reaction product. Some preference was indicated for II because of the pronounced acidity shown by the compound.



We have repeated this reaction according to the directions of Degering and Wilson[4] and have investigated the product formed. The n.m.r. spectrum (A-60, deuterated acetone) shows a singlet at 350 c.p.s. (reference line is tetramethylsilane) possessing an area of one proton attributable to vinyl hydrogen. The infrared spectrum shows a band at 3140 cm.$^{-1}$ attributable to O–H or N–H. These facts would argue against structure III. Furthermore, the compound possesses pronounced acidity (pK_a determined, 3.27), as reported by Degering and Wilson.[4]

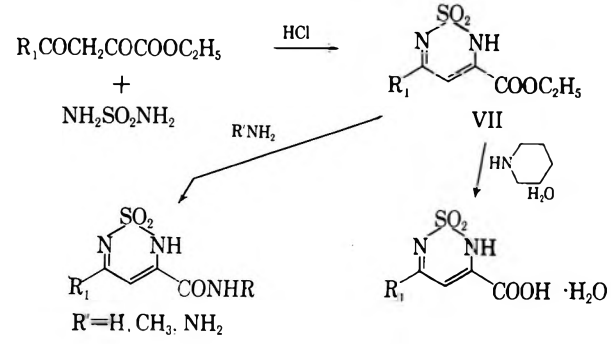
Structure II requires the sulfonyl group to be present in an enolic form, considered by some authors to be a less preferred configuration.[5] On the basis of the above facts structure IV would appear to be preferred. The acidity shown should not be incompatible with this structure.

We have investigated also a rather large number of β-diketones in the reaction with sulfamide and N-substituted sulfamides. The reactions were carried out as indicated.



The compounds prepared are listed in Table I. The structures V and VI are assigned on the basis of an analogy to structure IV. In those cases in compounds of the type V where R_1 and R_2 are different only one compound was isolated. This would indicate the presence of a tautomeric system.

Those compounds in Table I in which R_2 was various amide or hydrazide groupings were prepared by



(1) Allied Chemical Corp., General Chemical Division, New York, N. Y.

(2) A. M. Paquin, *Angew. Chem.*, A60, 316 (1948).

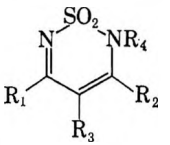
(3) (a) J. R. Geigy, A.-G, British Patent 859,316 (1961); (b) H. A Walter, U. S. Patent 2,454,261 (1948); (c) 2,454,262 (1948); (d) A. M. Paquin, *Kunstoffe*, **37**, 165 (1947); *Chem. Abstr.*, **43**, 5995[5] (1949); (e) R. Zimmermann and H. Hotze, *Angew. Chem.*, **75**, 1025 (1963).

(4) E. F. Degering and J. E. Wilson, *J. Org. Chem.*, **17**, 339 (1952).

(5) F. Arndt and B. Eistert, *Chem. Ber.*, **74**, 423 (1941).

TABLE I

1,2,6-THIADIAZINE 1,1-DIOXIDES

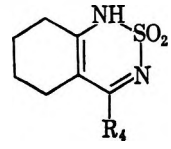


R_1	R_2	R_3	R_4	Procedure	Yield, %	M.p., °C.	Molecular formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
C_6H_5	C_6H_5	H	H	A	95[a]	278–279[b]	$C_{16}H_{12}N_2O_2S$	63.36	4.26	9.85	11.28	63.09	4.00	9.36	11.30
p-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	H	H	A	88	288–290[c]	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.97	10.26	65.43	5.01	8.59	10.08
$C_6H_5CH_2$–	CH_3	H	H	A	68	67–69[d]	$C_{11}H_{12}N_2O_2S$	55.91	5.12	11.86	13.57	56.01	4.94	11.54	13.47
CH_3	–$COOC_2H_5$	H	H	B	69	101.5–103.0[e]	$C_7H_{10}N_2O_4S$	38.53	4.62	12.84	14.69	38.75	4.76	12.42	14.77
CH_3	–$CONH_2$	H	H	C	61	243 dec.	$C_5H_7N_3O_3S$	31.74	3.73	...	16.95	31.68	3.64	...	17.00
CH_3	–$CONHCH_3$	H	H	C[f]	70	245 dec.[h]	$C_6H_9N_3O_3S$	35.46	4.46	20.68	15.78	36.05	4.41	20.82	15.84
C_6H_5	–$COOC_2H_5$	H	H	B	92	188–190[b]	$C_{12}H_{12}N_2O_4S$	51.42	4.32	10.00	11.44	51.22	4.00	9.61	11.52
C_6H_5	–$CONH_2$	H	H	C[g]	27	265 dec.[b]	$C_{10}H_9N_3O_3S$	47.80	3.61	16.72	12.76	47.99	3.31	16.30	12.89
C_6H_5	–$CONHCH_3$	H	H	C[f]	93.5	265 dec.[b]	$C_{11}H_{11}N_3O_3S$	49.80	4.18	15.84	12.09	49.91	3.81	15.41	12.15
C_6H_5	–COOH	H	H	...	67	203 dec.	$C_{10}H_8N_2O_4S\cdot H_2O$[h]	44.44	3.73	10.37	11.86	44.62	3.67	10.33	12.06
p-$CH_3C_6H_4$	–$COOC_2H_5$	H	H	B[i]	85	176–177[b]	$C_{13}H_{14}N_2O_4S$	53.05	4.79	9.52	10.86	53.16	4.64	9.12	10.89
p-$CH_3C_6H_4$	–$CONHNH_2$	H	H	...	43	223 dec.	$C_{11}H_{12}N_4O_3S$	47.14	4.32	19.99	11.44	47.20	4.52	19.61	11.21
p-ClC_6H_4	–$COOC_2H_5$	H	H	B[j]	81	170.5–172.5[b]	$C_{12}H_{11}ClN_2O_4S$[k]	45.79	3.52	8.90	10.19	46.30	3.62	8.71	10.15
p-ClC_6H_4	–$CONH_2$	H	H	C	26	225 dec.[l]	$C_{10}H_8ClN_3O_3S$[m]	42.04	2.82	...	11.22	42.72	2.64	...	11.05
p-ClC_6H_4	–$CONHCH_3$	H	H	C[f]	55	268 dec.[b]	$C_{11}H_{10}ClN_3O_3S$[n]	44.08	3.36	...	10.70	44.39	3.49	...	10.58
	CH_3	H	H	B[o]	55	291 dec.	$C_9H_9N_3O_2S$	48.40	4.06	18.85	14.40	48.08	3.75	18.48	14.37
	CH_3	H	H	B	77	276 dec.[p]	$C_9H_9N_3O_2S\cdot HCl$[q]	41.62	3.88	16.18	12.35	42.24	3.77	15.87	11.91
CH_3	CH_3	C_6H_5	H	B[r]	73	195–195.5	$C_{11}H_{12}N_2O_2S$	55.93	4.58	11.86	13.55	55.56	4.80	11.45	13.53
C_6H_5	C_6H_5	H	C_4H_9	...	39	99–100	$C_{19}H_{20}N_2O_2S$	67.03	5.92	8.23	9.42	66.59	5.89	8.19	9.51

[a] The yield is based upon the amount of diketone recovered. [b] Recrystallized from ethanol. [c] Recrystallized from dioxane and washed with acetone. [d] Recrystallized from benzene–cyclohexane (4:1). [e] Recrystallized from benzene. [f] Two molar equivalents of methylamine, as a 25% aqueous solution were used in place of an ammonia solution. [g] The solution was allowed to stand for several days instead of overnight. [h] *Anal.* Calcd. for H_2O: 6.67. Found: 7.02. [i] The reflux time was increased to 4 hr. [j] The reflux time was increased to 5 hr. [k] *Anal.* Calcd. for Cl: 11.26. Found: 11.28. [l] Recrystallized from water. [m] *Anal.* Calcd. for Cl: 12.41. Found: 12.45. [n] *Anal.* Calcd. for Cl: 11.83. Found: 11.86. [o] No precipitate formed following the reflux period. The solution was concentrated to dryness *in vacuo* and the residue recrystallized from water. [p] Recrystallized from methanol containing 1% water. [q] *Anal.* Calcd. for Cl: 13.65. Found: 13.48. [r] After filtration of the crude reaction product the filtrate was evaporated to dryness and the combined precipitate and residue recrystallized from benzene–cyclohexane (9:1).

TABLE II

5,6,7,8-TETRAHYDRO-(1H)-2,1,3-BENZOTHIADIAZINE 2,2-DIOXIDES

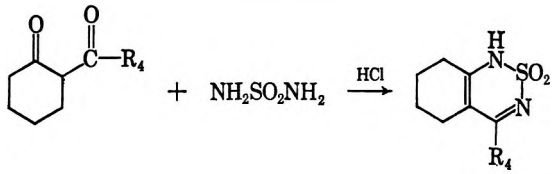


R4	Yield, %	M.p., °C.	Procedure	Molecular formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
CH_3	86	180–181	D[a]	$C_8H_{12}N_2O_2S$	47.98	6.04	13.99	16.01	48.25	6.28	13.60	16.18
C_6H_5	84.5	141–142	D[b]	$C_{13}H_{14}N_2O_2S$	59.52	5.38	10.68	12.22	59.35	5.21	10.77	12.26
p-$CH_3OC_6H_4$	83	149–151	D[b,c]	$C_{14}H_{16}N_2O_3S$	57.52	5.52	9.58	10.97	57.54	5.42	9.53	11.02
3,4,5-$(CH_3O)_3C_6H_2$	100	214–216	D[a,c]	$C_{16}H_{20}N_2O_5S$	54.53	5.72	7.59	9.10	54.70	6.06	7.84	9.03

[a] Recrystallized from ethanol. [b] Recrystallized from isopropyl alcohol. [c] The residue obtained upon concentration of the reaction mixture was triturated with an ether–water mixture to induce crystallization.

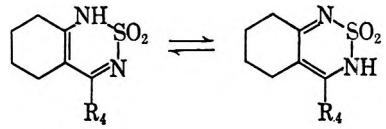
treatment of the carbethoxy derivative (VII) with ammonia, methylamine, or hydrazine. Treatment of the ester (VII) with piperidine in water followed by acidification with hydrochloric acid resulted in hydrolysis to the acid.

The use of 2-acylcyclohexanones in the reaction gave excellent yields of 5,6,7,8-tetrahydro-(1H)-2,1,3-benzothiadiazine 2,2-dioxides (VIII).



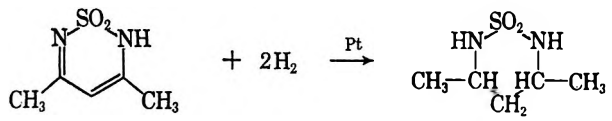
VIII

These compounds are listed in Table II. In each case only one product was formed. Although an isomeric structure may be written for VIII this probably tautomerizes readily.



VIII

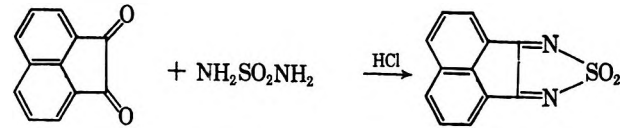
Catalytic hydrogenation of 3,5-dimethyl-1,2,6-thiadiazine 1,1-dioxide using Adams catalyst proceeded with the absorption of 2 moles of hydrogen.



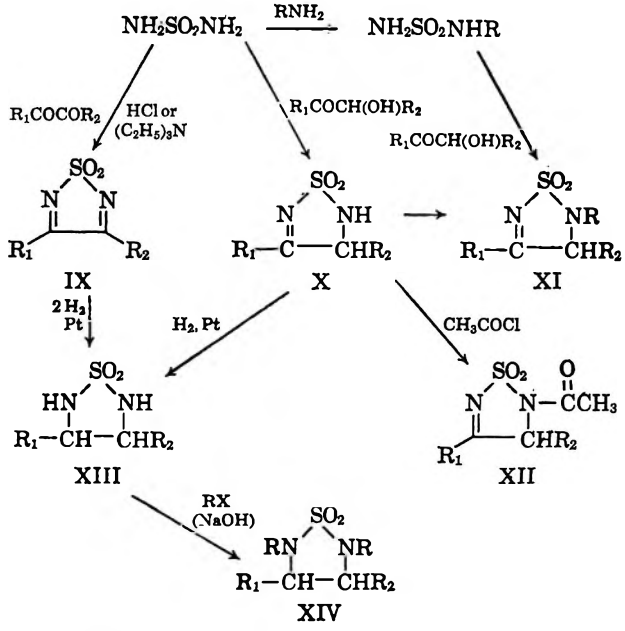
The infrared and nuclear magnetic resonance spectra were in agreement with the tetrahydro-3,5-dimethyl-(2H)-1,2,6-thiadiazine 1,1-dioxide structure. The infrared spectrum significantly showed no absorption in the C=C or C=N regions. Absorption bands were present at 3210 (attributable to NH), 1340 and 1175 (attributable to SO_2) and 1135 cm.$^{-1}$ (attributable to C–N). The n.m.r. spectrum showed a doublet centered at δ 1.2 (J = 7 c.p.s.), possessing an area of six protons, assignable to the two methyl groups. Absorption assignable to the tertiary hydrogens, possessing an area of two protons, was centered at δ 3.6. Also present were triplets showing an AB pattern, centered at δ 1.78 and 1.08, assignable to the hydrogens of the methylene group.[6]

Reaction of α-diketones with sulfamide proceeded readily under conditions of acidic (gaseous HCl) or basic [$(C_2H_5)_3N$] catalysis to give 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides (IX). The compounds of this type that were prepared are listed in Table III.

Acenaphthenequinone with sulfamide gave acenaphtho[1,2-c](1,2,5)thiadiazole 8,8-dioxide. Reaction of



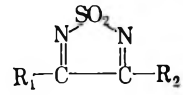
α-hydroxy ketones with sulfamide in the presence of gaseous hydrogen chloride gave the corresponding 3,4-disubstituted 1,2,5-thiadiazoline 1,1-dioxides (X). The use of an N-substituted sulfamide (N-butylsulfamide) in place of sulfamide in this reaction gave the corresponding 2-alkyl derivative XI. One 2-alkyl derivative (XI, R = CH_3; R_1 = R_2 = C_6H_5) was prepared by treatment of X (R_1 = R_2 = C_6H_5) with diazomethane. Acylation of X (R_1 = R_2 = C_6H_5) proceeded readily with boiling acetyl chloride to give the 2-acetyl derivative



(6) This spectrum was taken on an A-60 n.m.r. spectrometer (Varian Associates, Inc.) using tetramethylsilane as the reference standard.

TABLE III

1,2,5-THIADIAZOLE 1,1-DIOXIDES

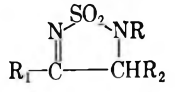


						Analyses, %							
						Calcd.				Found			
R_1	R_2	Yield, %	M.p., °C.	Procedure	Molecular formula	C	H	N	S	C	H	N	S
C_6H_5	C_6H_5	58	248–250	E	$C_{14}H_{10}N_2O_2S$	62.21	3.73	10.37	11.86	61.90	3.38	10.11	11.64
p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	82	206–207	F[a]	$C_{16}H_{14}N_2O_2S$	64.41	4.73	9.39	10.75	64.45	4.83	9.08	10.46
C_6H_5	CH_3	29	135 dec.	F[b,c]	$C_9H_8N_2O_2S$	51.91	3.87	...	15.40	52.05	3.64	...	15.50
p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	45	185–186	F[d]	$C_{16}H_{14}N_2O_4S$	58.17	4.27	8.48	9.71	58.31	4.11	8.41	9.70

[a] Recrystallized from butanone-2. [b] The reflux period was increased to 3 hr. The mother liquors from the filtration were concentrated *in vacuo* and the residue washed with water and then ether before recrystallization. [c] Recrystallized from benzene. [d] Recrystallized from ethyl acetate.

TABLE IV

1,2,5-THIADIAZOLINE 1,1-DIOXIDES



						Analyses, %							
						Calcd.				Found			
R_1	R_2	R	Yield %	M.p., °C.	Molecular formula	C	H	N	S	C	H	N	S
C_6H_5	C_6H_5	H	63	135.5–136.0	$C_{14}H_{12}N_2O_2S$	61.75	4.44	10.29	11.77	62.32	4.23	10.05	11.44
C_6H_5	C_6H_5	CH_3	42	158–160	$C_{15}H_{14}N_2O_2S$	62.92	4.93	9.79	11.20	62.87	4.87	9.54	11.06
C_6H_5	C_6H_5	C_4H_9	37	132.5–134	$C_{18}H_{20}N_2O_2S$	65.84	6.14	8.53	9.75	65.78	6.15	8.22	9.77
C_6H_5	C_6H_5	CH_3CO	92	170–171	$C_{16}H_{14}N_2O_3S$	61.13	4.49	8.91	10.20	61.35	4.62	8.78	10.03
p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	H	45	72–75 dec.	$C_{16}H_{16}N_2OS$	63.98	5.37	9.33	10.67	64.54	5.21	9.40	10.84

tive (XII, $R_1 = R_2 = C_6H_5$). The 1,2,5-thiadiazoline 1,1-dioxides that were prepared are listed in Table IV.

Catalytic hydrogenation of both 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide (IX, $R_1 = R_2 = C_6H_5$) and 3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (X, $R_1 = R_2 = C_6H_5$) proceeded readily with Adams catalyst with the absorption of 2 moles and 1 mole of hydrogen, respectively, to give the corresponding 3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide (XIII, $R_1 = R_2 = C_6H_5$). The latter compound underwent alkylation readily with 2 moles of methyl iodide in the presence of sodium hydroxide to give 2,5-dimethyl-3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide (XIV, R = CH_3; $R_1 = R_2 = C_6H_5$). It was also acylated readily, with dimethylcarbamyl chloride in the presence of sodium hydroxide, to give 2,5-bis(dimethylcarbamyl)-3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (XIV, R = $(CH_3)_2N—C(O)—$; $R_1 = R_2 = C_6H_5$). (See p. 1907.)

Experimental[7-9]

Procedure A. Preparation of 3,5-Diphenyl-(2H)-1,2,6-thiadiazine 1,1-Dioxide.—A mixture of 4.8 g. (0.05 mole) of sulfamide and 11.21 g. (0.05 mole) of 1,3-diphenylpropanedione-1,3 in 40 ml. of anhydrous ethanol was treated with hydrogen chloride gas for a short period of time. The mixture was heated at 60° for 3 hr. and then heated under reflux 5 min. The mixture was heated at 60° for 3 hr. and then heated under reflux 5 min. The mixture was evaporated to dryness *in vacuo* and the residue was triturated with several portions of ether and filtered after each treatment. From the ethereal filtrate there was obtained 5.91 g. of recovered 1,3-diphenylpropanedione-1,3. The ether-insoluble residue was stirred with several portions of water, filtered after each washing, and the residue recrystallized from ethanol.

Procedure B. Preparation of Ethyl 5-Methyl-(2H)-1,2,6-thiadiazine-3-carboxylate 1,1-Dioxide.—To a stirred mixture of 15.82 g. (0.1 mole) of ethyl acetopyruvate, 9.6 g. (0.1 mole) of sulfamide, and 100 ml. of anhydrous ethanol was added gaseous anhydrous hydrogen chloride until the temperature reached 50°. The mixture was then heated under reflux for 3 hr. and the product removed by filtration and purified by recrystallization from benzene.

Procedure C. Preparation of 5-Methyl-(2H)-1,2,6-thiadiazine-3-carboxamide 1,1-Dioxide.—A solution of 15.0 g. (0.069 mole) of ethyl 5-methyl-(2H)-1,2,6-thiadiazine-3-carboxylate 1,1-dioxide and 10 ml. of concentrated ammonium hydroxide in 50 ml. of water was allowed to stand at room temperature for 18 hr. and was then acidified with 1 *N* hydrochloric acid. The precipitate was removed by filtration, washed with water, and purified by recrystallization from water.

5-Phenyl-1,2,6-(2H)-thiadiazine-3-carboxylic Acid 1,1-Dioxide Hydrate.—To 2.80 g. (0.01 mole) of ethyl 5-phenyl-(2H)-1,2,6-thiadiazine-3-carboxylate 1,1-dioxide was added 1.70 g. (0.02 mole) of piperidine and 15 ml. of water. After standing overnight the yellow solution was acidified by the addition of 1 *N* hydrochloric acid; the precipitate was removed by filtration and recrystallized from water.

5-*p*-Tolyl-(2H)-1,2,6-thiadiazine 1,1-Dioxide 3-Carboxyhydrazide.—A solution of 8.0 g. (0.027 mole) of ethyl 5-*p*-tolyl-(2H)-1,2,6-thiadiazine-3-carboxylate 1,1-dioxide and 27 g. (0.54 mole) of hydrazine hydrate was allowed to stand overnight and was then acidified by the addition of 1 *N* hydrochloric acid. The precipitate was removed by filtration, washed with water, and recrystallized from ethanol–dimethylformamide (2:1).

2-Butyl-3,5-diphenyl-1,2,6-thiadiazine 1,1-Dioxide.—Into a stirred mixture of 6.88 g. (0.03 mole) of 1,3-diphenylpropanedione-1,3, 4.66 g. (0.03 mole) of butylsulfamide,[2] and 30 ml. of anhydrous ethanol was passed anhydrous hydrogen chloride gas until the temperature reached 50°. The solution was then heated under reflux for 5 hr., and concentrated *in vacuo*, the residue taken up in ether and water. The ether layer was separated, dried over anhydrous magnesium sulfate, and the ether removed. The residue was recrystallized from ethanol.

Procedure D. Preparation of 5,6,7,8-Tetrahydro-4-methyl-(1H)-2,1,3-benzothiadiazine 2,2-Dioxide.—Into a stirred mixture of 86.0 g. (0.61 mole) of 2-acetylcyclohexanone, 58.8 g. (0.61 mole) of sulfamide, and 480 ml. of anhydrous ethanol was

(7) All melting points are corrected.

(8) The author is indebted to Mr. Albert Lallinger for much technical assistance. He is indebted also to Dr. George Slomp and his associates for the nuclear magnetic resonance spectra, to Dr. Gerald Umbreit and his associates for the microanalytic data, and to Miss Lorraine Pachigoda for the infrared spectral data.

(9) Unless otherwise noted, the physical properties and analytical data are given in the tables.

bubbled hydrogen chloride gas until the temperature reached 60°. The solution was then heated under reflux for 30 min. and the solution concentrated to dryness *in vacuo*. The residue was purified by recrystallization.

Tetrahydro-3,5-dimethyl-(2H)-1,2,6-thiadiazine 1,1-Dioxide.—A solution of 8.0 g. (0.05 mole) of 3,5-dimethyl-(2H)-1,2,6-thiadiazine 1,1-dioxide in 100 ml. of ethanol was hydrogenated at 3 atm. of hydrogen using 200 mg. of platinum oxide as catalyst. Two moles of hydrogen were absorbed after 3 hr. The catalyst was removed by filtration, the solvent removed under vacuum, and the residue recrystallized from ethyl acetate. There was obtained 4.0 g. (49%) of colorless prisms melting at 140–144°. Additional recrystallization raised the melting point to 144–145°.

Anal. Calcd. for $C_5H_{12}N_2O_2S$: C, 36.57; H, 7.37; N, 17.06; S, 19.52. Found: C, 37.13; H, 7.39; H, 16.75; S, 19.50.

Procedure E. Preparation of 3,4-Diphenyl-1,2,5-thiadiazole 1,1-Dioxide.—A mixture of 10.5 g. (0.05 mole) of benzil, 4.8 g. (0.05 mole) of sulfamide, and 2 ml. of triethylamine in 100 ml. of ethanol was heated under reflux for 24 hr. The solution was concentrated to dryness *in vacuo;* the residue was triturated with water, then with ether, and purified by recrystallization from acetone.

Procedure F. Preparation of 3,4-Diphenyl-1,2,5-thiadiazole 1,1-Dioxide.—Into a mixture of 10.51 g. (0.05 mole) of benzyl and 4.8 g. (0.05 mole) of sulfamide in 50 ml. of anhydrous ethanol was bubbled hydrogen chloride gas until the temperature reached 55°. The mixture was heated under reflux for 2 hr., and the precipitate that formed on cooling was removed by filtration (6.33 g., m.p. 248–250°). An additional 0.53 g. was obtained by concentration of the mother liquors. The total yield was thus 6.86 g. (51%). This material gave no depression in melting point when mixed with the material made according to procedure E. The infrared spectra were also identical.

Acenaphtho[1,2-*c*](1,2,5)thiadiazole 8,8-Dioxide.—Into a stirred mixture of 9.1 g. (0.05 mole) of acenaphthenequinone, 4.8 g. (0.05 mole) of sulfamide, and 50 ml. of anhydrous ethanol was bubbled dry hydrogen chloride gas until the temperature reached 60°. The mixture was heated under reflux for 3 hr. with stirring, cooled, and the precipitate removed by filtration. Recrystallization from pyridine gave 8.62 g. (71%) of material melting at 227–232°. Additional recrystallization raised the melting point to 233–234°.

Anal. Calcd. for $C_{12}H_6N_2O_2S$: C, 59.50; H, 2.49; N, 11.57; S, 13.23. Found: C, 59.70; H, 2.09; N, 11.80; S, 13.32.

3,4-Diphenyl-1,2,5-Δ²-thiadiazoline 1,1-Dioxide.—Into a stirred mixture of 127.2 g. (0.6 mole) of benzoin, 57.6 g. (0.6 mole) of (0.6 mole) of sulfamide, and 600 ml. of anhydrous ethanol was bubbled dry hydrogen chloride gas until the temperature rose to 50°. The mixture was then heated under reflux for 4 hr. and the resulting solution concentrated *in vacuo*. The residue was taken up in water and extracted with ether and once with chloroform. The extracts were concentrated by distillation and the residue was recrystallized from anhydrous ethanol–cyclohexane (1:1).

5-Methyl-3,4-diphenyl-1,2,5-Δ²-thiadiazoline 1,1-Dioxide.—To a solution of 3.20 g. (0.01172 mole) of 3,4-diphenyl-1,2,5-Δ²-thiadiazoline 1,1-dioxide in 50 ml. of methylene chloride was added an ethereal solution of diazomethane. After standing at room temperature for 1 hr. the excess diazomethane was destroyed by the addition of acetic acid and the solution evaporated to dryness. The residue was recrystallized from ethanol.

5-Butyl-3,4-diphenyl-1,2,5-Δ²-thiadiazoline 1,1-Dioxide.—The procedure described above for 3,4-diphenyl-1,2,5-Δ²-thiadiazoline 1,1-dioxide was employed using an equivalent amount of butylsulfamide.[2] The product was purified by recrystallization from ethanol.

5-Acetyl-3,4-diphenyl-1,2,5-Δ²-thiadiazoline 1,1-Dioxide.—A mixture of 5.45 g. (0.02 mole) of 3,4-diphenyl-1,2,5-Δ²-thiadiazoline 1,1-dioxide and 15 ml. of acetyl chloride was heated under reflux for 1 hr. and the excess acetyl chloride then removed by distillation under reduced pressure. The residue was triturated with ethanol and then recrystallized from ethyl acetate.

3,4-Di-*p*-tolyl-1,2,5-Δ²-thiadiazoline 1,1-Dioxide.—The procedure described above for 3,4-diphenyl-1,2,5-Δ²-thiadiazoline 1,1-dioxide was employed using an equivalent amount of 4,4'-toluoin in place of benzoin. The product was recrystallized from benzene–cyclohexane (3:1).

3,4-Diphenyl-1,2,5-thiadiazolidine 1,1-Dioxide.—A mixture of 43.2 g. (0.16 mole) of 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide in 500 ml. of ethanol was hydrogenated at 3 atm. of hydrogen using 1.2 g. of platinum oxide as catalyst. When the theoretical amount of hydrogen was absorbed (2 hr.) the mixture was heated to reflux on a steam bath and the catalyst removed by filtration of the hot solution. The precipitate that formed on cooling was removed by filtration. Additional material was obtained by concentration of the mother liquors, total yield, 32.60 g. (75%); m.p. 202–203.5°. Recrystallization from ethanol gave colorless needles melting at 202.5–203.5°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.08; H, 4.96; N, 10.03; S, 11.67.

Hydrogenation of 3,4-diphenyl-1,2,5-Δ²-thiadiazoline 1,1-dioxide (8.17 g., 0.03 mole) in 150 ml. of ethanol using 150 mg. of PtO_2 proceeded with the uptake of 1 mole of hydrogen in 30 min. The reaction mixture was worked up as described above, giving 4.16 g. (51%) of colorless needles melting at 202–203°. A mixture melting point with the material obtained above by reduction of 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide showed no depression. The infrared spectra of the two samples were also identical.

2,5-Dimethyl-3,4-diphenyl-1,2,5-thiadiazolidine 1,1-Dioxide.—To a stirred mixture of 5.49 g. (0.02 mole) of 3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide, 1.76 g. (0.044 mole) of sodium hydroxide, 10 ml. of water, and 20 ml. of ethanol was added 4 ml. of methyl iodide. The mixture was stirred at room temperature overnight. The mixture was diluted with 25 ml. of water and the solid removed by filtration and recrystallized from ethanol. There was obtained 5.35 g. (88%) of colorless prisms melting at 164–165°.

Anal. Calcd. for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.27; S, 10.60. Found: C, 63.74; H, 6.02; N, 9.25; S, 10.55.

2,5-Di(dimethylcarbamyl)-3,4-diphenyl-1,2,5-thiadiazolidine 1,1-Dioxide.—A mixture of 5.49 g. (0.02 mole) of 3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide, 5.6 g. (0.052 mole) of dimethylcarbamyl chloride, 16 g. of anhydrous potassium carbonate, and 90 ml. of dry benzene was heated under reflux using a water trap. The theoretical amount of water was collected after 20 hr. of refluxing. The mixture was filtered and the filtrate was concentrated *in vacuo*. Recrystallization of the residue from ethanol gave 4.43 g. (53%) of colorless prisms melting at 210–211°.

Anal. Calcd. for $C_{20}H_{24}N_4O_4S$: C, 57.68; H, 5.81; N, 13.45; S, 7.70. Found: C, 57.48; H, 5.88; N, 13.25; S, 7.82.

3,4-Di-*p*-Tolyl-1,2,5-thiadiazolidine 1,1-Dioxide.—A mixture of 7.45 g. of 3,4-di-*p*-tolyl-1,2,5-thiadiazole 1,1-dioxide and 200 ml. of ethanol was hydrogenated at 3-atm. pressure using 400 mg. of platinum oxide as catalyst. Two moles of hydrogen were absorbed in 7 hr. The catalyst was removed by filtration, the filtrate concentrated to dryness *in vacuo*, and the residue recrystallized repeatedly from a benzene–cyclohexane mixture (2:1). There was obtained 1.61 g. (21%) of colorless platelets melting at 165–167°. Further recrystallization raised the melting point to 167–168°.

Anal. Calcd. for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.27; S, 10.60. Found: C, 63.24; H, 6.03; N, 9.11; S, 10.55.

Thiolesters. Reaction of Thiols with Acrylyl and Crotonyl Chlorides

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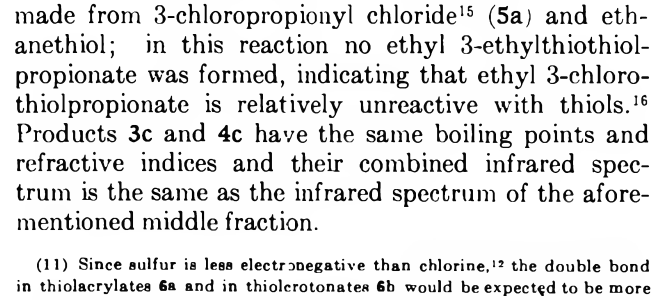
An improved method is described for preparation of thiolcrotonates by reaction of crotonyl chloride with thiols. General convenient and high-yield methods of making the new *dl*-3-chlorothiolbutyrates and the new *dl*-3-alkyl (aryl) thiothiolbutyrates involve addition of hydrogen chloride and of thiols, respectively, to thiolcrotonates. General procedures for making thiolesters by esterification of thiols with anhydrides involve use of 1 mole of amine base in the case of aliphatic thiols and only a catalytic amount of base in the case of aromatic thiols. A convenient, high-yield method for direct addition of thiols to acrylic and crotonic acids involves reaction of a molar quantity of a thiol with the trialkylammonium salt of the acid to produce 3-alkyl (aryl) thiopropionic and butyric acids.

In an investigation of the base-catalyzed reaction of open-chain α,β-unsaturated carboxylic acid anhydrides with thiols, a mixture of products was obtained. It was necessary, therefore, to study the preparation of thiolesters of unsaturated acids, the interaction of thiols with thiolcrotonates, the esterification of thiols with anhydrides in the presence of base, and the base-catalyzed addition of thiols to α,β-unsaturated acids.

Thiolacrylates.—Although thiolesters of saturated carboxylic acids can be prepared conveniently from alkanethiols by several standard acylation techniques,[1] the synthesis of thiolesters of α,β-unsaturated carboxylic acids is tedious. The yields usually are lower because losses are caused by side reactions and by polymerization of the highly reactive unsaturated thiolesters.

The first synthesis of thiolacrylates is that of Reppe and co-workers,[2,3] involving reaction of acetylene with nickel carbonyl and a thiol. Since the crude products from this process have a wide boiling range (up to 30°) it is likely they consist of mixtures of the desired thiolacrylates with their thiol addition products, S-substituted 3-mercaptothiolpropionates. To prevent thiol addition to the activated double bond, α,β-dibromo acid chlorides have been used as starting materials[4-7] and the resulting dibromo thiolesters debrominated to the α,β-unsaturated thiolesters. Somewhat better results are obtained by use of α,β-unsaturated acid chlorides with lead mercaptides in an inert solvent.[8] Acylation with methacrylyl chloride under Schotten–Baumann conditions gives reasonable yields of thiolmethacrylates only with benzenethiols[9] and *sec*- and *t*-alkanethiols,[10] whereas primary alkanethiols yield only the thiol addition products.[10] In acylation with the more reactive acrylyl chloride even benzenethiol and 2-methyl-2-propanethiol produce more addition product than thiolacrylate.[10]

In our work, reaction of acrylyl chloride with ethanethiol in the presence of zinc chloride as the catalyst and cuprous chloride as the polymerization inhibitor produces a rather complex mixture containing none of the desired ethyl thiolacrylate, which apparently reacts further[11] by addition of thiol and of by-product hydrogen chloride or polymerizes as fast as it is formed,[8-10] since polymer always is obtained. The volatile components of the mixture contain recovered acrylyl chloride (**1a**) and as the main product ethyl 3-ethylthiothiolpropionate (**2c**). A middle fraction consists of an inseparable mixture of the isomeric 3-ethylthiopropionyl chloride[13] (**3c**) and ethyl 3-chlorothiolpropionate (**4c**).



a, R = H
b, R = Me
c, R = H; R' = Et

An authentic sample of 3-ethylthiopropionyl chloride[14] was made from 3-ethylthiopropionic acid[14] and thionyl chloride. Pure ethyl 3-chlorothiolpropionate[15] was made from 3-chloropropionyl chloride[15] (**5a**) and ethanethiol; in this reaction no ethyl 3-ethylthiothiolpropionate was formed, indicating that ethyl 3-chlorothiolpropionate is relatively unreactive with thiols.[16] Products **3c** and **4c** have the same boiling points and refractive indices and their combined infrared spectrum is the same as the infrared spectrum of the aforementioned middle fraction.

(1) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962, p. 24.

(2) W. Reppe and K. Merkel, *Ann. Chem.*, **582**, 31 (1953).

(3) W. Reppe, O. Hecht, and K. H. Merkel, German Patent 856,293 (Nov. 20, 1952); *Chem. Abstr.*, **50**, 1895*h* (1956).

(4) S. L. Jacobs, *Univ. Microfilms* (Ann Arbor, Mich.) Publ. No. 11512; *Dissertation Abstr.*, **15**, 700 (1955); *Chem. Abstr.*, **49**, 10,894*d* (1955).

(5) C. S. Marvel, S. L. Jacobs, W. K. Taft, and B. G. Labbe, *J. Polymer Sci.* **19**, 59 (1956).

(6) C. S. Marvel and J. F. Porter, *J. Org. Chem.*, **24**, 137 (1959).

(7) Y. Nakayama, T. Tsuruta, J. Furukawa, A. Kawasaki, and G. Wasai, *Makromol. Chem.*, **43**, 76 (1961); *Chem. Abstr.*, **55**, 17,069*f* (1961).

(8) G. Braude, *J. Org. Chem.*, **22**, 1675 (1957).

(9) M. M. Koton, T. M. Kiselyeva, and K. S. Podgorskaya, *Zh. Obshch. Khim.*, **26**, 475 (1956); *Chem. Abstr.*, **50**, 13,815*a* (1956).

(10) G. Sumrell, G. E. Ham, and E. D. Hornbaker, *J. Am. Chem. Soc.*, **80**, 2509 (1958).

(11) Since sulfur is less electronegative than chlorine,[12] the double bond in thiolacrylates **6a** and in thiolcrotonates **6b** would be expected to be more electron deficient than the double bond in acrylyl chloride or crotonyl chloride. Consequently, thiolacrylates and thiolcrotonates would be expected to be the more vulnerable to nucleophilic attack by thiols and hydrogen chloride.

(12) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p. 89.

(13) Ref. 10 reports formation of small amounts of 3-*t*-butylthiopropionyl chloride and 3-*t*-butylthioisobutyryl chloride in the reaction of acrylyl chloride and methacrylyl chloride with 2-methyl-2-propanethiol in aqueous sodium hydroxide solution.

(14) I. N. Nazarov, S. M. Makin, and A. F. Grapov, *Zh. Obshch. Khim.*, **27**, 101 (1957); *Chem. Abstr.*, **51**, 12,903*g* (1957).

(15) S. Kushner, H. Dalalian, F. L. Bach, D. Centola, J. L. Sanjurjo, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 1154 (1955).

(16) According to H. Böhme, H. Pfeifer, and E. Schneider [*Chem. Ber.*, **75**, 902, 908 (1942)] halogen α to a carbonyl group can be replaced by a thio group in acidic medium. However, replacement of halogen β to a carbonyl group under these conditions appears to be unreported.

TABLE I

THIOLCROTONATES, $CH_3CH{=}CHCOSR$

R	Yield, %	B.p., °C. (mm.)[a]	$n^{25}D$	Formula	Sulfur, % Calcd.	Sulfur, % Found	Infrared, cm.$^{-1}$ (C=O)
C_2H_5	33.8	84–85 (30)[b]	1.5003[c]	$C_6H_{10}OS$	24.6	24.3	1667
n-C_4H_9	69.0	62–63 (0.8)	1.4940	$C_8H_{14}OS$	20.3	20.6	1670
t-C_4H_9	55.4	99–101 (25)	1.4880	$C_8H_{14}OS$	20.3	19.9	1669
C_6H_5	69.0	91–92 (0.3)[d]	1.5876	$C_{10}H_{10}OS$	18.0	17.9	1680
4-ClC_6H_4	47.6	112–113 (0.3)	1.5983	$C_{10}H_9ClOS$	15.1	14.9[e]	1685

[a] Boiling points are uncorrected. [b] Ref. 8 gives b.p. 74–75° (20 mm.) and 66–67° (13 mm.). [c] J. F. Arens, *et al.* [*Rec. trav. chim.*, **75**, 1471 (1956)], give $n^{20}D$ 1.5042. [d] Ref. 17 gives b.p. 140–153° (5 mm.). [e] Calcd.: Cl, 16.7. Found: Cl, 16.4.

Thiolcrotonates 6b.—Only two thiolcrotonates have been described previously. Ethyl thiolcrotonate[8] has been made by reaction of crotonyl chloride with lead ethyl mercaptide. Phenyl thiolcrotonate[17] has been made by reaction of crotonyl chloride with benzenethiol; an apparently impure product with a wide boiling range is obtained.

In our work crotonyl chloride (**1b**) reacted with thiols in the absence of a catalyst.[18] Since hydrogen chloride is formed in this reaction, the thiolcrotonates **6b** always contain considerable amounts of *dl*-3-chlorothiolbutyrates (**4b**) resulting from addition of hydrogen chloride, as well as appreciable amounts of *dl*-3-alkyl (aryl) thiothiolbutyrates (**2b**) resulting from addition of RSH to the thiolcrotonates. The absence of 3-chlorobutyryl chloride (**5b**) and 3-alkyl(aryl)thiobutyryl chlorides (**3b**) among the products suggests that the *dl*-3-chlorothiolbutyrates and *dl*-3-alkyl (aryl) thiothiolbutyrates are derived primarily from the thiolcrotonates. This view is supported further by the fact that thiolcrotonates add hydrogen chloride very rapidly, whereas crotonyl chloride adds hydrogen chloride only slowly; early in the reaction of crotonyl chloride with thiols hydrogen chloride is evolved from the reaction mixture although unreacted crotonyl chloride is present.

To obtain pure thiolcrotonates, the crude reaction product of crotonyl chloride and thiol, consisting of a mixture of thiolcrotonate and 3-chlorothiolbutyrate usually containing a small amount of an unidentified impurity, found by gas phase chromatography (g.p.c.) analysis, is dehydrochlorinated in benzene solution with triethylamine. The products obtained in this way are then at least 99% pure (g.p.c.). No polymerization of thiolcrotonates was encountered, as contrasted to easy polymerization of thiolacrylates.

Alkyl thiolcrotonates show a carbonyl absorption in the range of 1667–1670 cm.$^{-1}$ in the infrared suggesting a similarity to the carbonyl absorption of a ketone[22] as contrasted to ethyl crotonate which absorbs at 1698 cm.$^{-1}$. Since sulfur is less electronegative than oxygen, the double bond in thiolcrotonates should be more electron deficient than the double bond in crotonates and, therefore, more reactive with nucleophilic reagents. This difference indeed is found, for when ethanethiol is added to ethyl crotonate in the presence of 1 mole of triethylamine,[23] only a small yield (14%) of ethyl *dl*-3-ethylthiobutyrate is obtained after refluxing for 18 hr.; by contrast, essentially quantitative yields of adduct are obtained from ethanethiol and ethyl thiolcrotonate using only a catalytic quantity of triethylamine. This also demonstrates the diminished reactivity of the double bond in the crotonic system compared with the acrylic, because, under the same conditions, ethanethiol adds to ethyl acrylate in 93% yield.[24]

The thiolcrotonates made are shown in Table I.

***dl*-3-Chlorothiolbutyrates 4b.**—Hydrogen chloride adds rapidly to the thiolcrotonates producing essentially quantitative yields of *dl*-3-chlorothiolbutyrates. Gas phase chromatography shows that a single product is formed in each instance. The carbonyl absorption of these esters varies from 1672 to 1685 cm.$^{-1}$, depending on the ester group.

The 60-Mc. n.m.r. proton spectrum of phenyl *dl*-3-chlorothiolbutyrate in carbon tetrachloride with tetramethylsilane as a reference consists of a singlet at 7.00 p.p.m. due to the aromatic protons, a sextet at 4.15 p.p.m. due to >CHSR, a multiplet centered at 2.76 p.p.m. due to $-CH_2-$, and a doublet at 1.32 p.p.m. (J = 6.9 c.p.s.) due to $-CH_3$. The areas of these peaks are in the ratio of 5:1:2:3. On the basis of this spectrum, the thiolester clearly is the 3-chloro isomer.

No *dl*-3-chlorothiolbutyrates have been described previously. The esters made in this study are listed in Table II.

***dl*-3-Alkyl (Aryl) Thiothiolbutyrates 2b.**—Since hydrogen chloride adds very easily to thiolcrotonates it might have been anticipated that the more strongly nucleophilic thiols would add with even greater facility. We find that alkanethiols do not react with thiolcrotonates in the absence of a catalyst or under free-radical conditions, but react smoothly in the presence of catalytic amounts of base (triethylamine). Essentially quantitative yields of *dl*-3-alkyl (aryl) thiothiolbutyrates usually are obtained. The carbonyl absorption of these esters varies from 1672 to 1697 cm.$^{-1}$ depending upon the substituent present.

The same sequence of relative reactivities of different types of thiols is encountered as in the base-cata-

(17) K. Miyaki and S. Yamagishi, *J. Pharm. Soc. Japan*, **76**, 436 (1956); *Chem. Abstr.*, **50**, 13,808*b* (1956).

(18) Since acylation of thiols with acid chlorides sometimes is a very slow reaction, zinc chloride has been used as a catalyst[19,20] to increase the rate at lower temperatures. However, zinc chloride may catalyze further attack of the thiol on the thiolester formed to give the orthothioester,[20,21] which, in the presence of a catalytic amount of acid, may split off thiol to give thioacetals of ketenes.[21]

(19) C. M. Himel, U. S. Patent 2,445,142 (July 13, 1948); *Chem. Abstr.*, **24**, 7321*b* (1948).

(20) J. D. Kendall, British Patent 556,815 (Oct. 22, 1943); *Chem. Abstr.*, **39**, 1880[2] (1945); U. S. Patent 2,389,153 (Nov. 20, 1945); *Chem. Abstr.*, **40**, 1540[2] (1946).

(21) L. C. Rinzema, J. Stoffelsma, and J. F. Arens, *Rec. trav. chim.*, **78**, 354 (1959).

(22) It has been reported in ref. 5 that the carbonyl absorption for alkyl thiolacrylates occurs in the range of 1671–1685 cm.$^{-1}$ as compared with 1735 cm.$^{-1}$ for ordinary acrylates. It is concluded "that the carbonyl group in a thiolacrylate has more the character of a ketone carbonyl than does that in an alkyl acrylate."

(23) H. Weber [German Patent 891,391 (Sept. 28, 1953); *Chem. Abstr.*, **48**, 12,791*a* (1954)] reports that addition of alkanethiols to crotonates proceeds in good yields using the corresponding sodium thiolate as the catalyst.

(24) J. L. Szabo and E. T. Stiller, *J. Am. Chem. Soc.*, **70**, 3667 (1948).

TABLE II

3-CHLORO THIOLESTERS, $RCHClCH_2COSR'$

R	R'	Yield, %	B.p., °C. (mm.)[a]	$n^{25}D$	Formula	Chlorine, % Calcd.	Chlorine, % Found	Sulfur, % Calcd.	Sulfur, % Found	Infrared, cm.$^{-1}$ (C=O)
H	C_2H_5	79.0	103–105 (23)[b]	1.4890	C_5H_9ClOS	23.2	23.6	21.0	21.2	1675
CH_3	C_2H_5	100.0	100 (20)	1.4810	$C_6H_{11}ClOS$	21.3	21.4	19.2	19.6	1685
CH_3	n-C_4H_9	100.0	60–62 (0.2)	1.4730	$C_8H_{15}ClOS$	18.2	18.1	16.5	16.8	1681
CH_3	t-C_4H_9	94.5	43 (0.1)	1.4714	$C_8H_{15}ClOS$	...	...	16.5	17.1	1672
CH_3	C_6H_5	89.0	119 (1.2)	1.5600	$C_{10}H_{11}ClOS$	16.5	16.6	14.9	15.1	1681

[a] Boiling points are uncorrected. [b] Ref. 15 gives b.p. 75–78° (15 mm.).

TABLE III

3-ALKYL (ARYL) THIOTHIOLESTERS, $RCH(SR')CH_2COSR''$

R	R'	R''	Yield, %	B.p., °C. (mm.)[a]	$n^{25}D$	Formula	Sulfur, % Calcd.	Sulfur, % Found	Infrared, cm.$^{-1}$ (C=O)
H	C_2H_5	C_2H_5[b]	37.6	148–150 (55)	1.5093	$C_7H_{14}OS_2$	...	...	1685
CH_3	C_2H_5	C_2H_5	98.0	136–137 (20)	1.5009	$C_8H_{16}OS_2$	33.3	33.0	1685
CH_3	n-C_4H_9	n-C_4H_9	92.0	120–121 (1)	1.4915	$C_{12}H_{24}OS_2$	25.8	25.6	1680
CH_3	C_6H_5	C_6H_5	83.0	172–173 (0.2)	1.6106	$C_{16}H_{16}OS_2$	22.2	22.0	1697
CH_3	4-ClC_6H_4	4-ClC_6H_4	97.0	120–130 (0.001)[c]	1.6166	$C_{16}H_{14}Cl_2OS_2$	17.9	17.5	1695
CH_3	C_6H_5	C_2H_5	92.0	95–100 (0.001)[c]	1.5684	$C_{12}H_{16}OS_2$	26.7	26.5	1672
CH_3	4-ClC_6H_4	t-C_4H_9	85.0	105–110 (0.001)[c]	1.5542	$C_{14}H_{19}ClOS_2$	21.2	21.3[d]	1685

[a] Boiling points are uncorrected. [b] From acrylyl chloride and ethyl mercaptan. [c] Air-bath temperature. [d] Calcd.: Cl, 11.7. Found: Cl, 11.6.

lyzed addition of thiols to maleic anhydride.[25] Benzenethiols react the most rapidly; even at room temperature the highly exothermic reaction is complete after a few minutes. Primary alkanethiols react very slowly at room temperature and rapidly at elevated temperatures (>60°), but the *t*-alkanethiol, 2-methyl-2-propanethiol, does not add to thiolcrotonates under the conditions investigated. The inability of 2-methyl-2-propanethiol to add may be caused by steric hindrance.[26]

The 60-Mc. n.m.r. proton spectrum of phenyl *dl*-3-phenylthiothiolbutyrate in carbon tetrachloride with tetramethylsilane as a reference consists of a singlet at 6.87 p.p.m. due to the aromatic protons, a multiplet centered at 3.47 p.p.m. due to >CHSR, a multiplet centered at 2.60 p.p.m. due to $-CH_2-$, and a doublet at 1.19 p.p.m. (J = 7.0 c.p.s.) due to $-CH_3$. The areas of these peaks are in the ratio of 10:1:2:3. The spectrum clearly indicates the thiolester is the 3-phenylthio isomer.

No *dl*-3-alkyl (aryl) thiothiolbutyrates have been described previously. The esters made in this study are listed in Table III.

Base-Catalyzed Esterification of Thiols with Anhydrides.—Acylation of thiols with anhydrides in the presence of base is a known, but not extensively investigated, procedure.[1] Higher-boiling alkanethiols have been acetylated by refluxing for several hours with acetic anhydride containing sodium acetate[27,28] or a catalytic amount of pyridine.[29] Dodecyl monothiolsuccinate has been made from 1-dodecanethiol and succinic anhydride in excess pyridine,[27] and methylbenzenethiols and dimethylbenzenethiols have been acetylated with acetic anhydride in excess triethylamine.[30] The low-boiling alkanethiols have been acetylated by treating aqueous solutions of their sodium salts with acetic anhydride.[28] With 2-methyl-2-propanethiol, however, an acidic catalyst, zinc chloride, has been used for acetylation with acetic anhydride.[31]

A general, convenient, and high-yield method for making thiolesters involves acylation of thiols with anhydrides in the presence of 1 mole of amine base for the alkanethiols and a catalytic amount of base for the aromatic thiols. No solvent is used. Primary and secondary alkanethiols and the aromatic thiols react rapidly, whereas acylation of *t*-alkanethiols requires several hours at elevated temperatures. Solid thiols are dissolved in the anhydride and base is added to this solution. The low-boiling thiols are added to an equimolar mixture of anhydride and base. The method has been tested with acetic, propionic, 3-ethylthiopropionic,[32] and 3-ethylthiobutyric[32] anhydrides. These thiolesters show carbonyl absorption in the range of 1680 to 1704 cm.$^{-1}$, depending on the substituents present, compared with 1727 cm.$^{-1}$ for ethyl 3-ethylthiopropionate, an analogous normal ester. The results are shown in Table IV.

Base-Catalyzed Addition of Thiols to α,β-Unsaturated Acids.—Benzenethiol has been added to acrylic acid without a catalyst,[33] and thiols have been added to acrylic and cinnamic acids with hydrogen chloride or hydroben bromide catalysis.[34,35] Light-catalyzed addition of thiols to acrylic and maleic acids[36] and peroxide-catalyzed addition of α-toluenethiol to crotonic

(25) F. B. Zienty, B. D. Vineyard, and A. A. Schleppnik, *J. Org. Chem.*, **27**, 3141 (1962).

(26) This view is supported by the findings of R. M. Ross [*J. Am. Chem. Soc.*, **71**, 3458 (1949)] on the quaternary base-catalyzed addition of benzenethiol to crotononitrile, 3-isopropylacrylonitrile, and 3-*t*-butylacrylonitrile which gives yields of 54, 32, and 21%, respectively, of addition product.

(27) R. L. Frank, S. S. Drake, P. V. Smith, Jr., and C. Stevens, *J. Polymer Sci.*, **3**, 51 (1948).

(28) F. W. Wenzel and E. E. Reid, *J. Am. Chem. Soc.*, **59**, 1089 (1937).

(29) P. C. Ray and S. K. Mitra, *J. Indian Chem. Soc.*, **6**, 865 (1929); *Chem. Abstr.*, **24**, 2108 (1930).

(30) P. P. Croitoru and R. W. Freedman, *Anal. Chem.*, **34**, 1536 (1962).

(31) C. M. Himel, U. S. Patent 2,445,142 (July 13, 1948), *Chem. Abstr.*, **42**, 7321*b* (1948).

(32) These anhydrides were made from the corresponding acids by dehydration with acetic anhydride.

(33) B. Holmberg and E. Schjänberg, *Arkiv Kemi Mineral. Geol.*, **15A**, No. 20 (1942); *Chem. Abstr.*, **38**, 2943[4] (1944). These workers also added acetothiolic acid to a variety of acids [*Chem. Abstr.*, **35**, 2113[7] (1941)].

(34) T. Posner, *Chem. Ber.*, **40**, 4788 (1907).

(35) F. Arndt, W. Flemming, E. Scholz, and V. Loewensohn, *ibid.*, **56**, 1269 (1923).

(36) T. Kaneko and S. Mii, *J. Chem. Soc. Japan*, **59**, 1382 (1938); *Chem. Abstr.*, **33**, 2106[2] (1939).

TABLE IV

THIOLESTERS, RCOSR'

R	R'	Method	Yield, %	B.p. °C. (mm.) Found[a]	B.p. °C. (mm.) Lit.	$n^{25}D$ Found	$n^{25}D$ Lit.	Infrared, cm.$^{-1}$ (C=O)
CH_3	CH_3[b]	A	91.5	98–99 (760)	98 (760)[b]	1.4598	1.4600[b]	1698
CH_3	C_2H_5[b]	A	81.5	116 (760)	116.4 (760)[c]	1.4547	1.4540[b]	1695
CH_3	i-C_3H_7[c]	A	88.0	127 (760)	126–127 (760)[c]	1.4489	1.4502[c,d]	1695
CH_3	n-C_4H_9[b]	A	77.5	161–162 (760)	163.4 (760)[c,e]	1.4558	1.4570[b]	1695
CH_3	t-C_4H_9[f]	A	79.0	135 (760)	130–133[f]	1.4483	1.4435[f,g]	1695
CH_3	t-C_8H_{17}[h]	A	92.4	102–103 (14)	149–167[h]	1.4670		1693
CH_3	t-$C_{12}H_{25}$[i]	A	80.6	74–84 (1)	95–105 (2)[i]	1.4676–1.4695	1.4780[i,j]	1697
CH_3	C_6H_5[b]	B	90.0	60 (0.5)	82 (3)[k]	1.5671	1.5700[k,j]	1702
CH_3	4-ClC_6H_4[l]	B	91.0	142 (15)[m]	153–154 (35)[l]	1.5797	1.5830[l]	1704
C_2H_5	C_2H_5[n]	A	92.5	136 (760)	136[n]	1.4548	1.4584[n,j]	1680
C_2H_5	t-C_4H_9[o]	A	76.6	96–97 (100)		1.4495		1680
$C_2H_5SCH_2CH_2$	C_2H_5[p]	A	85.9	144–145 (26)		1.5077		1685
$C_2H_5SCH(CH_3)CH_2$	C_2H_5[q]	A	93.0	136–137 (20)		1.5009		1685

[a] All boiling points are uncorrected. [b] Ref. 28. [c] P. N. Rylander and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3021 (1950). [d] At 23.5°. [e] L. H. Noda, S. A. Kuby, and H. A. Lardy [*J. Am. Chem. Soc.*, **75**, 914 (1953)] report 159–160° (738 mm.). [f] R. E. Dunbar and A. N. Bolstad, *ibid.*, **77**, 4672 (1955). [g] At 30°. [h] Ref. 31. [i] Ref. 31. [j] At 20°. [k] D. S. Tarbell and A. H. Herz, *J. Am. Chem. Soc.*, **75**, 1670 (1953). [l] F. Taboury, *Ann. chim. phys.*, [8]**15**, 23 (1908). [m] M.p. 31–32°; lit.[k] m.p. 39–40°. [n] M. L. Wolfrom and J. V. Karabinos, *J. Am. Chem. Soc.*, **68**, 1455 (1946). [o] Calcd. for $C_7H_{14}OS$: S, 21.9. Found: S, 21.1. [p] Calcd. for $C_7H_{14}OS_2$: S, 35.9. Found: S, 35.3. [q] Calcd. for $C_8H_{16}OS_2$: S, 33.3. Found: S, 33.0.

TABLE V

3-ALKYLTHIO- AND ARYLTHIOPROPIONIC AND *dl*-BUTYRIC ACIDS, RCH(SR')CH_2COOH

R	R'	Yield, %	B.p., °C. (mm.)	$n^{25}D$	Formula	Sulfur, % Calcd.	Sulfur, % Found	Infrared, cm.$^{-1}$ (C=O)
H	C_2H_5	80.6	90–91 (2)[a]	1.4800[b]	$C_5H_{10}O_2S$	23.85	23.8	1695
H	n-C_4H_9	87.0	121–122 (0.4)[c]	1.4754	$C_7H_{14}O_2S$	19.76	19.8	1698
H	t-C_4H_9	53.8	94–95 (0.2)[d]	1.4728	$C_7H_{14}O_2S$	19.76	19.8	1700
H	t-C_8H_{17}[e]	97.5	134–138 (0.3)	1.4814	$C_{11}H_{22}O_2S$	14.48	15.3	1700
H	t-$C_{12}H_{25}$[e]	76.5	170–171 (0.5)	1.4794	$C_{15}H_{30}O_2S$	11.68	12.1	1700
H	t-$C_{16}H_{33}$	97.0	[f]	1.4800	$C_{19}H_{38}O_2S$	9.70	9.7	1695
CH_3	C_2H_5	84.5	91 (0.1)	1.4738	$C_6H_{12}O_2S$	21.63	21.0	1700
CH_3	n-C_4H_9	97.5	116–117 (0.7)	1.4716	$C_8H_{16}O_2S$	18.19	18.2	1698
CH_3	t-C_8H_{17}	24.6	139–140 (0.5)	1.4774	$C_{12}H_{24}O_2S$	13.80	13.5	1695
CH_3	C_6H_5	98.1	151 (0.8)[g]	1.5541	$C_{10}H_{12}O_2S$	16.34	16.3	1708
CH_3	4-ClC_6H_4	93.0	163–164 (0.3)	1.5661	$C_{10}H_{11}ClO_2S$	13.90	14.3[h]	1705

[a] Ref. 49 reports b.p. 131.5° (5 mm.). [b] Ref. 50 reports $n^{25}D$ 1.4756. [c] Ref. 50 gives b.p. 168–169° (20 mm.), $n^{25}D$ 1.4706. [d] T. L. Gresham and F. W. Shaver [U. S. Patent 2,449,992 (Sept. 28, 1948), *Chem. Abstr.*, **43**, 105*f* (1949)] report b.p. 98–99° (1 mm.). [e] A technical grade mixture of isomers was used. [f] Decomposed upon attempted distillation at about 180°. An analytical sample was prepared by removing all volatile material at 140° (0.1 mm.). [g] F. Krollpfeiffer, H. Schulze, E. Schlumbohm, and E. Sommermeyer [*Chem. Ber.*, **58**, 1663 (1925)] report b.p. 185° (10 mm.) and 60% yield. [h] Calcd.: Cl, 15.4 Found: Cl, 14.9.

acid[37] are reported. Benzenethiol adds to crotonic acid at 180° using a catalytic amount of piperidine.[38] Isopropylidenemalonic acid adds thiols when an excess of triethylamine is used, but 3,3-dimethylacrylic acid does not.[39] Thioglycolic acid adds to acrylic, methacrylic, and maleic acids[40,41] in aqueous solution without a catalyst, and other thiols react with aqueous solutions of salts of α,β-unsaturated carboxylic acids.[42–44]

Since the ionic mechanism for thiol additions is favored by a highly polar reaction medium no solvent was used and the liquid triethylammonium salts of the unsaturated carboxylic acids were treated directly with the thiols. A small excess of base usually was favorable. Under these conditions with a few exceptions both acrylic and crotonic acids added thiols directly in satisfactory to excellent yields.

Aromatic thiols react rapidly in an exothermic reaction. Primary alkanethiols require several hours' refluxing and the reluctant *t*-alkanethiols react even more slowly; however, yields increase with increasing molecular weight and the boiling point of the reaction mixture. This would suggest that, with any of the lower-boiling alkanethiols, reaction at elevated temperatures by operation under pressure would be favorable to both yield and reaction time. Crotonic acid is distinctly much less reactive than acrylic acid.

With the exception of *t*-hexadecylthiopropionic acid all of the substituted propionic and *dl*-butyric acids are colorless, distillable liquids which slowly yellow on storage at room temperature. The results are shown in Table V.

(37) R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, 3315 (1951).

(38) J. C. Petropoulos, M. A. McCall, and D. S. Tarbell, *J. Am. Chem. Soc.*, **75**, 1130 (1953).

(39) Z. Földi and J. Kollonitsch, *J. Chem. Soc.*, 1683 (1948).

(40) I. G. Farbenindustrie A.-G., French Patent 845,793 (Sept. 1, 1939); *Chem. Abstr.*, **35**, 1070[9] (1941).

(41) E. Larsson, *Chem. Abstr.*, **40**, 2796[4] (1946).

(42) C. D. Hurd and L. L. Gershbein, *J. Am. Chem. Soc.*, **69**, 2334 (1947).

(43) E. W. Bousquet, U. S. Patent 2,434,100 (Jan. 6, 1948); *Chem. Abstr.*, **42**, 2289*c* (1948).

(44) J. G. Hendrickson and L. F. Hatch, *J. Org. Chem.*, **25**, 1747 (1960).

Experimental[45]

Reaction of Ethanethiol with Acrylyl Chloride.—To a stirred mixture of 18.1 g. (0.2 mole) of acrylyl chloride,[46] 0.5 g. of cuprous chloride, and 0.1 g. of anhydrous zinc chloride, heated to 50°, there was added 12.4 g. (0.2 mole) of ethanethiol. Evolution of hydrogen chloride started at once; the mixture turned greenish and then became dark. Heating was continued, to 100°, until hydrogen chloride evolution ceased, and the mixture was distilled through a column packed with helices. Three fractions were collected: (a) b.p. 70–100° (55 mm.), $n^{25}D$ 1.4701, 4.6 g., consisting mainly of acrylyl chloride containing only a trace of ethyl thiolacrylate, which polymerized on standing; (b) b.p. 100–140° (55 mm.), $n^{25}D$ 1.4865, 2.8 g., a mixture of 3-ethylthiopropionyl chloride and ethyl 3-chlorothiolpropionate; and (c) b.p. 140–150° (55 mm.), $n^{25}D$ 1.5093, 6.7 g., almost pure ethyl 3-ethylthiothiolpropionate. Four grams of a dark resin remained in the still.

Reaction of Ethanethiol with Crotonyl Chloride.—A mixture of 20.9 g. (0.2 mole) of crotonyl chloride[47] and 12.4 g. (0.2 mole) of ethanethiol was warmed gently. Hydrogen chloride evolution started at about 50° and heating and stirring were continued until the temperature had reached 150° and hydrogen chloride evolution had stopped. The dark product was distilled, b.p. 34–133° (14 mm.), yielding 26.3 g. of a colorless liquid. G.p.c. analysis showed the following composition: crotonyl chloride, 31.5%; unknown low-boiling component, 1.5%; ethyl thiolcrotonate, 34.2%; ethyl *dl*-3-chlorothiolbutyrate, 19.8%; and ethyl *dl*-3-ethylthiothiolbutyrate, 12.9%. This amounts to a recovery of 0.147 mole of crotonyl chloride and 0.135 mole of ethanethiol.

In an attempt to prevent addition, the reaction was conducted in pyridine at low temperature. However, thiol addition again occurred, producing only 34% ethyl thiolcrotonate and 47% of ethyl *dl*-3-ethylthiothiolbutyrate.[48]

Reaction of 1-Butanethiol with Crotonyl Chloride.—The reaction mixture from 1-butanethiol and crotonyl chloride was fractionated carefully through a 10-in. column packed with helices. Five fractions were taken: (a) b.p. 43–55° (0.25 mm.), $n^{25}D$ 1.4803, 0.9 g., impure crotonyl chloride; (b) b.p. 55–58° (0.25 mm.), $n^{25}D$ 1.4880, 25.3 g. [on redistillation, after a small forerun of 0.7 g., b.p. 27–52° (0.7 mm.), the product had $n^{25}D$ 1.4928–1.4931 and a center cut of this product contained 3.1% of an unidentified low-boiling material, 93.6% of *n*-butyl thiolcrotonate, and 3.3% of *n*-butyl *dl*-3-chlorothiolbutyrate]; (c) b.p. 58–94° (0.25 mm.), $n^{25}D$ 1.4782, 8.0 g., a mixture of *n*-butyl thiolcrotonate and *n*-butyl *dl*-3-chlorothiolbutyrate; (d) b.p. 94–105° (0.25 mm.), $n^{25}D$ 1.4903, 3.8 g., almost pure *n*-butyl *dl*-3-*n*-butylthiothiolbutyrate, containing only a very small amount of *n*-butyl *dl*-3-chlorothiolbutyrate; and (e) b.p. 105–106° (0.25 mm.), $n^{25}D$ 1.4908, 11.4 g., pure *n*-butyl *dl*-3-*n*-butylthiothiolbutyrate.

When the 1-butanethiol was added dropwise with stirring to the crotonyl chloride, less chlorothiolbutyrate and 3-*n*-butylthiothiolbutyrate were formed than in the previous experiment.

Dehydrochlorination of Crude *n*-Butyl Thiolcrotonate.—The fractions, 46.1 g., containing *n*-butyl thiolcrotonate and *n*-butyl *dl*-3-chlorothiolbutyrate were diluted with an equal volume of benzene and 20 ml. of triethylamine was added with stirring. The solution darkened, deposition of triethylamine hydrochloride started at once, and the dehydrochlorination was finished by warming to 95° for 1 hr. Then the amine salt was removed by filtration, washed with benzene, and dried, yielding 5.3 g., corresponding to 1.4 g. of hydrogen chloride or 7.5 g. of *n*-butyl *dl*-3-chlorothiolbutyrate. The filtrate was flash-distilled (heavy foaming): the dark residue was distilled through a 10-in. column packed with helices. After a forerun of 3.5 g., b.p. 43–62° (0.8 mm.), $n^{25}D$ 1.4929, in which a low-boiling impurity was concentrated, the *n*-butyl thiolcrotonate was obtained, 35.4 g., 99% pure (g.p.c.).

t-**Butyl Thiolcrotonate.**—To 20.8 g. (0.2 mole) of crotonyl chloride containing 0.2 g. of anhydrous zinc chloride, there was added with stirring 18.0 g. (0.2 mole) of 2-methyl-2-propanethiol. A fast and exothermic reaction started at once and was allowed to proceed freely. When heat evolution ceased all the acid chloride had been consumed. The dark liquid was diluted with 40 ml. of benzene, 10.1 g. of triethylamine was added, and the mixture was refluxed for 30 min.; then it was poured into water. The organic layer was washed with 5% hydrochloric acid and water, dried over calcium chloride, and worked up in the usual way. Distillation of the crude afforded, after a small forerun, 17.2 g. (55.4%) of product.

Ethyl *dl*-3-Chlorothiolbutyrate.—Anhydrous hydrogen chloride was passed into 2.6 g. (0.02 mole) of ethyl thiolcrotonate. An exothermic reaction took place and g.p.c. showed that the thiolcrotonate was consumed rapidly and a single new compound was formed. After completion of the reaction, excess hydrogen chloride was pumped off under reduced pressure and the 3.4 g. (100%) of crude product was distilled as a colorless liquid.

Ethyl *dl*-3-Ethylthiothiolbutyrate.—Ethyl thiolcrotonate, 3.6 g. (0.027 mole), and 1.85 g. (0.03 mole) of ethanethiol were dissolved in 5 ml. of toluene, and 1 drop of triethylamine was added. At room temperature the addition proceeded slowly and was finished in 3 days. Distillation afforded 5.1 g. (98%) of the product, a greenish liquid.

Ethyl *dl*-3-Phenylthiothiolbutyrate.—Ethyl thiolcrotonate, 1.30 g. (0.01 mole), and 1.10 g. (0.01 mole) of benzenethiol were mixed, and 1 drop of a 1 *N* solution of triethylamine in benzene added. A highly exothermic reaction occurred and the addition reaction was complete after 5 min. according to infrared and g.p.c. examination. The solution was diluted with ether, washed with 5% hydrochloric acid and water, dried over calcium chloride, and worked up in the usual way. The crude product was distilled in a short-path apparatus. The yield was 2.2 g. (92%) of a colorless liquid, which turned yellow on standing at room temperature.

Ethyl *dl*-3-Ethylthiobutyrate.—A mixture of 22.8 g. of ethyl crotonate, 20.2 g. of triethylamine, and 12.4 g. of ethanethiol (0.2 mole each) was refluxed for 18 hr. and left at room temperature for 2 days. Then the mixture was washed with water, 5% hydrochloric acid, and again with water, dried over calcium chloride, and distilled. After a forerun of 16.3 g. (0.143 mole) of ethyl crotonate, b.p. 136–141°, distillation was continued under reduced pressure and the adduct was collected at 113–114° (18 mm.), $n^{25}D$ 1.4518, 5.0 g. (14.2%).

Anal. Calcd. for $C_8H_{16}O_2S$ (176.27): S, 18.2. Found: S, 18.0.

Base-Catalyzed Esterification of Thiols with Anhydrides. Method A.—A molar quantity of base was used.

Methyl Thiolacetate.—Methanethiol, 14.4 g. (0.3 mole), was fed into a stirred mixture of 30.6 g. (0.3 mole) of acetic anhydride and 30.3 g. (0.3 mole) of triethylamine. An exothermic reaction took place; the temperature was held at 60–70° with a cold-water bath. The thiol was consumed immediately. After addition was completed the reaction mixture was poured into ice–water, the organic layer was separated, and the aqueous phase was extracted with ether. The combined organic layer and ethereal extract were washed with cold 10% hydrochloric acid, water, sodium bicarbonate solution, and water again, dried over sodium sulfate, and distilled through a 10-in. column packed with helices. The yield was 24.8 g. (91.5%).

t-**Dodecyl Thiolacetate.**—A mixture of 40.2 g. (0.2 mole) of *t*-dodecanethiol (Phillips Petroleum "Sulfole"), 20.4 g. (0.2 mole) of acetic anhydride, and 20.2 g. (0.2 mole) of triethylamine was heated with stirring at 130° for 3 hr. and then worked up in the usual way. Distillation through a 10-in. packed column afforded 5.7 g. of a forerun, b.p. 55–74° (1 mm.), mainly unreacted thiol, and 30.3 g. (80.6%) of product.

Method B.—A catalytic quantity of base was used.

4-Chlorophenyl Thiolacetate.—4-Chlorobenzenethiol, 14.4 g. (0.1 mole), was dissolved in 10.2 g. (0.1 mole) of acetic anhydride with stirring. Then 3 drops of triethylamine was added and the highly exothermic reaction was allowed to proceed freely. The usual work-up afforded on distillation 16.9 g. (91.0%) of product, which crystallized on standing, m.p. 31–32°.

Direct Addition of Thiols to α,β-Unsaturated Acids. ***dl*-3-Ethylthiobutyric Acid.**—A mixture of 43.0 g. (0.5 mole) of crotonic acid, 33.0 g. (0.5 mole) of ethanethiol, and 50.5 g. (0.5 mole) of triethylamine was refluxed for 44 hr.; a highly efficient double-jacketed condenser was used. The reaction temperature

(45) All melting and boiling points are uncorrected. The infrared spectra were taken on a Perkin-Elmer Infracord spectrophotometer.

(46) C. E. Rehberg, M. B. Dixon, and C. H. Fisher, *J. Am. Chem. Soc.*, **67**, 209 (1945).

(47) H. Staudinger, J. Becker, and H. Hirzel, *Chem. Ber.*, **49**, 1991 (1916).

(48) In pyridine 4-chlorobenzenethiol with crotonyl chloride affords about equal amounts of thiolcrotonate and 4-chlorophenyl *dl*-3-(4′-chlorophenylthio)thiolbutyrate.

rose gradually from 46 to 109°. The crude product was poured into water, the clear solution was acidified with concentrated hydrochloric acid, the oily product was separated, and the aqueous layer was extracted with two 100-ml. portions of ether. Distillation afforded 3.5 g. of a forerun, b.p. 62–90° (0.1 mm.), which partially solidified and consisted mainly of recovered crotonic acid, and 62.5 g. (99%) of product.[49,50]

dl-**3-Phenylthiobutyric Acid.**—To a mixture of 17.2 g. (0.2 mole) of crotonic acid and 20.2 g. (0.2 mole) of triethylamine there was added with stirring 22.0 g. (0.2 mole) of thiophenol. An exothermic reaction took place, the temperature rose rapidly to 65°, remained there for about 10 min., and then dropped. The mixture was heated for 10 min. at 115°; a small sample of the reaction mixture was completely soluble in water. The usual work-up afforded on distillation 38.5 g. (98.1%) of colorless viscous liquid product.

3-*t*-Octylthiopropionic Acid.—A mixture of 29.2 g. (0.2 mole) of *t*-octanethiol (technical grade, mixture of isomers), 20.2 g. (0.2 mole) of triethylamine, and 14.4 g. (0.2 mole) of acrylic acid was refluxed for 16 hr., then worked up in the usual way.[51] Distillation afforded 42.5 g. (97.5%) of colorless product.

Acknowledgment.—The n.m.r. spectra were run and interpreted by Dr. Martin W. Dietrich.

(49) M. H. Palomaa and T. Kaski [*Suomen Kemistilehti*, **19B**, 85 (1946); *Chem. Abstr.*, **41**, 5453 (1947)] made the analogous propionic acid.

(50) L. J. Desha and G. H. Denny, Jr. (thesis, Washington and Lee University, 1950, cited in E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., Inc., New York, N. Y., 1960, p. 208) reported the corresponding propionic acid.

(51) The triethylamine salts of the higher *t*-alkylthiopropionic acids tend to form gels in water.

Aminocyanopyrazoles

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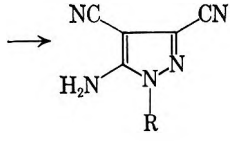
Tetracyanoethylene reacts with monosubstituted hydrazines and hydrazides to give 5-amino-3,4-dicyanopyrazoles. A number of pyrazoles have been prepared from a variety of cyanoethylenes that contain replaceable groups.

The synthesis of aminopyrazoles from cyanoethylenes containing a replaceable group on the 2-position and hydrazine or substituted hydrazines has been reported.[1] In these cases, the group replaced was alkoxy, amino, or alkylthio. We have applied this method to a number of cyanoethylenes in which the leaving group is cyano, sulfonyl, or chloro. In these cases, the reaction conditions are very mild, and hydrazides work as well as or better than hydrazines.

Tetracyanoethylene reacts with hydrazine to give the highly colored acid, 1,1,2,5,6,6-hexacyano-3,4-diazahexadiene.[2] We have now found that the reaction of monosubstituted hydrazines and hydrazides with tetracyanoethylene gives 5-amino-3,4-dicyanopyrazoles in excellent yields. The facile reaction takes place at or below room temperature.

$$(NC)_2C{=}C(CN)_2 + RNHNH_2 \longrightarrow [(NC)_2C{=}C(CN)NHNHR]$$



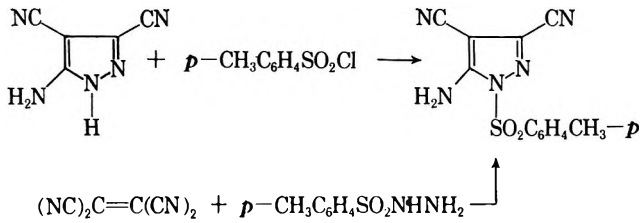
The initial step involves replacement of a cyano group to give a tricyanovinylhydrazine intermediate, which then cyclizes to the aminodicyanopyrazole. With semicarbazide, the reaction was run in water, and a yellow color characteristic of tricyanovinylamines appeared in an early stage of the reaction. A white crystalline product slowly separated, and the yellow color diminished in intensity as more product formed. Since substituted hydrazines react much faster, the stages of reaction are not so evident.

(1) (a) W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2829 (1958); (b) R. A. Carboni, D. D. Coffman, and E. G. Howard, *ibid.*, **80**, 2838 (1958); (c) R. K. Robins, *ibid.*, **78**, 784 (1956); (d) R. Gomper and W. Töpfl, *Ber.*, **95**, 2881 (1962); (e) E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.*, **81**, 2452 (1963).

(2) W. J. Middleton, E. L. Little, D. D. Coffman, and V. A. Engelhardt, *ibid.*, **80**, 2795 (1958).

Since initial attack on tetracyanoethylene by arylhydrazines or hydrazides would be expected to be by the unsubstituted nitrogen, the product from cyclization would be expected to be the 3-amino isomer rather than the 5-amino isomer. The product from methylhydrazine should be the 5-amino isomer, however, since the nitrogen to which the methyl group is attached is the more nucleophilic.

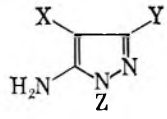
Although 5-amino-3,4-dicyanopyrazole cannot be prepared from hydrazine and tetracyanoethylene directly, it is readily available from 5-amino-3,4-dicyano-1-carbamoylpyrazole by hydrolysis in boiling water. A number of 1-substituted derivatives of 5-amino-3,4-dicyanopyrazole can be prepared by acylation, alkylation, or reaction with isocyanates. By the action of *p*-toluenesulfonyl chloride, dimethylcarbamoyl chloride, or isocyanic acid on 5-amino-3,4-dicyanopyrazole, we were able to prepare compounds identical with those from the reaction of tetracyanoethylene with *p*-toluenesulfonyl hydrazide, 4,4-dimethylsemicarbazide, or semicarbazide. Alkylation with dimethylsulfate gave two isomers. The lower melting isomer, obtained in lower yield, was identical with that from methyl-

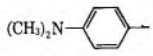


hydrazine and tetracyanoethylene. That the major product from methylation would be expected to be the 5-amino isomer by analogy with the acylation experiments is consistent with the assignments of the 3-amino structure to the methylhydrazine–tetracyanoethylene product.

TABLE I

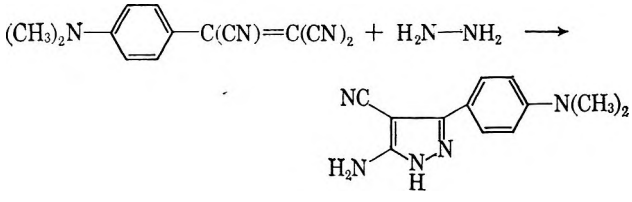
5-AMINOPYRAZOLES



X	Y	Z	Method	Q[d]	Reaction solvent
CN	CN	CH_3	A, B	CN	H_2C
CN	CN	C_6H_5	A	CN	C_2H_5OH
CN	CN	p-$O_2NC_6H_5$	A	CN	C_2H_5OH
CN	CN	CH_3CO	A	CN	H_2O
CN	CN	C_6H_5CO	A	CN	H_2O
			B		C_4H_8O
CN	CN	p-$CH_3C_6H_4SO_2$	A	CN	C_2H_5OH
			B		C_4H_8O
CN	CN	$BrCH_2CO$	B		C_4H_8O
CN	CN	$CONH_2$	A	CN	H_2O
			B		C_4H_8O
CN	CN	$CSNH_2$[a]	A	CN	DMF
CN	CN	$CONHCH_3$[b]	B		C_4H_8O
CN	CN	$CONHC_2H_5$[b]	B		C_4H_8O
CN	CN	$CONHC_4H_9$	B		$CH_3CO_2C_2H_5$
CN	CN	$CONHC_6H_5$	B		C_4H_8O
CN	CN	$CON(CH_3)_2$	A	CN	C_2H_5OH
			B		C_4H_8O
CN	CN	$CON(C_2H_5)_2$	B		C_4H_8O
CN	CN	$(CONHCH_2CH_2CH_2-)_2$	B		C_4H_8O
CN	CN	$CONHCH_2CO_2C_2H_5$	B		C_4H_8O
CN	CN	$CO_2C_2H_5$	B		C_4H_8O
CN	CN	$SO_2N(CH_3)_2$[c]	B		C_4H_8O
$CH_3C_6H_4SO_2$	CN	$CH_3C_6H_4SO_2$	A	$CH_3C_6H_4SO_2$	$HCON(CH_3)_2$
$CH_3C_6H_4SO_2$	CN	$CONH_2$	B		C_4H_8O
			C		CH_3CO_2H
$CH_3C_6H_4SO_2$	CN	$CON(CH_3)_2$	B		C_4H_8O
			C		CH_3CO_2H
CH_3SO_2	CN	$CONH_2$	C		CH_3CO_2H
CH_3SO_2	CN	$CON(CH_3)_2$	C		CH_3CO_2H
$C_6H_5SO_2$	CN	$CONH_2$	C		CH_3CO_2H
CN	CH_3SO_2	$CONH_2$	B		C_4H_8O
CN	H	$CONH_2$[a]	A	OC_2H_5	C_2H_5OH
CN	CH_3	$CONH_2$	A	OC_2H_5	C_2H_5OH
CN	C_6H_5	$CONH_2$[a]	A	OCH_3	C_2H_5OH
CN		$CONH_2$	B		C_4H_8O
CN		$CONH_2$	B		C_4H_8O
CN	CH_2CN	$CONH_2$	B		C_4H_8O
CN	SCH_3	$CONH_2$	A	SCH_3	C_2H_5OH
CN	OCH_2CH_3	$CONH_2$	A	OC_2H_5	C_2H_5OH
CN	Cl	$SO_2C_6H_4CH_3$	A	Cl	C_4H_8O
CN	C_6H_5	C_6H_5	A	OCH_3	C_2H_5OH

[a] This compound was prepared by Dr. L. M. Ellis. [b] This compound was prepared by Dr. W. Wayne. [c] This compound was pre-

Hydrazine reacted readily with 2-tricyanovinyl-1-methylpyrrole and p-tricyanovinyl-N,N-dimethylaniline, but these compounds are much less reactive than tetracyanoethylene. 5-Amino-4-cyano-3-(p-N,N-dimethylaminophenyl)pyrazole was easily carbamylated with isocyanic acid.



Other cyanoethylenes that we used were 1,1-dichloro-2,2-dicyanoethylene, 1,1-bis(methylmercapto)-2,2-dicyanoethylene,[1d] and 1,2-bis(p-toluenesulfonyl)-1,2-dicyanoethylene. In the latter case, the reaction could be run by combining sodium p-toluenesulfinate, dichlorofumaronitrile, and a hydrazide.[3] Presumably,

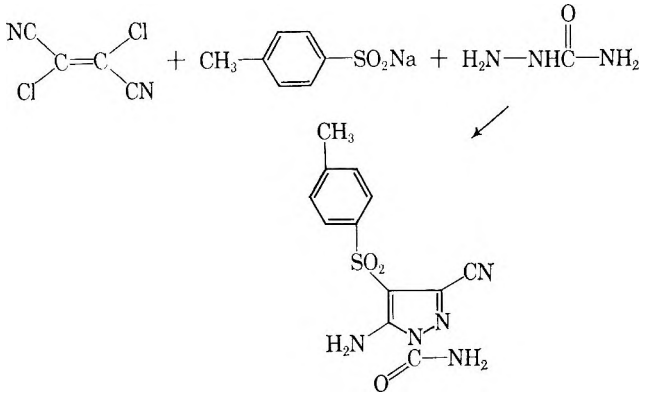
(3) We are indebted to Dr. E. L. Martin for suggesting this modification.

Recrystallization solvent	M.p., °C.	Yield, %	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H_2O	131.5–133	25	$C_6H_5N_5$	49.0	49.2	3.4	3.4
C_2H_5OH	195 dec.	58	$C_{11}H_7N_5$	63.2	63.3	3.4	3.5
C_2H_5OH	252–253	82	$C_{11}H_6N_6O_2$	52.0	52.1	2.4	2.6
CH_3CO_2H	203–207	68	$C_7H_5N_5O$	48.0	48.0	3.0	3.1
CH_3CO_2H	>200 dec.	68	$C_{12}H_7N_5O$	60.8	60.5	3.0	3.1
C_2H_5OH	214.5–216	87	$C_{12}H_9N_5SO_2$	50.2	50.4	3.1	3.3
CH_3CO_2H	210–211.5	35	$C_7H_4N_5OBr$	33.0	32.8	1.6	2.0
$C_4H_8O_2$ (dioxane)	>240 dec.	93	$C_6H_4N_6O$	40.9	41.4	2.3	2.4
CH_3OH	dec.	35	$C_6H_4N_6S$	*f*			
C_4H_8O	>280	60	$C_7H_6N_6O$	44.2	44.5	3.2	3.3
C_4H_8O	234–235 dec.	53	$C_8H_8N_6O$	47.0	47.2	4.0	4.1
$CH_3CO_2C_2H_5$	188–189	70	$C_{10}H_{12}N_6O$	51.7	52.0	5.2	5.6
$CH_3CO_2C_2H_5$	223–224	63	$C_{12}H_8N_6O$	57.2	57.5	3.2	3.4
$C_4H_8O_2$	227–228	80	$C_8H_8N_6O$	47.1	47.1	3.9	4.0
		70					
C_2H_5OH	170–173	66	$C_{10}H_{12}N_6O$	51.7	52.0	5.2	5.1
$HCON(CH_3)_2$–C_2H_5OH	>300	82	$C_{18}H_{18}N_{12}O_2$	49.8	49.8	4.1	4.4
C_6H_6–C_4H_8O	200.5–201	70	$C_{10}H_{10}N_6O_3$	45.8	45.8	3.8	3.8
$CH_3CO_2C_2H_5$	207–208	90	$C_8H_7N_5O_2$	47.3	47.5	3.4	3.7
C_2H_5OH	166–168	50	$C_7H_8N_6SO_2$	*e*			
C_2H_5OH	207.5–209	60	$C_{18}H_{16}N_4F_4S$	51.9	52.0	3.8	4.0
$CH_3CO_2C_2H_5$	191–192.5	52	$C_{12}H_{11}N_5O_3S$	47.2	47.6	3.6	3.5
		59					
$CH_3CO_2C_2H_5$	163–164	30	$C_{14}H_{15}N_5O_3S$	50.4	50.1	4.5	4.8
		56					
CH_3CN	203–204	72	$C_6H_7N_5O_3S$	31.4	32.0	3.1	3.2
$CH_3CO_2C_2H_5$	186–187	40	$C_8H_{11}N_5O_3S$	37.4	37.2	4.3	4.2
CH_3CN	194–195	50	$C_{11}H_9N_5SO_3$	45.4	45.4	3.1	3.1
CH_3CN	190–193	90	$C_6H_7N_5O_3S$	31.4	31.4	3.1	3.0
	253 dec.	20	$C_5H_5N_5O$	39.7	40.0	3.3	3.5
CH_3CN	206 dec.	30	$C_6H_7N_5O$	43.6	44.0	4.3	4.0
	200–201	70	$C_{11}H_9N_5O$	58.1	58.1	4.0	4.1
$HCON(CH_3)_2$–C_2H_5OH	220–222	79	$C_{12}H_{14}N_6O$	57.8	58.0	5.2	5.3
$CH_3CO_2C_2H_5$	187–188	82	$C_{10}H_{10}N_6O$	52.2	52.4	4.3	4.6
$HCON(CH_3)_2$–CH_3CO_2H	>300	78	$C_7H_6N_6O$	44.2	44.4	3.2	3.4
CH_3CN	214.5–215	68	$C_6H_7N_5SO$	36.5	36.6	3.6	3.5
CH_3CN	214–215	30	$C_7H_9N_5O_2$	43.1	43.3	4.6	4.6
$CH_3CO_2C_2H_5$	190–192	90	$C_{11}H_9N_4SO_2Cl$	44.6	44.6	3.0	3.4
	172–173	80	$C_{16}H_{12}N_4$	73.8	73.5	4.6	4.7

pared by Dr. E. W. Bousquet. [d] In the precursor NCC(X)=C(Y)Q. [e] Calcd.: S, 13.3; N, 35.0. Found: S, 12.9; N, 35.3. [f] Calcd.: S, 16.7. Found: S, 16.9.

the sulfinate reacted first with the dichlorofumaronitrile and the resulting ethylene reacted further with the hydrazide to give the pyrazole. (see p. 1918, col. 1).

The amino group of the dicyanoaminopyrazoles is not basic, for it cannot be titrated with perchloric acid in glacial acetic acid. 5-Amino-3,4-dicyanopyrazole is weakly acidic (pK_a = 7). The amino group can be diazotized with nitrosylsulfuric acid. The resulting diazonium group has been replaced with hydrogen and chlorine, but in the latter case one of the nitrile groups was hydrolyzed to an amide group. The amino group of 5-amino-3,4-dicyano-1-phenylpyrazole was condensed with *p*-dimethylaminobenzaldehyde to give a stable, yellow anil. Acetylation of 5-amino-3 4-dicyano-1 carbamoylpyrazole with acetic anhydride gave 3-acetamido-4,5-dicyanopyrazole. The carbamoyl group was probably intact during the acetylation, but was cleaved in the work-up with water even under acidic conditions. The 1-carbamoyl derivative of 3-acctamido-4,5-dicyanopyrazole was not obtained when that compound was treated with isocyanic acid in tetrahydrofuran.



Another example of the 1-carbamoyl group serving as a protective function and being subsequently cleaved is found in the oxidation of 5-amino-4-cyano-3-methylthio-1-carbamoylpyrazole to 5-amino-4-cyano-3-methylsulfonylpyrazole with hydrogen peroxide in glacial acetic acid.

Both nitrile groups of 5-amino-3,4-dicyanopyrazole may be hydrolyzed to amide groups by dissolving the compound in concentrated sulfuric acid and then pouring the solution into water. A more convenient synthesis is to use the 1-carboxamide directly.

The synthesis of pyrazolo[2,3-*a*]pyrimidines is readily carried out by condensation of 5-amino-3,4-dicyanopyrazole with ethyl acetoacetate or acetylacetone. This reaction has been reported previously for 3(5)-aminopyrazoles.[1a,e]

Experimental[4]

N-Substituted 5-Aminopyrazoles (Table I). Method A.—The hydrazine or hydrazide is dissolved in a suitable solvent, such as ethanol or water, and the cyanoolefin is added with stirring. Reactive olefins such as tetracyanoethylene react at room temperature with hydrazides, and with hydrazines the reaction mixture is cooled in ice. In a typical experiment, 12.8 g. (0.10 mole) of tetracyanoethylene was added to a solution of 18.6 g. (0.10 mole) of tosylhydrazide in 200 ml. of ethanol. This mixture was cooled in ice and stirred for 1 hr. and then boiled on a steam bath for 15 min. The solution was cooled, and the white crystalline precipitate of 5-amino-3,4-dicyano-1-tosylpyrazole was collected and washed with alcohol, yield 25.0 g. (87%), m.p. 211–213°. It was recrystallized from alcohol to give 21.5 g., m.p. 214.5–216°.

Method B.—A pyrazole unsubstituted on the nitrogen is treated with an acyl halide or an isocyanate in a nonreactive solvent, such as ethyl acetate or tetrahydrofuran. In a typical experiment, a solution of 10.0 g. of 5-amino-3,4-dicyanopyrazole and 9.0 g. of phenyl isocyanate in 100 ml. of tetrahydrofuran was heated under reflux for 2 hr. and then evaporated to dryness. The residue of 5-amino-3,4-dicyanopyrazole-1-carboxanilide was recrystallized from ethyl acetate, yield 11.9 g. (63%), m.p. 223–224°.

Method C.—Dichlorofumaronitrile and the appropriate hydrazide in acetic acid is treated with a sodium sulfinate. In a typical experiment, a mixture of 14.7 g. (0.10 mole) of dichlorofumaronitrile, 16.4 g. (0.10 mole) of sodium benzenesulfinate, 7.5 g. (0.1 mole) of semicarbazide, and 100 ml. of glacial acetic acid was stirred overnight and then diluted with 200 ml. of water. The precipitate of 5-amino-4-benzenesulfonyl-1-carbamyl-3-cyanopyrazole was collected and recrystallized from acetonitrile, yield 14.5 g. (50%), m.p. 194–195°.

5-Amino-3,4-dicyanopyrazole.—5-Amino-1-carbamoyl-3,4-dicyanopyrazole (160 g., 0.91 mole) was added in portions with occasional stirring to 1.5 l. of boiling water in a 4-l. beaker. This must be done carefully since carbon dioxide is evolved and foaming occurs. Boiling was continued for 5 min. after the final addition, and the reaction mixture was allowed to cool. The precipitate was collected and recrystallized from water, yield 73.5 g. (60%), m.p. *ca.* 260° dec.

Anal. Calcd. for $C_5H_3N_5$: C, 45.1; H, 2.3; N, 52.6. Found: C, 45.7; H, 2.1; N, 52.3.

5-Amino-4-cyano-3[2-(1-methylpyrrolo)]pyrazole.—Hydrazine hydrate (8.5 g.) was added to 29.0 g. of 2-tricyanovinyl-1-methylpyrrole in 200 ml. of ethanol, and the resulting solution was heated under reflux for 2 hr. The solution was then concentrated to 100 ml., and the precipitate of 5-amino-4-cyano-3-[2-(1-methylpyrrolo)]pyrazole was collected, yield 13.9 g. (46%). After recrystallization from ethanol, the melting point was 209–210°.

Anal. Calcd. for $C_9H_9N_5$: C, 57.8; H, 4.8; N, 37.4. Found: C, 57.9; H, 5.0; N, 37.6.

5-Amino-4-cyano-3-(*p*-dimethylaminophenyl)pyrazole.—Hydrazine hydrate (8.0 g.) was added to a solution of 33.3 g. of *p*-tricyanovinyl-N,N-dimethylaniline in 100 ml. of dimethylformamide, whereupon the magenta solution changed to yellow-orange. After 10 min., the solution was diluted with 250 ml. of water and the 5-amino-4-cyano-3-(*p*-dimethylaminophenyl)-pyrazole was collected and recrystallized from ethanol, yield 22.4 g. (67%), m.p. 193–196°.

Anal. Calcd. for $C_{12}H_{13}N_5$: C, 63.4; H, 5.7; N, 30.8. Found: C, 63.2; H, 5.6; N, 30.8.

3,4-Dicyano-5-*p*-dimethylaminobenzylimino-1-phenylpyrazole.—A solution of 8.0 g. (0.038 mole) of 5-amino-3,4-dicyano-1-phenylpyrazole, 5.5 g. (0.037 mole) of *p*-dimethylaminobenzaldehyde, and 0.5 g. of *p*-toluenesulfonic acid in 20 ml. of dimethylformamide was heated on a steam bath for 1 hr., cooled, and diluted with 80 ml. of ethanol. The bright yellow precipitate of 3,4-dicyano-5-*p*-dimethylaminobenzylimino-1-phenylpyrazole was collected, yield 7.9 g., m.p. 194.5–196.0°. A sample was recrystallized from ethanol for analysis.

Anal. Calcd. for $C_{20}H_{16}N_6O$: C, 70.6; H, 4.7. Found: C, 70.3; H, 4.6.

3-Methylsulfonyl-4-cyano-5-aminopyrazole.—A mixture of 149 g. of 1-carbamyl-3-methylthio-4-cyano-5-aminopyrazole, 1 l. of glacial acetic acid, and 210 g. of 30% hydrogen peroxide was heated under reflux for 2 hr. and then allowed to stand at room temperature for 11 hr. The clear amber solution was seeded and cooled in ice for 0.5 hr. The solid that crystallized was collected to give 91 g. (64.5%) of crude, yellow 3-methylsulfonyl-4-cyano-5-aminopyrazole. Recrystallization of 86 g. of this crude product from water ("Darco") gave 78 g. of pale, tan needles, m.p. 200–203°, with softening at 131°.

A sample prepared for analysis by two additional crystallizations from water melted at 200–202.5° after drying at 100° (0.2 mm.) for 18 hr.

Anal. Calcd. for $C_5H_6N_4SO_2$: C, 32.3; H, 3.2; N, 30.1. Found: C, 32.32; H, 3.3; N, 29.9.

5-Acetamido-3,4-dicyanopyrazole.—A mixture of 10.0 g. of 5-amino-1-carbamyl-3,4-dicyanopyrazole, 40 ml. of acetic anhydride, and 5 ml. of pyridine was heated on a hot plate until a solution was obtained. The solution was then poured into 400 ml. of ice water and stirred until all of the acetic anhydride had reacted. The precipitate of 5-acetamido-3,4-dicyanopyrazole was collected and recrystallized from ethanol, yield 6.0 g. (60%), m.p. 250° dec.

Anal. Calcd. for $C_7H_5N_5O$: C, 48.0; H, 2.9. Found: C, 48.0; H, 3.1.

5-Aminopyrazole-3,4-dicarboxamide.—3-Amino-4,5-dicyanopyrazole (20 g.) was added carefully to 88 ml. of concentrated sulfuric acid in small portions so that the evolution of carbon dioxide was not too vigorous. The resulting solution was stirred overnight and then poured into 500 ml. of ice–water. The precipitate was collected, suspended in 200 ml. of water, made alkaline with 10% sodium hydroxide, and acidified with 5% hydrochloric acid. The 5-aminopyrazole-3,4-dicarboxamide was collected and recrystallized from water, yield 15.5 g. (81%), m.p. >300°.

2,3-Dicyano-5,7-dimethylpyrazolo[2,3-*a*]pyrimidine.—A mixture of 26.6 g. (0.20 mole) of 5-amino-3,4-dicyanopyrazole, 50 ml. of 2,4-pentanedione, and 0.5 g. of *p*-toluenesulfonic acid was heated at 150–155° for 5 hr. The mixture was cooled and diluted with 100 ml. of ethanol. The precipitate of 2,3-dicyano-5,7-methylpyrazolo[2,3-*a*]pyrimidine was collected, yield 32.3 g. (82%). It was recrystallized from ethanol to give 23.7 g., m.p. 186–188°.

(4) (a) C. L. Dickinson and W. J. Middleton, U. S. Patent 2,998,419 (1961); (b) C. L. Dickinson and B. C. McKusick, U. S. Patent 2,998,426 (1961).

Anal. Calcd. for $C_{10}H_7N_5$: C, 60.9; H, 3.6; N, 35.5. Found: C, 60.3; H, 3.6; N, 35.2.

2,3-Dicyano-7-hydroxy-5-methylpyrazole[2,3-*a*]pyrimidine.—A solution of 13.0 g. of 5-amino-3,4-dicyanopyrazole in 56 ml. of ethyl acetoacetate was heated at 150–160° until no more vapor was evolved. The mixture was then cooled and diluted with 100 ml. of ethanol, and the 2,3-dicyano-7-hydroxy-5-methylpyrazolo-[2,3-*a*]pyrimidine was collected, yield 13.3 g. (71%), m.p. >300°. An analytical sample was prepared by recrystallization from dimethylformamide–acetic acid.

Anal. Calcd. for $C_9H_5N_5O$: C, 54.3; H, 2.5; N, 35.2. Found: C, 54.4; H, 2.7; N, 35.0.

3-Chloro-4(5)-cyano-5(4)-carbamylpyrazole.—Sodium nitrite (14.0 g.) was added to 100 ml. of concentrated sulfuric acid, and the resulting mixture was heated with stirring at 70° until solution was complete. The solution was then cooled in ice and a suspension of 24 g. of 5-amino-3,4-dicyanopyrazole in 280 ml. of glacial acetic acid was added while the temperature was kept eblow 20°. After the mixture had been stirred for 30 min., a solution of 20 g. of cuprous chloride in 200 ml. of concentrated hydrochloric acid was added slowly. The resulting solution was stirred for an additional hour and diluted with 1 l. of water; the resulting solution was extracted with three 300-ml. portions of ethyl acetate. The ethyl acetate extracts were combined, washed with water, dried over magnesium sulfate, and evaporated to dryness. The yield of chloroamide after recrystallization from water was 7.4 g., m.p. 233–235°.

Anal. Calcd. for $C_5H_3N_4OCl$: C, 35.2; H, 1.7; N, 32.8; Cl, 20.8. Found: C, 35.1; H, 1.5; N, 32.8; Cl, 20.7.

3,4-Dicyanopyrazole.—The diazotization was carried out exactly as in the preparation of the chlorocyanopyrazolecarboxamide except that one-fourth the quantities were used. The solution of the diazonium compound was slowly added to 100 ml. of ethanol that contained 0.50 g. of copper sulfate and had been preheated to 60°. The resulting solution was boiled for 30 min., diluted with 400 ml. of water, and extracted with three 150-ml. portions of ethyl acetate. The ethyl acetate extracts were combined, dried over magnesium sulfate, and evaporated to dryness to give 3.1 g. of tan solid. The 3,4-dicyanopyrazole was difficult to purify further, and an analytical sample was prepared by recrystallization one time each from water and benzene and then by sublimation. After repeating this process, the melting point was 196–197°.

Anal. Calcd. for $C_5H_2N_4$: C, 50.8; H, 1.7; N, 47.5. Found: C, 50.9; H, 1.8; N, 47.4.

5(3)-Amino-3(5), 4-dicyano-1-methylpyrazole.—To a solution of 11.5 g. of sodium hydroxide in 50 ml. of water was added 33.3 g. of 5-amino-3,4-dicyanopyrazole, and 42 g. of dimethyl sulfate immediately after the pyrazole had dissolved. After 15 min., the solid that formed was collected and washed with water, yield 22.5 g. The filtrate deposited more solid upon standing and this (B) was collected, yield 5.5 g., m.p. 110–120°. The 22.5-g. sample was heated with 100 ml. of ethanol and filtered hot to remove the undissolved solid. This solid (18.0 g.) melted at 243–245° and the melting point was unchanged after recrystallization from dioxane.

Anal. Calcd. for $C_6H_3N_5$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.6; N, 47.3.

B was recrystallized several times from ethanol and the melting point was raised to 128–130°. A mixture melting point determination with the tetracyanoethylene–methylhydrazine product (Table I) showed no depression of the melting point.

Acknowledgment.—We wish to acknowledge the discussion with Dr. W. J. Middleton which contributed to this work.

The Synthesis of 1*H*,3*H*-Thieno[3,4-*c*]thiophene[1,2]

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In order to study the effect of ring strain (Mills–Nixon effect) on the properties of five-membered heteroaromatics, the title compound, I, has been synthesized using a highly improved thiophene ring synthesis.

Although the Mills–Nixon[4] or ring-strain effect in indane derivatives recently[5,6] has been shown to be of little actual importance in changing the properties of the benzene ring, it seemed reasonable to expect a much larger effect by fusing the five-membered ring to a five-membered heterocyclic system. One fundamental question which might be resolved and which has received conflicting answers[6,7] thus far concerns in essence the bond order of the bond common to both rings.

To investigate the chemical and physical properties of some five-membered heteroaromatic systems fused to five-membered (or four-membered) rings, the synthesis of several compounds of type I and II has been undertaken.

I II

X = S, O, NR
Y = S, SO_2, NR, CR_2, O

This paper describes the synthesis of two compounds of type I, namely, 1*H*,3*H*-thieno[3,4-*c*]thiophene (I, X = Y = sulfur) and a derivative of 1*H*,3*H*-thieno-[3,4-*c*]thiophene 2,2-dioxide (I, X = S; Y = SO_2) by the reaction sequence outlined in eq. 1.

The reaction between biacetyl and diethyl thiodiacetate has been described[8] but furnished in our hands under the reaction conditions specified a nearly intractable tar. The desired diester could not be isolated, although 10–20% yields of the dibasic acid (IIIe) were realized. We discovered recently, however, in other work in progress in this laboratory,[9] that the reaction of α-diketones with glutaric ester analogs to furnish furans, thiophenes, and pyrroles[10]

(1) Part I of a series of papers entitled "Steric effects in heterocyclic systems."

(2) Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(3) Predoctoral Fellow of the Netherlands Organization for Pure Scientific Research (Z. W. O.).

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(5) L. d'Albis, *Chim. Mod.*, **5**, 209 (1960); *Chem. Abstr.*, **55**, 17,585 (1961).

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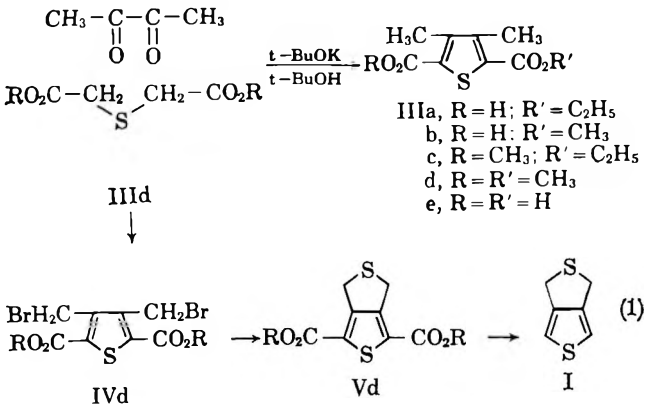
(9) H. Wynberg and H. J. Kooreman, in preparation.

(10) D. E. Wolf and K. Folkers, *Org. Reactions*, **6**, 435 (1951).

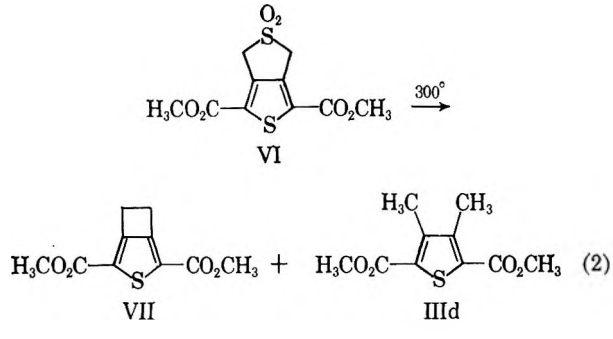


is a Stobbe-type[11] condensation proceeding *via* a δ-lactone intermediate. Utilizing the Stobbe–Johnson[11] conditions, *viz.*, potassium *t*-butoxide in *t*-butyl alcohol for a short (15–45 min.) time at room temperature, the monoester (IIIa) could be isolated in nearly quantitative yield by extraction with ammonia and acidification. The structure of the pure monoethyl ester, m.p. 232°, was supported by the elementary analysis and its conversion in high yield into the monomethyl monoethyl ester (IIIc), m.p. 93°. The n.m.r. spectrum of IIIc (see Experimental) was consistent with the structure assigned.

N-Bromosuccinimide bromination of the dimethyl ester (IIId) furnished the crystalline dimethyl 3,4-bisbromomethyl-2,5-thiophenedicarboxylate (IVd), m.p. 125°, in 71% yield. The latter could be cyclized to dimethyl 1*H*,3*H*-thieno[3,4-*c*]thiophene-4,6-dicarboxylate (Vd) using a freshly prepared sodium sulfide solution in anhydrous methanol. The thienothiophene, m.p. 163°, isolated in 58% yield as a pink[12] solid was converted to the dicarboxylic acid (Ve), m.p. >350°, by hydrolysis. The latter (Ve), also a pink solid and showing yellow fluorescence in alkaline solution, was decarboxylated using copper powder at 325° to furnish 1*H*,3*H*-thieno[3,4-*c*]thiophene (I), m.p. 61–62°. Its elemental analysis, n.m.r. spectrum in acetone (two singlets at τ 6.12 and 3.02, area ratio 2:1), and ultraviolet spectrum ($\lambda_{max}^{95\%\ EtOH}$ 232 mμ, ε 6100) are in accord with the structure assigned.

Oxidation of Vd with hydrogen peroxide in acetic acid gave the sulfone (VI), m.p. 199–200°, in 55% yield.

Initial attempts at conversion of VI and VII using



methods described in the literature[13] were not successful, although the presence of 3,4-dimethyl thiophene-2,5-dicarboxylate (IIId) indicated that sulfur dioxide had been expelled.

In order to be able to compare the spectral properties of I with those of an appropriate model compound, 3,4-bis[(ethylthio)methyl]thiophene (VIII) was prepared according to the general scheme shown in eq. 1 (see Experimental for details).

Discussion

Since the publication in 1930 by Mills and Nixon[5] of the hypothesis of bond fixation in hydrindanes, considerable work has been done to substantiate or dispute this contention. Substitution reactions,[4] coupling reactions,[14] lactone formation,[15] ozonolysis,[16] hydrogenation,[17] epoxidation,[17] bromination,[18] and dehydrogenation[19] are all examples of reactions used to investigate the theory. In addition to the chemical reactivity, the studies have included an investigation of chelation behavior,[20,21] p*K* values of phenols,[22,23] and dipole moments.[24] Electron diffraction patterns,[25] oxidation–reduction potentials,[26] heats of hydrogenation,[27] and ultraviolet absorption measurements[28] have been made. Several quantum mechanical treatments have been given.[7,29] It is evident from a review of these studies that no single theory satisfactorily explains the many experimental results obtained. This is not surprising since some phenomena are a measure of differences in the stability or reactivity in the ground state, others of the transition state, while still others compare the (electronically) excited states. Furthermore, since it appears that the ring-strain effect one attempts to evaluate is, at best, a rather small effect, additional parameters such as entropies of activation and solvation influences may well obscure any trend. In certain recent cases, however, steric effects in π-electron systems have markedly altered the properties of the conjugated system as evidenced

(11) W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

(12) Analytically pure diester (Vd) retained this characteristic pink (λ_{max} *ca.* 500 mμ in CH_2Cl_2) color, even after sublimation and chromatography.

(13) M. P. Cava and A. A. Deana, *J. Am. Chem. Soc.*, **81**, 4266 (1959).

(14) L. F. Fieser and W. C. Lothrop, *ibid.*, **58**, 2050 (1936); **59**, 945 (1937); W. C. Lothrop, *ibid.*, **62**, 132 (1940).

(15) B. I. Arventi, *Ann. Sci. Univ. Jassy I*, **25**, 692 (1939); *Chem. Abstr.*, **34**, 415 (1940).

(16) L. Long and L. F. Fieser, *J. Am. Chem. Soc.*, **62**, 2670 (1940); J. P. Wibaut and F. P. K. de Jong, *Koninkl. Ned. Akad. Wetenschap. Proc.*, **59B**, 285 (1956).

(17) E. Giovannini and H. Wegmüller, *Helv. Chim. Acta*, **41**, 933 (1958); **42**, 1142 (1959).

(18) N. MacLeish and N. Campbell, *J. Chem. Soc.*, 1103 (1937).

(19) N. P. Buu-Hoï and P. Cagniant, *Bull. soc. chim. France*, **10**, 139 (1943).

(20) W. Baker, *J. Chem. Soc.*, 476 (1937), and previous papers.

(21) I. M. Hunsberger, H. S. Gutowsky, W. Powell, L. Morin, and V. Bandureo, *J. Am. Chem. Soc.*, **80**, 3294 (1958), and previous papers.

(22) F. Kieffer and P. Rumpf, *Compt. rend.*, **230**, 2302 (1950).

(23) R. T. Arnold and R. L. Evens, *J. Am. Chem. Soc.*, **62**, 556 (1940).

(24) N. V. Sidgwick and H. D. Springall, *J. Chem. Soc.*, 1532 (1936); H. D. Springall, G. C. Hampson, C. G. May, and H. Spedding, *ibid.*, 1524 (1949).

(25) H. D. Springall and A. Kossiakoff, *J. Am. Chem. Soc.*, **63**, 2223 (1941).

(26) R. T. Arnold and H. E. Zaugg, *ibid.*, **63**, 1317 (1941); W. A. Waters, *J. Chem. Soc.*, 727 (1948).

(27) L. O. Brockway and T. W. J. Taylor, *Ann. Rept. (Chem. Soc. London)*, **34**, 196 (1937).

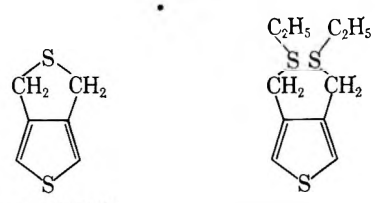
(28) R. H. Horning and E. D. Amstutz, *J. Org. Chem.*, **20**, 1069 (1955); R. T. Arnold and J. Richter, *J. Am. Chem. Soc.*, **70**, 3505 (1948), and previous papers.

(29) G. W. Wheland, *J. Am. Chem. Soc.*, **64**, 900 (1942); F. Seel, *Angew. Chem.*, **60**, 300 (1948); B. Pullman *Bull. soc. chim. France*, **14**, 337 (1947); G. Berthier and A. Pullman, *ibid.*, **17**, 88 (1950).

by chemical reactivity[30] or spectral behavior,[31] thus encouraging further research in this direction.

The pertinent physical properties of the two compounds are listed below. Chart I shows that although the effects are not large they are consistent with the hypothesis that the five-membered ring in the thienothiophene has perturbed the aromaticity of the thiophene ring. The hypsochromic shift from the characteristic thiophene absorption at 245–250 mμ towards that of a diene chromophore and the weakening of the ring current effect as evidenced by the n.m.r. absorption at higher field both indicate that this perturbation may well be caused by diminished π-orbital overlap.

CHART I[a]



[a] Ultraviolet, $\lambda_{max}^{95\%\ EtOH}$ mμ (ε): 232 (6100) and 246 (5600), respectively. N.m.r. (acetone), aromatic protons (sweep width 50 c. p. s.): τ 3.02 and 2.75, respectively.

Experimental

N.m.r. spectra were determined on a Varian A-60 using tetramethylsilane (TMS) (τ 10) as internal standard, ultraviolet spectra in 95% alcohol using a Zeiss PMQ II, infrared spectra on a Perkin-Elmer Infracord or Model 125. Microanalyses were made by W. M. Hazenberg of this department. Melting points are uncorrected.

3,4-Dimethylthiophene-2,5-dicarboxylic Acid Monoethyl Ester (IIIa).—Using the apparatus for carrying out Stobbe condensations under nitrogen described by Johnson and Daub,[11] 77.0 g. of diethyl thiodiacetate [0.375 mole, b.p. 135–136° (10 mm.)] and 48.2 g. of diacetyl (0.56 mole, b.p. 88°) were added simultaneously as rapidly as possible to a stirred solution containing 30.0 g. of potassium (0.77 g.-atom) in 0.5 l. of dry *t*-butyl alcohol; during the addition the reaction mixture was cooled in an ice bath. The solution turned dark almost at once. Stirring was continued for 45 min. While cooling in ice the solution was acidified with 120 ml. of dilute (1:1) hydrochloric acid and most of the alcohol was removed *in vacuo*. Water was added, the organic material was extracted with ether, and the ether was extracted with five 200-ml. portions of 2.5% ammonia solution. Acidification with dilute hydrochloric acid furnished a tan solid which was removed by filtration and dried, yielding 86.0 g. of IIIa (~100%), m.p. 175–200°. Recrystallization from acetic acid gave 43.0 g. (50% based on thiodiacetate) of almost pure monoester, m.p. 228–230°. The analytical sample melted at 231–232.5° after further crystallizations from acetic acid and from chloroform; ultraviolet absorption: $\lambda_{max}^{95\%\ EtOH}$ 209, 280 mμ (ε 11,000, 15,800).

Anal. Calcd. for $C_{10}H_{12}O_4S$ (mol. wt. 228.86): C, 52.60; H, 5.30; S, 14.05. Found: C, 52.4, 52.6; H, 5.0, 4.9; S, 13.9, 13.9.

The structure was confirmed by conversion to the methyl ethyl ester (IIIc) with diazomethane. A sample, recrystallized from methanol, melted at 93–94°; n.m.r. spectrum (in chloroform): two sharp singlets at τ 7.56 and 6.15, one triplet (τ 8.76, 8.64, 8.52), one quadruplet (τ 5.84, 5.72, 5.61, 5.49), area ratio 6:3:3:2; ultraviolet spectrum: $\lambda_{max}^{95\%\ EtOH}$ 209, 280 mμ (ε 12,000, 17,500).

Anal. Calcd. for $C_{11}H_{14}O_4S$ (mol. wt. 242.29): C, 54.55; H, 5.82; S, 13.22. Found: C, 54.5, 54.7; H, 5.7, 5.6; S, 13.1, 13.1.

The dimethyl ester (IIId) was prepared from the monoethyl ester by passing a stream of dry hydrogen chloride through a solution containing 22.8 g. (0.10 mole) of the monoester in 0.5 l. of absolute methanol for 4 hr. The reaction was completed by heating the solution for 2 hr. under reflux. Cooling furnished a solid which was removed by filtration and recrystallized from carbon tetrachloride yielding 17.5 g. (77%) of the dimethyl ester (IIId), m.p. 170–171°; n.m.r. spectrum: two sharp singlets at τ 7.56 and 6.15 (chloroform), area ratio 1:1; ultraviolet spectrum: $\lambda_{max}^{95\%\ EtOH}$ 209, 280 mμ (ε 11,400, 16,500).

Anal. Calcd. for $C_{10}H_{12}O_4S$ (mol. wt. 228.26): C, 52.60; H, 5.30; S, 14.05. Found: C, 52.8; 52.8; H, 5.4, 5.3; S, 13.6, 13.6.

Using dimethyl thiodiacetate, the monomethyl ester (IIIb), m.p. 230–231.5°, was prepared as described above in 51% yield (~100% crude yield) and converted to the dimethyl ester (IIId), m.p. 170–170.5°, in 94% yield, using diazomethane.

3,4-Bis(bromomethyl)thiophene-2,5-dicarboxylic Acid Dimethyl Ester (IVd).—The diester (IIId, 22.8 g., 0.10 mole) was dissolved in 200 ml. of dry, hot carbon tetrachloride and 35.6 g. (0.20 mole) of N-bromosuccinimide[32] (NBS) was added, followed by 0.3 g. of dibenzoyl peroxide. The mixture was heated to boiling on a steam bath and shaken occasionally. After 40 min., the NBS had disappeared and succinimide was suspended in the organic layer. It was removed by filtration of the warm solvent. Concentration of the solvent furnished 27.4 g. (71%) of IVd, m.p. 124.5–126°, as colorless crystals after recrystallizations from methanol and from petroleum ether (b.p. 60–80°); n.m.r. spectrum: two sharp singlets at τ 4.98 and 6.05 (in chloroform), area ratio 2:3; ultraviolet spectrum: $\lambda_{max}^{95\%\ EtOH}$ 234, 282.5 mμ (ε 19,900, 12,100).

Anal. Calcd. for $C_{10}H_{10}BrO_4S$ (mol. wt. 386.09): C, 31.11; H, 2.61; Br, 41.40; S, 8.30. Found: C, 31.5, 31.3; H, 2.6, 2.6; Br, 41.7, 41.5; S, 8.6, 8.4.

1H,3H-Thieno[3,4-c]thiophene-4,6-dicarboxylic Acid Dimethyl Ester (Vd).—Using 2.53 g. (0.11 g.-atom) of sodium dissolved in 50 ml. of dry methanol, a dry sodium sulfide solution was prepared in the usual manner.[33] To the boiling solution was added during 1 hr. a warm solution of the dibromide (19.3 g., 0.05 mole) in 400 ml. of dry methanol. The solution was heated under reflux for an additional 1.5 hr. whereupon the solid was removed from the cooled mixture. Recrystallization from tetrahydrofuran–ether (3:1) furnished 7.5 g. (58%) of pink[12] needles, m.p. 163–164°, of pure Vd; n.m.r. spectrum: two singlets at τ 5.85 and 6.12 (in chloroform), area ration 2:3; ultraviolet spectrum: $\lambda_{max}^{95\%\ EtOH}$ 205, 278 mμ (ε 14,000, 21,000).

Anal. Calcd. for $C_{10}H_{10}O_4S_2$ (mol. wt. 258.31): C, 46.49; H, 3.90; S, 24.83; Found: C, 46.4, 46.2; H, 3.9, 3.9; S, 24.3, 24.4.

The free dicarboxylic acid (Ve, R = H), m.p. >350°, was obtained as a pink solid upon hydrolyzing the ester (Vd, R = CH_3) by refluxing for 5 hr. with potassium hydroxide solution to which 5% methanol was added. The alkaline solution showed yellow fluorescence.

1H,3H-Thieno[3,4-c]thiophene (I).—The pink dicarboxylic acid (Ve, 460 mg., 2 mmoles) was mixed with 150 mg. of copper powder and the mixture was heated to 325° in a sublimation apparatus. A colorless solid deposited on the cold finger (cooled with a Dry Ice–acetone mixture) and was purified by a second sublimation at 55° (0.2 mm.), furnishing 88 mg. (31%) of 1H,3H-thieno[3,4-c]thiophene (I), m.p. 61–62°; n.m.r. spectrum: two singlets at τ 6.12 and 3.02 (in acetone), area ratio 2:1; ultraviolet spectrum: $\lambda_{max}^{95\%\ EtOH}$ 232 mμ (ε 6,100); infrared spectrum: strongest absorption at 784 cm.$^{-1}$ (KBr).

Anal. Calcd. for $C_6H_6S_2$ (mol. wt. 142.24): C, 50.67; H, 4.25; S, 45.08. Found: C, 50.9, 50.9; H, 4.3, 4.2; S, 45.0.

3,4-Bis[(ethylthio)methyl]thiophene (IX).—The sodium salt of ethyl mercaptan was prepared by adding under ice cooling, 3.10 g. [0.05 mole, b.p. 34.5–35° (760 mm.)] of ethyl mercaptan to a solution containing 1.15 g. (0.05 g.-atom) of sodium in 50 ml. of absolute methanol. A solution of 7.72 g. (0.02 mole) of 3,4-bis(bromomethyl)thiophene-2,5-dicarboxylic acid dimethyl ester (IVd) in 100 ml. of dry benzene was added in the cold. Sodium bromide precipitated from the solution which was heated under reflux for 1 hr. after the addition was complete. After removal of the salt by filtration and of the solvent by

(30) E. E. von Tamelen and S. P. Pappas, *J. Am. Chem. Soc.*, **84**, 3789 (1962).

(31) H. Wynberg, A. de Groot, and D. W. Davies, *Tetrahedron Letters*, **No. 17**, 1083 (1963).

(32) Freshly prepared according to the direction of L. Horner and E. H. Winkelmann ("Neuere Methoden der präp. org. Chemie," Vol. III, Verlag Chemie, Berlin, 1961, p. 98).

(33) R. W. Bost and M. W. Conn, *Org. Syn.*, **15**, 72 (1935).

evaporation, the residue was washed thoroughly with water. These aqueous extracts contained monoester, m.p. 137–139°, and dibasic acid, m.p. 235–240°. The water insoluble portion was recrystallized from methanol–water (4:1) to furnish 3.81 g. (55%) of **3,4-bis[(ethylthio)methyl]thiophene-2,5-dicarboxylic acid dimethyl ester**, m.p. 79.5–80.5°; n.m.r. spectrum ($CHCl_3$): singlets at τ 5.67 and 6.10, triplet at τ 8.62, 8.75, and 8.88, and quadruplet at τ 7.28, 7.40, 7.52, and 7.63, area ratio 2:3:3:2; ultraviolet spectrum: $\lambda_{max}^{95\% EtOH}$ 218, 277 mμ (ϵ 22,000, 17,000).

Anal. Calcd. for $C_{14}H_{20}O_4S_3$ (mol. wt. 348.51): C, 48.25; H, 5.78; S, 27.61. Found: C, 47.8, 48.1; H, 5.9, 5.8; S, 27.3, 27.3.

After hydrolysis to the decarboxylic acid, m.p. 235–240°, the decarboxylation was carried out by heating 6.50 g. (0.0203 mole) of the diacid with 2 g. of copper powder in 50 ml. of quinoline. Carbon dioxide evolution commenced at 220°. Removal of the quinoline (from the distillate) with hydrochloric acid and distillation furnished 2.30 g. of VIII as a straw-colored liquid, b.p. 182–183° (15 mm.), $n^{20}D$ 1.5840. 3,4-Bis[(ethylthio)methyl]-thiophene (VIII) was obtained as a colorless liquid, $n^{20}D$ 1.5823, after passage over alumina; n.m.r. spectrum: singlets at τ 6.26 and 3.02, triplet at τ 8.68, 8.80, and 8.92, and quadruplet at τ 7.44, 7.55, 7.70, and 7.80; area ratio 2:1:3:2 (in CCl_4); ultraviolet spectrum: $\lambda_{max}^{95\% EtOH}$ 246 mμ (ϵ 5,600); infrared spectrum: strongest absorption 801 cm.$^{-1}$ (neat).

Anal. Calcd. for $C_{10}H_{16}S_3$ (mol. wt. 232.44): C, 51.67; H, 6.94; S, 41.39. Found: C, 52.2; H, 6.9; S, 40.9.

A mercurichloride derivative, m.p. 111–112° (70% ethanol), was prepared in 90% yield.

1*H*,3*H*-Thieno[3,4-*c*]thiophene-4,6-dicarboxylic Acid Dimethyl Ester 2,2-Dioxide (VI).—A solution containing 2.58 g. (0.01 mole) of Vd in 30 ml. of glacial acetic acid was heated with 3.06 ml. (0.03 mole) of a 30% hydrogen peroxide solution. The solution was refluxed for 30 min., causing disappearance of the pink color. Upon addition of water to the reaction mixture VI precipitated. Recrystallization of the solid (1.5 g., 55% yield) from benzene–petroleum ether (4:1) furnished the sulfone (VI) as colorless crystals, m.p. 199–200°; n.m.r. spectrum ($CHCl_3$): singlets at τ 5.52 and 6.08, area ratio 2:3.

Anal. Calcd. for $C_{10}H_{10}O_6S_2$ (mol. wt. 290.31): S, 22.09. Found: S, 21.7.

Pyrolysis of VI at 350° in a sublimation apparatus using copper powder or over a heated coil (500°)[13] furnished as the only identifiable product 3,4-dimethylthiophene-2,5-dicarboxylic acid dimethyl ester (infrared spectrum identical with that of IIIc, undepressed mixture melting point).

Mechanisms of Photochemical Reactions in Solution. XXIV.[1] Photochemical and Catalytic Decomposition of Diazoacetophenone

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Diazoacetophenone has been decomposed under a variety of conditions. The sensitized and direct photochemical decomposition both appear to produce the triplet ketocarbene which adds to *cis*- and *trans*-2-butene in a nonstereospecific manner. The ketocarbene is relatively unreactive and exhibits radical properties as characterized by the large amounts of bicyclohexenyl and acetophenone produced in the direct and sensitized photolysis of diazoacetophenone in cyclohexene. Phenacyl chloride was formed in addition to the expected cyclopropanes when metal chlorides were used to catalyze the reaction of diazoacetophenone with olefins.

When diazomethane is photochemically decomposed in solutions the resulting methylene reacts in a stereospecific manner with olefins[4,5] and gives indiscriminate insertion to hydrocarbons.[6,7] These properties are consistent with assigning the singlet state to methylene produced under these conditions. The singlet–triplet decay of methylene has not yet been observed in solution because of the extreme reactivity of methylene, but this decay has been postulated for the gas phase photolysis of diazomethane to explain both spectroscopic[8] and chemical results.[9] The only manner in which triplet methylene has been prepared in solution is by the photosensitized decomposition of diazomethane.[7]

In this process, benzophenone is selectively excited to a singlet state, whereupon intersystem crossing takes place to produce excited triplet benzophenone with the nearly unit efficiency. The triplet benzophenone can then transfer its energy (with conservation of spin angular momentum) to ground singlet diazomethane molecules to generate diazomethane in the excited triplet state. The triplet diazomethane then decomposes to give methylene which reacts as predicted for triplet methylene.

The synthetic importance of the photochemical decomposition of substituted diazomethanes (diazo ketones) has been recently emphasized by Meinwald's synthesis of D-norsteroids[10] and the reinvestigation of the photolysis of diazocamphor.[11]

The photochemical decomposition of diazo ketones is intriguing because of the possibility that the triplet ketomethylene could be produced upon direct irradiation. The result is predicted as a consequence of the high rates of intersystem crossing by carbonyl compounds in general.

Results and Discussion

The photolysis of diazoacetophenone in solution gave only traces of the dilactone (m.p. 268–270°) which Wiberg[12] obtained from the photolysis of solid diazoacetophenone. This is reasonable since the postulated mechanism for the formation involves the bimolecular reaction of either diazoacetophenone or the corresponding ketomethylene with phenylketene. The principal products from the direct and sensitized photolysis of diazoacetophenone in cyclohexene were 3,3′-bicyclohexenyl, acetophenone (70% yield), and 7-norcaryl

(1) Part XXIII: G. S. Hammond, P. Wyatt, C. DeBoer, and N. J. Turro, *J. Am. Chem. Soc.*, **86**, 2532 (1964).

(2) National Science Foundation Undergraduate Research Participant, 1962.

(3) To whom inquiries should be addressed.

(4) P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **78**, 4496 (1956).

(5) R. C. Woodworth and P. S. Skell, *ibid.*, **81**, 3383 (1959).

(6) W. v. E. Doering, R. G. Buttery, R. G. Laughlin, and N. Chaudhuri, *ibid.*, **78**, 3224 (1956).

(7) K. R. Kopecky, G. S. Hammond, and P. A. Leermakers, *ibid.*, **84**, 1015 (1962).

(8) G. Herzberg and I. Shoosmith, *Nature*, **183**, 1801 (1959).

(9) H. M. Frey, *J. Am. Chem. Soc.*, **82**, 5947 (1960).

(10) J. Meinwald, G. G. Curtis, and P. G. Gassman, *ibid.*, **84**, 116 (1962).

(11) J. Meinwald, A. Lewis, and P. G. Gassman, *ibid.*, **84**, 977 (1962).

(12) K. B. Wiberg and T. W. Hutton, *ibid.*, **76**, 5367 (1954).

phenyl ketone (10–12%). The high yields of acetophenone and bicyclohexenyl suggest that the ketomethylene is highly reactive in hydrogen abstraction.

Because of the relatively large extinction coefficient of Michler's ketone at 3660 Å., it was possible to activate selectively Michler's ketone (MK) in the presence of diazoacetophenone using light filtered to isolate the 3660-Å. line from a mercury arc. Under these conditions, the triplet ketomethylene should be formed.

$$\underset{\text{MK}}{(p\text{-Me}_2\text{NC}_6\text{H}_4)_2\text{CO}} \xrightarrow{h\nu} \underset{\text{MK}^{*(1)}}{(p\text{-Me}_2\text{NC}_6\text{H}_4)\text{CO}^{*(1)}} \quad (1)$$

$$\text{MK}^{*(1)} \longrightarrow \text{MK}^{*(3)} \quad (2)$$

$$\text{MK}^{*(3)} + \text{C}_6\text{H}_5\text{COCHN}_2 \longrightarrow \text{MK} + \text{C}_6\text{H}_5\text{COCHN}_2{}^{*(3)} \quad (3)$$

$$\text{C}_6\text{H}_5\text{COCHN}_2{}^{*(3)} \longrightarrow \text{C}_6\text{H}_5\text{COCH}:(\uparrow\downarrow) + \text{N}_2 \quad (4)$$

The process involving transfer of energy from Michler's ketone in the excited singlet state to ground state diazoacetophenone is endoenergetic and, as such, should not compete with intersystem crossing of Michler's ketone from the singlet to triplet state.

Since both the sensitized and direct photolysis in cyclohexene give the same product distribution (see Table I), this again implicates the triplet state in the direct photolysis.

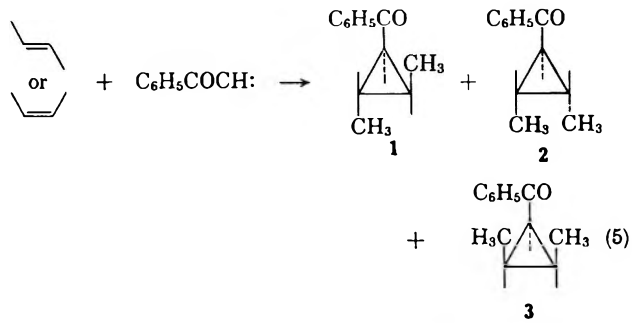
TABLE I

YIELD OF 7-NORCARYL PHENYL KETONE FROM THE REACTION OF DIAZOACETOPHENONE AND CYCLOHEXENE

Catalyst	Yield, %	$t_{1/2}$	Temp., °C.
Cu_2Cl_2	29	5 min.	28
Cu_2Cl_2[a]	22	6 min.	28
$CuCl_2$	44	85 min.	28
CuO	55	3+ hr.	60
$CuSO_4$	62 (50)	3+ hr.	28
$Cu(DPM)_2$[b]	19		28 then 60
$Ni(CP)_2$[c]	5	3 hr.	28
$Ni(CO)_4$	Trace		28
$AgNO_3$	Trace		28
Direct irradiation	10–12[e]		28
Photosensitized[d]	12[e]		28

[a] Equimolar amounts of Cu_2Cl_2 and diazoacetophenone. [b] DPM is dipivaloylmethide. [c] CP is cyclopentadiene. [d] Michler's ketone was the sensitizer. [e] These reactions also produced >70% acetophenone.

The reaction of ketomethylenes produced by direct and sensitized photolysis of diazoacetophenone with *cis*- and *trans*-2-butene in isooctane have also been studied. Both methods of photolysis produced low yields of the expected cyclopropanes in a nonstereo-



(5)

specific manner. The low yield of cyclopropanes in this case could result from the competition with reaction 6, rearrangement of the ketomethylene to the corresponding ketene, and reaction 7, radical reaction with either the solvent or olefin molecules.

$$\text{C}_6\text{H}_5\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—CH}: \longrightarrow \text{C}_6\text{H}_5\text{C}(\text{H})\text{=C=O} \quad (6)$$

$$\text{C}_6\text{H}_5\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—CH} + \text{RH} \longrightarrow \text{R}\cdot + \text{C}_6\text{H}_5\text{—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—CH}_2 \quad (7)$$

Doering[13] and Griffin[14] have shown that cyclopropanes can isomerize under the influence of light; to reduce this isomerization as much as possible, the irradiations were carried out for relatively short periods of time. Experimentally it was found that, under our conditions, a very small amount of isomerization does take place during the period of irradiation.

Since the isomer distribution is similar for the sensitized and direct photolysis of diazoacetophenone in a solution with *cis*- or *trans*-2-butene, the triplet ketomethylene must be produced by both methods. The triplet ketomethylene apparently adds to the double bond of olefins to produce a short-lived biradical in which the electrons are unpaired. Since *cis*- and *trans*-2-butene do not give exactly the same product mixture, the rate of internal rotation is not much larger than the rate of spin inversion. Thus when starting out with *cis*-2 butene, more **2** is produced than when starting with *trans*-2 butene (see Table II). Identical product distribution from the reaction of *cis*- and *trans*-2-butenes and triplet methylene was not obtained either.[7]

TABLE II

RELATIVE YIELDS OF CYCLOPROPANES FROM PHOTOLYSIS OF DIAZOACETOPHENONE IN THE PRESENCE OF *cis*- AND *trans*-2-BUTENE

Alkene	Method of photolysis	Relative per cent[a] **1**[b]	**2**	**3**
cis	Direct	50	40	10
cis	Sensitized	55	35	10
trans	Direct	73	15	12
trans	Sensitized	74	17	9

[a] The total yield of cyclopropanes varied from 8–12%. [b] On long irradiation the relative amount of **1** increased slightly.

Although the results strongly implicate the triplet ketomethylene as the principal reactive intermediate in both reactions, we have no good grounds for specification of a path for its formation in the direct irradiations. Intersystem crossing could occur either before or after decomposition of the diazo compound. Since no phosphorescence of diazoacetophenone could be detected when the compound was irradiated in a hydrocarbon glass at 77° K., we infer that the lifetime of the triplet diazoketone must be very short if it is formed at all.

Ziffer and Sharpless[15] have correlated Horner's[16] data for substituent effects on the quantum yields for photolysis of substituted diazoacetophenones with the Hammett constants of the substituents. The correlation, although rough, is probably statistically significant, but we are unable to understand the author's

(13) W. v. E. Doering and M. Jones, Jr., *Tetrahedron Letters*, 791 (1963).
(14) G. W. Griffin, E. J. O'Connell, and H. A. Hammond, *J. Am. Chem. Soc.*, **85**, 1001 (1963).
(15) H. Ziffer and N. E. Sharpless, *J. Org. Chem.*, **27**, 1944 (1962).
(16) W. Kirmse and L. Horner, *Ann.*, **625**, 34 (1959).

rationalization of the results.[17] As we look at the data, which show that maximum quantum yields are actually measured for the parent compound and for two *ortho*-substituted derivatives, it seems that we could provide a rationalization based upon effects of substituents on the efficiency of intersystem crossing. The lowest excited states of these molecules probably have mixed n,π^* and π,π^* character, and it might be expected that the members of the series of which the triplets have the most nearly "pure" n,π^* character would undergo intersystem crossing most efficiently. This prediction follows from both empirical experience and from the fact that the singlet–triplet separation is ordinarily small in n,π^* states. Introduction of various substituents which increase conjugative interaction between the aryl moieties and the carbonyl group might well increase the coupling of n,π^* and π,π^* states with consequent increase in the singlet–triplet splitting and decrease in the efficiency of intersystem crossing. This view is consistent with the fact that an improvement of the correlation by the Hammett equation was obtained when log $\Phi\epsilon$, rather than log Φ, was plotted against σ. The fact that quantum yields tend to be lowest for those compounds that have the largest extinction coefficients for the first allowed transitions makes sense since the high extinction coefficients may reflect considerable mixing of excited states. This explanation (which makes correlation with the Hammett parameters seem almost incidental) does not account perfectly for all the data, and is certainly not persuasive mechanistic evidence. Analysis of the problem is highly complicated by the fact that the fate of the excited molecules is probably determined only after they have decayed from initially formed excited states to lower lying states for which direct excitation is rather highly forbidden.

The mechanism of catalytic decomposition of diazoacetophenone in the presence of metal salts must be different from the photolytic processes. As is shown by the data in Table I, catalytic decomposition in the presence of cyclohexene leads to formation of norcaryl phenyl ketone, usually in much larger yield than was obtained by either direct or sensitized photolysis. Products expected from hydrogen abstraction from the alkene were not found. Catalytic decomposition in the presence of the butenes also led to higher yields (30–45%) of cyclopropanes than were obtained in the photochemical experiments. Furthermore, as is shown in Table III, the relative amounts of **1**, **2**, and **3** were also quite different. Reaction with *trans*-2-butene gives only **1** in a reaction that is entirely stereospecific. Compounds **2** and **3**, which would be expected from stereospecific addition to *cis*-2-butene, are the predominant products when the latter alkene is the substrate, although some **1** was also produced in all experiments. Phenacyl chloride is also produced in reactions in which cuprous chloride was used as the catalyst.

(17) The authors seem, on the one hand, to imply that the existence of a correlation implies that loss of nitrogen is determined by competitive actions of the triplet diazo compound; *i.e.*, that intersystem crossing occurs with constant efficiency. On the other hand, the sign of ρ is discussed as though it were determined by the migratory aptitudes of the aryl groups *in the ketocarbene*. The latter effects should have little relevance to the quantum yields for nitrogen evolution unless loss of nitrogen and rearrangement to a ketene are a single, concerted process. Such a mechanism is obviously not applicable, at least under our reaction conditions, since rearranged products are not obtained in significant yield.

TABLE III

RELATIVE YIELDS OF PRODUCTS FROM THE CATALYZED REACTIONS OF DIAZOACETOPHENONE WITH *cis*- AND *trans*-2-BUTENES

Reaction catalyst	Olefin	Solvent	Relative yields,[a] % 1	2	3
Cu_2Cl_2	*cis*	Isooctane	21	54	25[b]
Cu_2Cl_2	*cis*	None	22	57	22[b]
Cu_2Cl_2	*cis*	Isooctane	25	58	17[b]
$CuSO_4$	*cis*	Isooctane	28	67	5
$CuSO_4$	*trans*	Isooctane	100		

[a] The total yield of cyclopropane compounds varied from 30–45%. [b] Component **3** was an unsymmetrical v.p.c. peak, not resolved on any of the columns tried.

The relatively high stereospecificity of catalyzed addition to the 2-butenes might be indicative of the involvement of the singlet ketocarbene. We regard such an explanation as being unattractive, largely because the reagent involved seems to be more selective than the triplet carbene believed to be the active agent in photolysis. It is most probable that the attacking reagent is an organometallic compound such as $C_6H_5COCHCu$ or $C_6H_5COCHCuCl_2$. The latter species would be a logical precursor of phenacyl chloride and would be structurally analogous to the species $ZnCH_2I_2$ formed by the reaction of diazomethane with zinc iodide.[18] The fact that the catalytic reactions with *cis*-2-butene are not entirely stereospecific may indicate that the catalyzed reactions proceed by some mixture of mechanisms.

Experimental

Catalyzed Diazoacetophenone–Cyclohexene Reactions.—All of the metal-catalyzed diazoacetophenone–cyclohexene reactions listed in Table I were carried out in the same manner. The diazoacetophenone used in these reactions was prepared by the method of Newman and Bell.[19] Diazoacetophenone (0.5 g.) was dissolved in 25 ml. of distilled cyclohexene in a 50-ml., one-necked round-bottomed flask connected to a mercury-filled buret. The metal catalyst (50 mg.) was added, and the resulting suspension was stirred magnetically until the reaction was finished. The solution was thermostated in a water bath at 28 ± 1°. Reaction mixtures were analyzed by vapor phase chromatography (v.p.c.) using a diethylene glycol succinate (DEGS) column and an internal standard.

The high boiling component of the copper sulfate catalyzed reactions was isolated by distillation and also by v.p.c. on a DEGS column. The properties of this material agree with those that Mousseron[20] reported for 7-norcaryl phenyl ketone, b.p. 140° at less than 1 mm., reported 145° at 1 mm.; λ_{max}^{EtOH} 244 mμ (log ε 4.5), reported 244 mμ (log ε 4.2); 2,4-dinitrophenylhydrazone, m.p. 200.5–202.5°, $\lambda_{max}^{CHCl_3}$ 383 (log ε 4.37), reported m.p. 195–196, $\lambda_{max}^{CHCl_3}$ 383 (log ε 4.42).

Anal. of the 2,4-dinitrophenylhydrazone. Calcd. for $C_{19}H_{19}O_4N_4$: 14.75. Found: N, 14.80.

The only other product isolated from the metal chloride catalyzed reactions was phenacyl chloride. This material had n.m.r., ultraviolet, and infrared spectra identical with those for authentic phenacyl chloride. The starting diazoacetophenone was tested (v.p.c.) for phenacyl chloride and none was observed; phenacyl chloride was not found in the reactions catalyzed by copper sulfate.

Direct Irradiation in Cyclohexene.—The direct photolysis reactions were carried out in an immersion reactor[7] with a 2900-Å. cut-off filter sleeve. The light source was a 200-w. Hanovia mercury vapor lamp Type S, No. 654A. In a typical experiment, diazoacetophenone (0.5 g.) dissolved in 75 ml. of purified cyclohexene was charged into this reactor and irradiated until

(18) G. Wittig and K. Schwarzenbach, *Ann.*, **650**, 1 (1961).
(19) M. S. Newman and P. Bell, *J. Am. Chem. Soc.*, **71**, 1056 (1949).
(20) M. Mousseron, *Compt. rend.*, **243**, 1880 (1956).

the theoretical amount of nitrogen had been produced, about 2.5 hr. The reaction solution was concentrated by fractional distillation through a short column packed with Pyrex helices to a volume of 25 ml. The products were identified by comparison of v.p.c. retention times on a DEGS column, using known compounds as standards, and by infrared spectrometric analysis of fractions trapped at the proper time from the effluent of the chromatograph. In two determinations an internal standard was added to the irradiated solution before concentration so that the absolute amount of each component could be calculated.

The major products were 7-norcaryl phenyl ketone (10–12%), acetophenone (65–75%), and a considerable amount of 3,3′-bicyclohexenyl. Norcaryl phenyl ketone was isolated by preparative vapor chromatography and identified by comparison of its physical constants with those reported in the literature.[20] The n.m.r. spectrum showed, in addition to the signals expected from the benzoyl group, intense, broad signals at τ 9.0 and ~8.45, and a less intense signal at 7.75. Although the spectra showed, by weak signals in the vinyl proton region, the presence of small amounts of impurities, the integrals of the three high-field signals were approximately in the ratio 2:8:1. Consequently the high-field resonance is attributed to the two protons at the junction of the six- and three-membered rings, and the signal at 7.75 is attributed to the proton attached to the cyclopropane carbon atom which also bears the benzoyl group. The signal at ~8.45 is obviously due to eight methylene protons.

The 3,3′-bicyclohexenyl was isolated by preparative vapor chromatography and compared directly with an authentic sample prepared by reaction of 3-bromocyclohexene with magnesium in ether, b.p. 132–134° at 30 mm., n^{28}D 1.5083.[21]

Catalytic Decomposition of Diazoacetophenone in the Presence of 2-Butenes.—The isomeric 2-butenes were obtained from Phillips Petroleum Company. The specified purities, *cis* >99 mole % purity and *trans* 99.47 mole % purity, were confirmed by v.p.c. analysis using a silver nitrate column and a flame ionization detector.

A solution of 20 g. of either *cis*- or *trans*-2-butene, 0.5 g. of diazoacetophenone, and 50 mg. of the copper salt was prepared in a 150-ml., three-necked round-bottomed flask fitted with a Dry Ice condenser protected from the atmosphere by a calcium chloride tube. The reaction mixtures were stirred for 24 hr. keeping the temperature of the solution below 0°. Most of the butene was then distilled from the reaction mixture by replacing the Dry Ice condenser with a column packed with helices and warming the solution to 30°. The relative yields of the high-boiling compounds reported in Table III were obtained from a vapor phase chromatogram of a sample from the reaction mixtures. The total yield of components **1**, **2**, and **3** varied from 15 to 40%. Several minor, low boiling components were noted by using temperature-programmed vapor phase chromatography but these were not further identified.

The reaction solution from an experiment carried out as described above with *cis*-2-butene using copper sulfate as the catalyst was combined with that from an experiment using 2 g. of diazoacetophenone, 50 g. of *cis*-2-butene, and the same catalyst. The mixture was concentrated by fractional distillation through a column packed with Pyrex helices to a volume of about 15 ml. The compounds **1**, **2**, and **3** were isolated by vapor phase chromatography using a column of 10% Ucon Polar on C-22 firebrick. The properties of the major component of the mixture from reaction with *cis*-2-butene (the second compound off the Ucon Polar column) are consistent with assigning the substance structure **2**. The n.m.r. spectrum exhibits signals at τ 2.3 and 2.75 (multiplets), at 8.05 (triplet, J = 4 c.p.s.), at 8.5 (multiplet), and 8.82 (doublet). If the integrated area of the aromatic protons is assigned a weight of 5, then the other signals represent correspondingly 1, 2, and 6 protons. The ultraviolet spectrum (ethanol) is similar to that for the 7-norcaryl phenyl ketone with absorption maxima at 244 mμ (log ε 4.06), 280 (2.8) and a shoulder at 315 (2.1). The infrared spectrum exhibits significant bands at 5.95 and 9.75 μ. The n.m.r. spectrum, especially the coupling constant for the triplet at 8.05, and the retention time on a Ucon Polar column strongly support the structure assignment of **2** and not **3** or **1**. Component **1** (first off the Ucon Polar column) is identical with the only compound isolated from the copper salt catalyzed reaction of *trans*-2-butene and diazoacetophenone (retention time, ultraviolet, and n.m.r. spectra) and is therefore assigned structure **1** (*vide infra*). Inasmuch as component **3** was formed in about 1% yield, not enough of this compound was isolated for a complete analysis. It is suggested that this compound could be the all-*cis*-substituted cyclopropane **3** since it has an ultraviolet spectrum similar to the other cyclopropanes [244 mμ (log ε ≈4), 280 (≈3), and a shoulder at 315 (≈2)] but has a slightly longer retention time on a Unicon Polar column.

It should be noted that phenacyl chloride was formed in about fourfold higher yield in reactions carried out in the presence of *cis*-2-butene than in reactions in the presence of cyclohexene.

Compound **1** was isolated from the reaction of both *cis*- and *trans*-2-butene with diazoacetophenone in the presence of copper sulfate. In the reaction of *cis*-2-butene, the compound was a minor product (20%), while with *trans*-2-butene it was the only cyclopropane formed. This is consistent with assignment of the stereochemistry of **1** inasmuch as diazomethane, copper sulfate, and an olefin are known[7] to give a cyclopropane which retains the stereochemistry of the olefin. The ultraviolet and infrared spectra of **1** were very similar to those of **2**. The ultraviolet spectrum (ethanol) had absorption maxima at 244 mμ (log ε 4.1), at 280 (3.0), and a shoulder at 315 (≈2). The infrared again showed the bands due to carbonyl and cyclopropane ring absorption. The n.m.r. and infrared spectra indicated that the compound had undergone some partial rearrangement or decomposition in the isolation process since, besides the bands assignable to the cyclopropane compound, others were found in the olefinic region. Thus the integral of the n.m.r. signal for this sample could not be interpreted in terms of *one* simple compound but only in terms of compound **1** and an olefin with the same molecular weight.

Direct and Sensitized Photolysis of Diazoacetophenone in the Presence of *cis*- or *trans*-2-Butene.—The irradiations were carried out in an immersion reactor with a uranium glass filter (cut-off, 3300 Å.) for the sensitized reactions and with a pyrex filter (cut-off, 2900 Å.) for the direct photolysis reactions. The reactor was cooled in a bath at 0° and ice–water was circulated through the cooling jacket of the reactor during the experiment.

A solution containing 0.5 g. of diazoacetophenone, 28 g. of *trans*-2-butene, 10 ml. of anhydrous ether, and 75 ml. of isooctane was saturated with Michler's ketone. The resulting solution was diluted with 10 ml. of isooctane and charged into the reactor. This solution was then irradiated until the theoretical amount of nitrogen had been produced, about 3 hr. The solution was concentrated by fractional distillation to a volume of about 20 ml. and the reaction mixture was analyzed by vapor phase chromatography. The three components listed in Table II had the same v.p.c. retention times on a Ucon Polar column as the three products isolated from the copper catalyzed reactions. They also had the same ultraviolet absorption bands. These three components were formed in from 8 to 12% yields along with a host of other products, such as acetophenone and about ten others. The relative yields of the three cyclopropanes under different experimental conditions are listed in Table II.

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(21) A. Berlande, *Bull. soc. chim. France*, **9**, 641 (1942).

Infrared Spectra of Arylimidazoles and Arylisoimidazoles[1]

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From a study of the infrared spectra of aryl-substituted imidazoles and 2*H*- and 4*H*-isoimidazoles, characteristic absorptions are determined which permit differentiation of the three isomeric ring systems. The sharp absorptions between 1500 and 1565 cm.$^{-1}$ are found to be most useful since the characteristic band of each of the three heterocyclic rings occurs in a region of low absorption by the others. Several other regions of the spectra are also discussed. Fourteen new arylimidazoles and arylisoimidazoles have been prepared. Included among these is 2,4,4,5-tetraphenylisoimidazole, the first example of a 4*H*-isoimidazole ring system which contains only aryl substituents.

The infrared spectra of imidazole,[2] some of its derivatives,[2] benzimidazoles,[3] and similar heterocyclic systems[4] have been described, although few correlations of characteristic bands have been reported. The infrared spectra of 2*H*- and 4*H*-isoimidazoles have not appeared in the literature. The infrared spectra of a variety of arylimidazoles and several aryl-2*H*- and 4*H*-isoimidazoles have now been examined and characteristic absorptions have been determined which can be used to characterize and differentiate between the isomeric ring systems.

Results and Discussion

The arylimidazoles which have been examined are listed in Table I; the aryl 2*H*- and 4*H*-isoimidazoles are listed in Table II. The lists include mono-, di-, tri-, and tetraarylimidazoles and arylisoimidazoles, derivatives substituted with electron-donating and electron-attracting groups, the related 2,4,5-triphenyl-1-imidazoline and imidazole.[5] The 1625–1475-cm.$^{-1}$ regions of the spectra are presented in detail (Tables I and II) and are described below. Representative spectra are shown in Fig. 1. Other regions are described when they are characteristic of a specific structure. The spectra were determined on solid samples in potassium bromide pellets since many of the materials were insoluble in appropriate solvents.

The arylimidazoles absorb in the 1625–1475 region (Table I) at approximately 1602 (m), 1585 (m–w), 1563 (w), 1538 (w), 1502 (m–s), and 1484 (s) cm.$^{-1}$. The 1602- and 1585-cm.$^{-1}$ bands, in most cases, appear to be due to the ν_{16} (E_{2g}) ring stretching vibrations for phenyl groups, some of which are partially restrained from coplanarity with the imidazole ring.[6] In the unsubstituted compounds and the halogenated derivatives (I–VIII) the higher frequency band does not occur above 1610 cm.$^{-1}$. The band is usually shifted to higher values, or a new band at approximately 1615 cm.$^{-1}$ is present, however, when other electron-donating groups are present on the 2-phenyl ring (Table I). The new band may be a result of a splitting of the degenerate ν_{16} band by the substituents into two components. The bands near 1563 and 1538 cm.$^{-1}$ are normally weak and often occur as shoulders. They do not occur so regularly as the two higher frequency bands and in some compounds are accompanied by an additional band. The 1502-cm.$^{-1}$ band is frequently strong and seldom is shifted more than ±4 cm.$^{-1}$. A band occurs in imidazole at 1498 cm.$^{-1}$ but not in certain aliphatic imidazoles (*e.g.*, 4-methylimidazole[2b]). The 1502-cm.$^{-1}$ band is present in all the substituted imidazole in Table I but is not present in the 2*H*-isoimidazoles, 2,4,5-tetraphenyl-4*H*-isoimidazole, or 2,4,5-triphenylimidazoline (XXX). Thus, the band is probably a skeletal stretching vibration of the aryl-substituted imidazole ring. The phenyl ring band which corresponds to the ν_{13} (E_{1u}) vibration of benzene is present in the arylimidazoles near 1485 cm.$^{-1}$ except in a few materials with strong electron-donating substituents (*e.g.*, both the 1500- and 1485-cm.$^{-1}$ bands are shifted to higher frequency by *ca.* 15 cm.$^{-1}$ in the tris-*p*-methyl and *p*-dimethylamino derivatives, XVI and XIX).

Aryl-2*H*-isoimidazoles (Table II, XXXI–XXXV) absorb in the 1625- to 1475-cm.$^{-1}$ region at approximately 1615 (w), 1603 (w–m), 1575 (vw), 1550 (m–s), 1537 (w–vw), and 1485 cm.$^{-1}$ (m–s). The 1615-cm.$^{-1}$ band appears to be characteristic of the aryl-2*H*-isoimidazoles.[7] The use of this band to differentiate between the isomeric ring systems is limited to some extent, however, since some imidazoles with electron-donating substituents (XI–XIV, XVI, and XIX) absorb near 1615 cm.$^{-1}$. The 1603- and 1575-cm.$^{-1}$ bands are similar to those in the arylimidazoles. All the 2*H*-isoimidazoles have the 1550 ± 2-cm.$^{-1}$ band, while only two imidazoles (V and XIX) have appreciable absorption in this region. The 1537-cm.$^{-1}$ band is normally weak and is shifted only in the *p*-anisyl derivative (XXXV). The *p*-anisyl derivative is also unique with a strong band at 1511 cm.$^{-1}$. In all of the 2*H*-isoimidazoles, a strong phenyl band occurs at 1485 cm.$^{-1}$, usually accompanied by another weaker band near 1490 cm.$^{-1}$. None of the 2*H*-isomidazoles have a band at 1502 cm.$^{-1}$, the characteristic absorption in the arylimidazole compounds.

In the 1625–1475-cm.$^{-1}$ region, 2,4,4,5-tetraphenyl-4*H*-isoimidazole (XXXVI) is similar to the aryl-2*H*-isoimidazoles with bands at 1616, 1602, 1532, and 1492 cm.$^{-1}$. Compound XXXVI differs, however, with two new strong bands at 1594 and 1563 cm.$^{-1}$.

(1) Presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, Abstracts, p. 55M.

(2) (a) W. Otting, *Chem. Ber.*, **89**, 1940, 2887 (1956); (b) D. Garfinkel and J. T. Edsall, *J. Am. Chem. Soc.*, **80**, 3807 (1958).

(3) K. J. Morgan, *J. Chem. Soc.*, 2343 (1961), and references cited.

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 277–285.

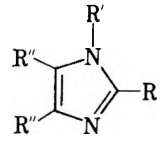
(5) The imidazole spectrum in Table I was similar to that of Otting[2a] but differed from that of Garfinkel and Edsall.[2b] The differences in the latter spectrum involved omissions of medium-to-weak bands and shifts in frequency in adjacent stronger bands. Improved resolution and exclusion of water vapor from the spectrophotometer can account for the differences.

(6) For notation and a discussion of spectra of heteroaromatic compounds, see A. R. Katritzky, *Quart. Rev.* (London), **13**, 353 (1959).

(7) The strong 1608-cm.$^{-1}$ band of the *p*-anisyl derivative XXXV prevents the determination of a band near 1615 cm.$^{-1}$.

TABLE I

INFRARED SPECTRA OF IMIDAZOLES BETWEEN 1625 AND 1475 CM.$^{-1}$

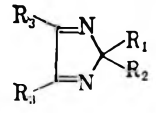


Compound	R	R′	R″	Wave numbers and relative intensity[a]							
				1615	1600	1585	1560	1540	1515	1500	1485
I	C_6H_5	H	C_6H_5		1601 m	1587 m	1565 w	1537 w		1503 s	1488 s
II	*o*-ClC_6H_4	H	C_6H_5		1602 m	1581 w	1563 wsh			1502 m	1478 s
III	*m*-ClC_6H_4	H	C_6H_5		1604 m	1584 m 1575 w	1565 vwsh	1533 vw		1503 m	1479 s
IV	*p*-ClC_6H_4	H	C_6H_5		1602 m	1583 w	1569 vwsh			1502 s	1485 s
V	2,4-$Cl_2C_6H_3$	H	C_6H_5		1600 vw	1592 m 1581 w	1572 vw	1551 m 1530 w		1501 s	1475 s
VI	2,6-$Cl_2C_6H_3$	H	C_6H_5		1604 s	1593 sh	1559 s			1502 m	1480 m
VII	*p*-ClC_6H_4	H	*p*-ClC_6H_4		1608 vw 1600 vwsh	1583 w	1557 vw			1500 s	1483 s
VIII	*o*-BrC_6H_4	H	C_6H_5		1602 m	1582 w 1575 vw	1563 w	1536 w		1503 s	1478 s
IX	*o*-Anisyl	H	C_6H_5		1600 m	1584 m	1560 vw	1527 m		1504 w	1480 s
X	*m*-Anisyl	H	C_6H_5		1604 mw 1603 m	1588 s	1565 vw	1533 w		1503 m	1485 s
XI	*p*-Anisyl	H	C_6H_5	1612 s	1603 sh		1565 vvwsh	1545 m		1506 s	1495 s
XII	*o*-HOC_6H_4	H	C_6H_5	1618 vwsh	1602 s	1583 m	1567 vw	1539 mw		1502 s	1490 s
XIII	*m*-HOC_6H_4	H	C_6H_5	1619 m	1602 m	1590 s 1582 sh		1533 w		1503 m	1482 s
XIV[b]	*p*-HOC_6H_4	H	C_6H_5	1613 m		1595 m 1575 vw		1546 w		1507 m	1491 s
XV	*p*-Tolyl	H	C_6H_5		1600 m	1586 mw 1574 w				1506 ms	1494 s
XVI	*p*-Tolyl	H	*p*-Tolyl	1618 s		1590 w			1521 s	1501 s	
XVII	α-Naphthyl	H	C_6H_5		1602 m	1587 w	1564 w		1508 s	1499 s	1475 s
XVIII	*p*-$NO_2C_6H_4$	H	C_6H_5		1600 s	1580 m		1547 vvw	1510 s	1504 ssh	1483 m
XIX	*p*-$(CH_3)_2NC_6H_4$	H	C_6H_5	1616 s	1604 sh	1585 wsh	1557 wsh	1550 ms	1509 s	1497 s	
XX	C_6H_5	H	H		1609 w	1587 vw	1570 ms 1563 m			1505 s	1475 m
XXI	H	H	C_6H_5		1602 m	1579 mw	1563 vw		1514 s	1500 ms	1485 sh
XXII	CH_3	H	C_6H_5		1602 m	1585 m		1540 s		1503 m	1475 w
XXIII[c]	C_6H_5	H	C_6H_5; H		1608 m	1583 w	1565 w	1538 w	1519 vw	1494 ms	1489 sh
XXIV	C_6H_5	C_6H_5	C_6H_5	1620 vvw	1600 s	1594 s	1560 vw		1512 w	1494 s	1479 s
XXV	C_6H_5	C_2H_5	C_6H_5		1601 m	1575 w		1550 vvw	1522 vw	1500 m	1480 m
XXVI	C_6H_5	CH_3	C_6H_5		1600 s	1577 w	1555 vvw		1519 vw	1502 s	1478 s
XXVII	*p*-Tolyl	CH_3	C_6H_5		1601 m	1583 vw 1572 vw		1530 w		1502 s	1482 s
XXVIII	C_6H_5	$C_6H_5CH_2$	C_6H_5		1601 m	1587 vw 1572 vw			1521 vw	1498 s	1480 s
XXIX	H	H	H			1576 w		1543 m		1498 m	1477 m
XXX	2,4,5-Triphenylimidazoline			1612 m	1598 m	1576 m			1510 ms		

[a] Abbreviations: w, weak; m, medium; s, strong; v, very; sh, shoulder. [b] Also absorbs at 1640 cm.$^{-1}$ (w). [c] One R″ = C_6H_5; the other R″ = H.

TABLE II

INFRARED SPECTRA OF 2*H*- AND 4*H*-ISOIMIDAZOLES BETWEEN 1625 AND 1475 CM.$^{-1}$



Compound	R_1	R_2	R_3	Wave numbers and relative intensity							
				1615	1600	1575	1563	1550	1535	1515	1485
XXXI	C_6H_5	CH_3	C_6H_5	1614 w	1602 m	1578 vvwsh 1571 vvw		1549 s	1537 sh	1527 wsh	1490 sh 1485 s
XXXII	C_6H_5	C_6H_5	C_6H_5	1614 m	1600 m	1580 vw		1550 s	1535 w	1518 vwsh	1487 s
XXXIII	—$(CH_2)_4$—		C_6H_5	1617 w	1604 w	1575 vw		1552 m	1537 w		1490 sh 1484 m
XXXIV	*p*-ClC_6H_4	CH_3	C_6H_5	1618 w	1603 w	1573 w		1552 s	1539 vw		1490 s 1484 sh
XXXV	*p*-Anisyl	CH_3	C_6H_5	1608 s	1605 wsh	1578 w		1548 m	1530 vw	1511 s	1495 vw 1485 m
XXXVI	2,4,4,5-Tetraphenyl-4*H*-isoimidazole			1616 vw	1602 ms 1594 s		1563 s		1532 m		1492 s

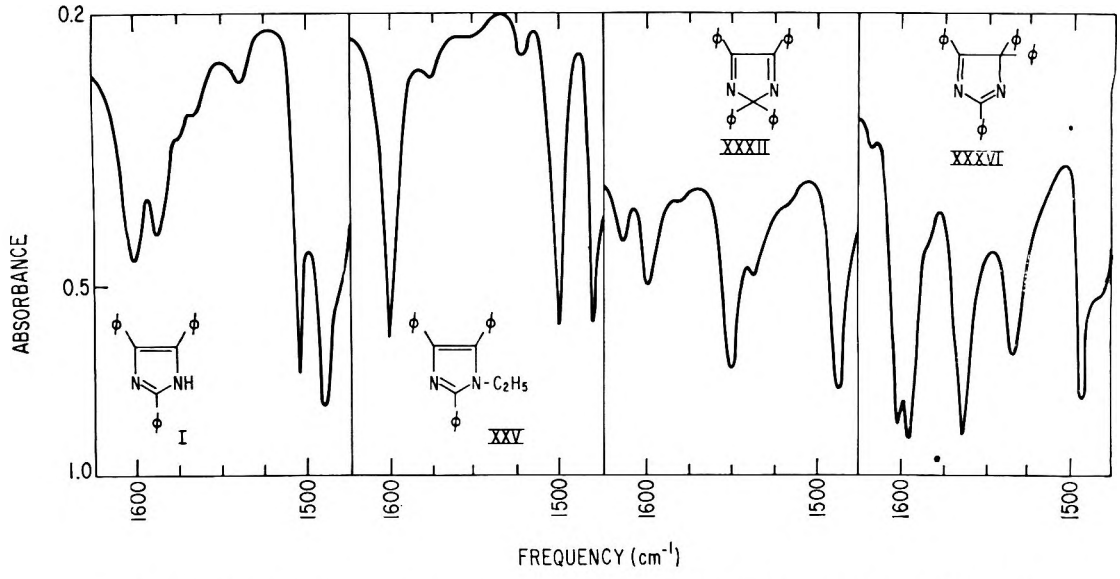


Fig. 1.—Infrared spectra of typical imidazoles and isoimidazoles between 1625 and 1475 cm.$^{-1}$.

The characteristic arylimidazole and arylisoimidazole bands between 1625 and 1475 cm.$^{-1}$ make it possible to distinguish these isomeric ring systems.[8] The 1615-(w) and 1550-cm.$^{-1}$ (m–s) bands of the 2*H*-isoimidazoles and the 1563-cm.$^{-1}$ (s) band of the 4*H*-isoimidazole occur in areas of low absorption for the aryl imidazoles. The 1502-cm.$^{-1}$ (m–s) absorption band similarly denotes the imidazole ring. The exceptions to these correlations have been noted above and normally involve compounds with electron-donating substituents. The 4*H*-isoimidazole assignment is tentative owing to the lack of additional examples.

All of the compounds containing an imidazyl N–H group displayed a characteristic absorption with a series of strong broad bands in the region 3000–2400 cm.$^{-1}$. This pattern which is observed in the solid state or relatively concentrated solution has been described previously for imidazole[9] and benzimidazole[3,10] and is attributed to coupled vibrations of strongly hydrogen-bonded aggregates.[9] The N-substituted imidazoles and the 2*H*- and 4*H*-isoimidazoles have only aromatic C–H absorptions at 3060 and 3040 cm.$^{-1}$ and in some cases appropriate aliphatic C–H bands between 3000 and 2800 cm.$^{-1}$. In addition, the N-substituted imidazoles (XXV–XXVII) have an N-alkyl C–H stretching band[11] at 2860 cm.$^{-1}$.

A number of bands other than those from phenyl or substituted phenyl groups occur consistently in the imidazoles and less consistently in the isoimidazoles. These bands are in the regions of 965, 915, 775, 720, and 705 cm.$^{-1}$ (Table III). In these compounds C–H out-of-plane deformations for unsubstituted phenyl groups usually occur at 765 and 695 cm.$^{-1}$ and for *p*-substituted phenyl groups at 835 cm.$^{-1}$.

Experimental

The infrared spectra were determined with a Beckman IR-7 spectrophotometer. Precautions were taken to avoid the presence of water vapor in the instrument. Thoroughly dried crystalline samples were analyzed in potassium bromide pellets with concentrations of approximately 6 mg./g. of potassium bromide.

Imidazole (XXIX) and **2,4,5-triphenylimidazole** (I, lophine) were obtained from Eastman Kodak Company. Other compounds which have been reported previously are listed below with pertinent analytical data for their characterization. The new compounds and their physical properties are presented in Table IV. The procedures used to prepare these compounds are described below.

The following compounds were prepared by the procedure of Davidson, Weiss, and Jelling[12] from benzil (0.05 mole), the appropriate aldehyde (0.05 mole), and 40 g. of ammonium acetate in 100 ml. of acetic acid. The procedure (A in Table IV) was modified slightly: after the reaction mixture had been heated 1 hr., water was added to the hot solution until crystals formed or clouding persisted. After cooling, the crystalline product was collected on a filter, washed, dried, and recrystallized. **2-(*o*-Chlorophenyl)-4,5-diphenylimidazole**[13] (II) was prepared in 82% yield and recrystallized from ethanol, m.p. 197.3–197.8°, lit.[14] m.p. 192°. **2-*p*-Anisyl-4,5-diphenylimidazole** (XI) was recrystallized from ethanol, m.p. 233.7–233.9°, lit.[15] m.p. 229°. **2-(*o*-Hydroxyphenyl)-4,5-diphenylimidazole** (XII) was recrystallized from aqueous ethanol, m.p. 214–215, lit.[15] m.p. 209°. **2-(*p*-Hydroxyphenyl)-4,5-diphenylimidazole**[13] (XIV) was recrystallized from aqueous ethanol, m.p. 268–268.5°, lit.[16,17] m.p. 258–259°, 256–258°. **2-(*p*-Tolyl)-4,5-diphenylimidazole** (XV) was recrystallized from ethanol, m.p. 237–237.5°, lit.[18] m.p. 233°. **2-(α-Naphthyl)-4,5-diphenylimidazole**[13] (XVII) was recrystallized from decalin, m.p. 291.5–292°, lit.[18] m.p. 283°. **2-(*p*-Nitrophenyl)-4,5-diphenylimidazole** (XVIII) was recrystallized from ethanol, m.p. 241–242°, lit.[15] m.p. 240°. **2-(*p*-Dimethylaminophenyl)-4,5-diphenylimidazole**[13] (XIX) was isolated in 71% yield and recrystallized from ethanol, m.p. 259.5–260.0°, lit.[17] m.p. 264–274°. **4,5-Diphenylimidazole** (XXI) was recrystallized from aqueous pyridine, m.p. 233–234°, lit.[12] m.p. 232°. **2-Methyl-4,5-diphenylimidazole** (XXII) was recrystallized from aqueous pyridine, m.p. 242–243.5°, lit.[12] m.p. 243°.

The following two imidazoles were prepared by the trimerization of the appropriate nitriles and reduction of the intermediate triazines with zinc and acetic acid.[15] **Tris-2,4,5-(*p*-chlorophenyl)-imidazole** (VII) was recrystallized from decalin, m.p. 275.0–275.5°, lit.[15] m.p. 268°. **Tris-2,4,5-(*p*-tolyl)imidazole**[13] (XVI)

(8) Use of these characteristic absorptions has been made in elucidating the structures of the piezochromic and photochromic dimers from oxidation of 2,4,5-triphenylimidazole (see ref. 1).

(9) L. J. Bellamy and P. E. Rogosh, *Proc. Roy. Soc.* (London), **257A**, 98 (1960).

(10) C. G. Cannon, *Spectrochim. Acta*, **10**, 341 (1958).

(11) R. D. Hill and G. D. Meakins, *J. Chem. Soc.*, 760 (1958).

(12) D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 319 (1937).

(13) Satisfactory elemental analyses were obtained.

(14) H. Bredereck, R. Gompper, and D. Hayer, *Chem. Ber.*, **92**, 338 (1959).

(15) A. H. Cook and D. G. Jones, *J. Chem. Soc.*, 278 (1941).

(16) F. R. Japp and H. H. Robinson, *Chem. Ber.*, **15**, 1269 (1882).

(17) C. V. Deliwala and S. Rajagopalan, *Proc. Indian Acad. Sci.*, **31A**, 107 (1950).

(18) B. Radziszewski, *Chem. Zentr.*, **80**, I, 1884 (1909).

TABLE III

CHARACTERISTIC IMIDAZOLE BANDS BETWEEN 1200 AND 700 CM.$^{-1}$[a]

Compound	Wave numbers and intensity					
	965	915	770	735	720	705
I	965 m	917 m	776 m	734 m	712 m	705 sh
II	968 m	910 w	775 sh	733 m	717 w	703 sh
III	967 w	917 w	779 s	727 s	722 sh	703 sh
IV	967 m	915 m	773 m	733 s	723 m	
V	969 m	913 m	776 m	737 m	723 w	705 w
VI	973 m	913 w	778 s	737 m	730 sh	712 w
VII	957 m		757 w	739 w	723 w	702 w
VIII	973 s	911 w	771 w	732 s	715 w	702 w
IX	971 w	915 w	771 m	731 w		708 w
X	967 w	917 w	777 m	732 s	725 sh	706 w
XI	966 m	912 w	773 w	738 m	724 w	708 sh
XII	976 w	912 w	776 m	742 m	725 w	708 w
XIII	971 m	914 m	779 m	730 s		705 sh
XIV	969 m	914 w	777 m	740 m	727 w	711 w
XV	967 m	913 w	774 m	731 s	725 w	707 w
XVI	968 m		767 w	737 w	728 m	708 sh
XVII	968 w	908 w	772 s	741 w	722 w	703 sh
XVIII	967 m	913 m	773 w	742 w	720 m	709 m
XIX	964 m	912 m	774 w	737 m	720 w	704 sh
XX	960 m	920 w	[a]	736 s		705 s
XXI	962 sh	912 w	779 w		722 m	702 sh
XXII	966 w	913 w	776 w	750 sh	712 w	
XXIII	963 m	913 m	775 s		715 s	
XXIV	965 w, 959 m	920 m	775 s	733 w	719 m	708 m
XXV	958 m	919 w	778 m	742 w	722 s	703 sh
XXVI	958 m	918 w	787 s	750 m	725 m	705 m
XXVII	958 m	918 w	779 s	732 s	721 w	705 m
XXVIII	962 w, 955 w	912 w	775 m	738 w	725 m, 718 m	700 sh
XXIX	938 m	924 sh, 897 w	758 m	738 w		

[a] Phenyl and substituted phenyl bands are not included and in some cases may mask out other bands.

TABLE IV

PROPERTIES OF NEW ARYLIMIDAZOLES AND ARYLISOIMIDAZOLES

Compound[a]	Procedure[b]	Yield,[c] %	Recrystn. solvent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
III	A	85	Pyridine	302–304	$C_{21}H_{15}N_2Cl$	76.2	76.1	4.6	4.6	8.5	8.6	10.7	10.7
IV	A	84	Ethanol	266–268	$C_{21}H_{15}N_2Cl$	76.2	76.0	4.6	4.5	8.5	8.4	10.7	10.7
V	A	82	Ethanol	176.5–177	$C_{21}H_{14}N_2Cl_2$	69.0	69.1	3.9	3.9	7.7	7.8	19.4	19.5
VI	A	95	Ethanol	239–240	$C_{21}H_{14}N_2Cl_2$	69.0	68.6	3.9	4.0	7.7	7.9	19.4	19.3
VIII	A	99	Ethanol	207–208	$C_{21}H_{15}N_2Br$	67.2	67.3	4.0	4.2	7.5	7.7	21.3	21.1
IX	A	87	Aq. pyridine	210–210.5	$C_{22}H_{18}N_2O$	81.0	81.0	5.6	5.6	8.6	8.6		
X	A	98	Ethanol	267–268	$C_{22}H_{18}N_2O$	81.0	81.0	5.6	5.5	8.6	8.3		
XIII[d]	A	70	Ethanol	266.5–268	$C_{21}H_{16}N_2O$	80.8	80.5	5.2	5.2	9.0	9.2		
XXV[e]	B	*b*	*n*-Hexane	119.5–120	$C_{23}H_{20}N_2$	85.1	85.2	6.2	6.3	8.6	8.6		
XXVI	C	*b*	*n*-Hexane	143.5–144.5	$C_{22}H_{18}N_2$	85.1	85.3	5.8	5.8				
XXXI	D	60[f]	Aq. pyridine	114.5–115.5	$C_{22}H_{18}N_2$	85.1	85.1	5.8	5.6	9.0	9.4		
XXXIV	D	80	Methanol–benzene	154–154.5	$C_{22}H_{17}N_2Cl$	76.7	77.0	4.9	5.1	8.1	8.2		
XXXV	D	75	Benzene–hexane	128.5–129.5	$C_{23}H_{20}N_2O$	81.2	81.2	5.9	6.1	8.2	8.2		
XXXVI		*b*	Aq. pyridine	177–178	$C_{27}H_{20}N_2$	87.1	87.3	5.4	5.5	7.5	7.7		

[a] Structures are given in Tables I and II. [b] Described in the Experimental section. [c] Based on dried product after first crystallization. [d] The melting point of 182° dec. attributed to XIII by J. Tröger and H. Thomas [*J. prakt. Chem.*, **110**, 51 (1925)] indicates their material was either impure or another compound. [e] The pyrolysis product (m.p. 234°) of diethyllophine iodide described by V. Kulisch [*Monatsh.*, **17**, 300 (1896)] does not appear to be N-ethyl-2,4,5-triphenylimidazole, since the infrared and ultraviolet spectra of XXV strongly support this structure. [f] Yield after chromatography on neutral, activity I, Woelm alumina.

was recrystallized from aqueous ethanol, m.p. 240.5–241.5°, lit.[19] m.p. 235°.

The following six compounds were prepared by specific literature procedures. **2-Phenylimidazole** (XX) was recrystallized from water, m.p. 147.5–148.0°, lit.[20] m.p. 148–149°. **2,4(5)-Diphenylimidazole** (XXIII) was recrystallized from ethanol, m.p. 160–162°, lit.[21] m.p. 167–168°. **1,2,4,5-Tetraphenylimidazole** (XXIV) was recrystallized from ethanol, m.p. 220.5–221°, lit.[12] m.p. 221°. **2,4,5-Triphenylimidazoline-1** (XXX) was recrystallized from ether, m.p. 131–133°, lit.[22] m.p. 131–133°. **N-Benzyl-2,4,5-triphenylimidazole** (XXVIII) was recrystallized from ethanol, m.p. 163.5–164.5°, lit.[23] m.p. 163–164°.

N-Ethyl-2,4,5-triphenylimidazole (XXV). Procedure B (*Table* IV).—Ethyl bromide (10 g., 0.092 mole) was added dropwise in several minutes to a solution of 2,4,5-triphenylimidazole (10 g., 0.034 mole) and sodium (4 g., 0.17 g.-atom) in 100 ml. of ethanol at 40°. The solution was heated and a white precipitate formed. After 2 hr. at reflux, the mixture was evaporated and the solid residue was washed with water, dried, and extracted with 60 ml.

(19) A. Fürth, *Monatsh.*, **27**, 843 (1906).
(20) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, **115**, 217 (1919).
(21) P. G. Haines and E. C. Wagner, *J. Am. Chem. Soc.*, **71**, 2793 (1949).
(22) H. H. Strain, *ibid.*, **49**, 1558 (1927).
(23) M. Weiss, *ibid.*, **74**, 5193 (1952).

of ether. Evaporation of the ether yielded a glassy foam, 1.4 g., which was dissolved in benzene and chromatographed on Woelm neutral alumina, activity I. Benzene eluted an oil which was crystallized and recrystallized from *n*-hexane, 0.6 g., m.p. 119.5–120.0°.

N-Methyl-2,4,5-triphenylimidazole (XXVI). Procedure C (Table IV).—A mixture of 2,4,5-triphenylimidazole (0.5 g., 0.0017 mole) and diazomethane (0.006 mole) in 230 ml. of ether was irradiated 1 hr. with a G.E. sunlamp after standing 5 days at 5°. After evaporation of the ether and excess diazomethane, the yellow residue was chromatographed on Woelm neutral alumina, activity I. Elution with benzene afforded a white solid (0.1 g., m.p. 135–145°) which was recrystallized from *n*-hexane, m.p. 143.5–144.5°.

N-Methyl-2-(*p*-tolyl)-4,5-diphenylimidazole (XXVII) was prepared by procedure C. The product was recrystallized from *n*-hexane, m.p. 209–215°, lit.[18] m.p. 217°.

The 2*H*-isoimidazoles were prepared by the method of Weiss[23] from benzil (0.05 mole), the appropriate ketone (0.05 mole), and 40 g. of ammonium acetate in 100 ml. of acetic acid (procedure D). **2,2,4,5-Tetraphenyl-2*H*-isoimidazole** (XXXII) was recrystallized from pyridine, m.p. 195–198°, lit.[23] m.p. 199–201°. **2,2-Spirocyclohexane-4,5-diphenyl-2*H*-isoimidazole** (XXXIII) was recrystallized from aqueous pyridine, m.p. 105.5–106°, lit.[23] m.p. 107–108°.

2,4,4,5-Tetraphenyl-4*H*-isoimidazole (XXXVI).—A dried chloroform solution of benzamidine prepared from 14.0 g. of the hydrochloride salt was refluxed for 4 hr. with 9.0 g. of diphenylbenzoylbromomethane.[24] Water was removed as formed. The reaction mixture was freed of chloroform by evaporation and the brown residue was washed three times with warm dilute ammonium hydroxide. The orange residue was taken up in benzene and filtered. The evaporated benzene solution (9.2 g.) was chromatographed on alumina, and gave rise to 6.2 g. of crude material using petroleum ether (b.p. 30–60°) and benzene as eluents. Two recrystallizations from benzene–heptane gave 2.5 g. of impure isoimidazole, m.p. 170–177°. This sample was again chromatographed on alumina and a small amount of kyaphenine, m.p. 238–238.5°, lit.[15] m.p. 232°, was removed. Recrystallization from benzene–heptane gave 1.7 g. of the isoimidazole, m.p. 177–178°. A further recrystallization from aqueous pyridine did not affect the melting point.

The structural assignment for XXXVI was based on the method of synthesis, the elemental analysis (Table IV), infrared spectrum (no N–H stretching absorption), and direct comparison with the other two possible isomers, XXIV and XXXII.

Acknowledgment.—The authors are indebted to Dr. R. S. McDonald for helpful discussions and to Miss D. V. McClung for determining the infrared spectra.

(24) The bromo ketone [A. Werner, *Chem. Ber.*, **39**, 1286 (1906)] was prepared by refluxing diphenylbenzoylcarbinol with 32% hydrobromic acid and acetyl bromide in acetic acid for 2 hr.

Preparation of 9(11)-Unsaturated Steroids. A Novel Reagent System

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Sulfur dioxide in conjunction with various otherwise unreactive acid chlorides has been found to bring about the facile dehydration of 11β-hydroxy steroids. A rationale for this phenomenon is suggested.

Several instances are recorded in the literature[1] in which organic sulfonyl halides have been used to introduce the 9(11)-double bond into the steroid nucleus by the elimination of the elements of water from 11-hydroxylated starting materials. When the reaction involves an 11α-hydroxyl group, the intermediate sulfonic ester can be isolated and subjected to the action of a base such as pyridine or sodium acetate to complete the two-step reaction.[1a-d] Various sulfonyl halides may be used, the most common being *p*-toluenesulfonyl chloride[1a-d] and methanesulfonyl chloride.[1b] Alternatively, the reaction mixture (containing an excess of base such as pyridine) containing the sulfonic ester may be refluxed to complete the dehydration.

11β-Hydroxy steroids also respond to the action of methanesulfonyl chloride and base to furnish 9(11)-unsaturated products.[1e-g] There are two interesting points concerning this reaction. Among sulfonyl halides none except lower alkanesulfonyl halides have been made to work in the dehydration of 11β-hydroxy steroids. Furthermore, in limited cases only[2] has the isolation of the presumed intermediate 11β-mesylate been reported. The construction of a molecular model of this intermediate is at best difficult, creating some doubt that such an ester is truly a step in the mechanistic path from 11β-hydroxy steroids to 9(11)-unsaturated steroids. In addition, vigorous conditions or prolonged reaction times have been found necessary to bring about the desired reaction.[1g]

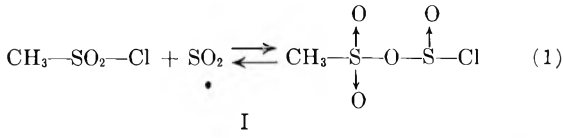
However, when mesyl chloride is distilled at atmospheric pressure prior to use, decomposition takes place in the still pot and the colorless distillate becomes a far more active agent in the dehydration reaction. Upon addition of this reagent to a cold solution of steroid, collidine, and dimethylformamide, a vigorous reaction ensues, the temperature rises, and, after a few minutes at 25–30°, the reaction is complete. Vapor phase chromatography revealed a volatile impurity in distilled mesyl chloride which was not present prior to distillation. Vacuum-distilled reagent likewise lacks the impurity and fails to bring about dehydration under the mild conditions employed. The volatile component was shown by experiment to be sulfur dioxide. Samples of mesyl chloride which failed to accomplish the desired reaction were rendered effective by the addition of small quantities of sulfur dioxide.

It may be interjected at this point that methyl chlorosulfite is also an effective agent for the elimination of the elements of water from 11β-hydroxy steroids.[1g]

(1) (a) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **75**, 2273 (1953); (b) **79**, 1130 (1957); (c) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaur, W. Gebert, C. T. Conigilio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *ibid.*, **80**, 4431 (1958); (d) G. Rosenkranz, O. Mancera, and F. Sondheimer, *ibid.*, **76**, 2227 (1954); (e) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman, and F. M. Singer, *ibid.*, **77**, 4181 (1955); (f) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *ibid.*, **80**, 3161 (1958); (g) E. M. Chamberlin, E. W. Tristram, T. Utne, and J. M. Chemerda, *J. Org. Chem.*, **25**, 295 (1960).

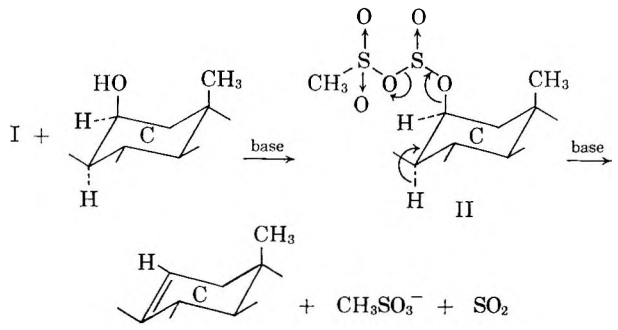
(2) E. J. Agnello and G. D. Laubach, U. S. Patent 2,877,157 (March 10, 1959); U. S. Patent 2,877,222 (March 10, 1959); U. S. Patent 2,877,233 (March 10, 1959). These authors report the isolation of the 11β-mesylates of $\Delta^{8(14)}$-androstene and $\Delta^{8(14)}$-19-norandrostene derivatives. Molecular models reveal that steric interference by the 18- and/or 19-methyl groups with the 11β-position is distinctly less than when the 8,14-bond is saturated.

The intermediate methyl sulfite ester can be isolated and a model can be constructed.[3] This reagent resembles methanesulfonyl chloride in its over-all geometry except for the presence of only one branch (oxygen) on sulfur, whereas mesyl chloride possesses two branches. This knowledge, coupled with the fact that less than molar quantities of sulfur dioxide are ample, allow the formulation of a mechanism for the action of sulfur dioxide. It is first proposed that mesyl chloride and sulfur dioxide interact reversibly to form an unstable, reactive, mixed anhydride of methanesulfonic acid and the hypothetical chlorosulfinic acid (eq. 1).



I (1)

This compound, being an acid chloride also, reacts readily in the presence of base to form a labile ester (II), which decomposes to furnish 9(11) steroid, methanesulfonate ion, and sulfur dioxide. The latter then can participate again in the reaction sequence.



In support of the proposed mechanism, *p*-toluenesulfonyl chloride, benzenesulfonyl chloride, benzoyl chloride, and *p*-nitrobenzoyl chloride are all transformed from ineffective dehydrating agents to useful reagents by small amounts of sulfur dioxide.[4] The quantities of sulfur dioxide were in the range of 5–50 mole %, or greater (based on the steroid); values below 5 mole % were insufficient. The larger amounts were unnecessary. Consistently good results were obtained with about 10–20 mole %.

Experimental

For maximum yields, all solvents and reactants must be anhydrous. All melting points were taken in open-end glass capillary tubes and are uncorrected.

16α-Methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-Acetate. A. Methanesulfonyl Chloride and Sulfur Dioxide.—A solution of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate in 33 ml. of natural collidine and 100 ml. of dimethylformamide was cooled to 10°. The cooling bath was removed and during the course of 1–2 min., 10.0 ml. (14.7 g., 0.128 mole) of methanesulfonyl chloride (Eastman White Label) containing 3.5% (0.5 g., 0.008 mole) by weight of anhydrous sulfur dioxide was added to the clear solution. Efficient stirring was maintained throughout the reaction period. The temperature rose quickly and cooling was employed to maintain the mixture at 25–35°. The reaction was allowed to proceed between these temperatures for a period of 5 min., during which a light-colored precipitate separated and the solution assumed a reddish hue. At the end of the reaction period, the cooling bath was replaced and the excess mesyl chloride was decomposed by the slow addition of 17 ml. of water. The proper amount of water caused the precipitate to dissolve without causing precipitation of the product. The clear, orange to red solution was then added dropwise with efficient stirring to 1 l. of water during a period of 20 min. A small amount of methanol and then water were used to complete transfer of solution. After stirring the resulting slurry for 1 hr. at 20–25°, the product was collected, washed with water, and air-dried at 60° to constant weight. The yield of product which melted at 203–211° was 15.3 g. (96%). Recrystallization from ethanol raised the melting point to 216.5–218°; lit.[1c] m.p. 210–213°. Paper-strip chromatography showed that the crude product contained no unchanged starting material. An experiment similar in all respects except that sulfur dioxide was omitted gave only unchanged starting material.

B. *p*-Toluenesulfonyl Chloride and Sulfur Dioxide.—A solution of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, 24.5 g. (0.128 mole) of *p*-toluenesulfonyl chloride, and 100 ml. of dimethylformamide was cooled to 10° and 33 ml. of collidine was added. After 5 min. at room temperature, a portion of the deep red solution was removed and quenched with water. Paper-strip analysis of this portion revealed that no dehydration had occurred.

The main batch was cooled to 10° immediately after removal of the aliquot, and was treated with 5.0 ml. of a solution of sulfur dioxide in dimethylformamide (4.7% by weight, *ca.* 3.5 mmoles). The temperature again rose sharply to a maximum of 33°. Five minutes after the temperature had reached 25°, the reaction was halted and the product was precipitated as in method A. The yield of bright yellow product was 14.9 g. (93%), m.p. 198–208°. Paper-strip analysis showed that complete dehydration had occurred.

Additional experiments showed that toluenesulfonyl chloride and sulfur dioxide together in dimethylformamide solution may be added as one reagent, or the collidine and sulfur dioxide may be mixed and added to the remaining reactants in solution.

C. Benzenesulfonyl Chloride and Sulfur Dioxide.—A mixture of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, 90 ml. of dimethylformamide, and 33 ml. of collidine was cooled to 15° and treated with 16.4 ml. (22.6 g., 0.128 mole) of benzenesulfonyl chloride. The temperature rose sharply and the color of the mixture deepened to a red-orange. When the temperature reached 30°, the mixture was cooled to 10° by means of an ice bath and treated with 10 ml. of a solution of sulfur dioxide in dimethylformamide (3.6% by weight). The temperature again rose and was maintained at 25–28° by external cooling. Precipitation of the quenched solution into water gave 14.5 g. (91%) of yellow powder which melted at 184–204°. Recrystallization from ethanol raised the melting point to 211–215° (62% recovery).

D. Benzoyl Chloride and Sulfur Dioxide.—A mixture of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, 33 ml. of collidine, and 95 ml. of dimethylformamide was cooled to 10° and 14.8 ml. (18.0 g., 0.128 mole) of freshly distilled benzoyl chloride was added gradually. Heat was evolved, a precipitate appeared, and the color of the solution changed gradually to chocolate brown. After 5 min. at 25–30°, an aliquot was removed and analyzed by paper-strip chromatography. No dehydration had occurred.

The remaining mixture was cooled to 10° immediately after the aliquot was removed and was treated with 5.0 ml. of 4.7% sulfur dioxide in dimethylformamide (*ca.* 3.5 mmoles). The temperature was allowed to rise to 30°, and, after 5 min. at 25–30°, the excess reagent was destroyed by a small quantity of water. Only gum was obtained when the clear, red solution was added to water. The aqueous phase was decanted from the gum which was then washed with fresh water, dried by azeotropic distillation with benzene, and finally dissolved by warming in 100 ml. of ethanol. Cooling and seeding the solution caused white crystals of 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate to separate. The product was collected, washed with cold ethanol, and dried in air at 50°. The yield was 4.0 g. (*ca.* 25%), m.p. 210–213°. Paper-strip analysis showed that the product contained about 98% of the desired triene and about 2% of unchanged starting material.

(3) Unpublished communication from Dr. Erwin Schoenewaldt of the Merck, Sharp and Dohme Research Laboratories Division. The workers in ref. 1g report that they were unable to isolate the intermediate methyl sulfite ester.

(4) Small, highly reactive acid chlorides, such as acetyl chloride, lead only to the formation of the 11β esters. No dehydration products were detected.

The mother liquor solids consisted of about 60% product and 40% starting material.

In another experiment, the sulfur dioxide solution was added to the mixture of steroid, dimethylformamide, and collidine prior to the addition of benzoyl chloride. Only unchanged starting material was recovered. This observation has not been checked.

E. *p*-Nitrobenzoyl Chloride and Sulfur Dioxide.—A mixture of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, 33 ml. of collidine, and 90 ml. of dimethylformamide at 10° was treated with a solution of 23.7 g. (0.128 mole) of *p*-nitrobenzoyl chloride in 10 ml. of dimethylformamide which also contained about 3% sulfur dioxide by weight. After 5 min. at 25–45° (initial heat evolution quite pronounced), the reaction mixture was worked up in the manner described for the benzoyl chloride run. The gum, which separated when the batch was added to water, solidified upon standing over the weekend. It was collected, washed with water, and recrystallized still wet, from 75 ml. of ethanol (hot filtration). There was obtained 6.55 g. (*ca.* 41%) of 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate which melted at 212–215.5°. Paper-strip analysis of this product and its mother liquor revealed that essentially quantitative conversion had taken place.

4,9(11)-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate [11-(9)-Anhydrocortisol Acetate].—A change of 60.0 g. (0.148 mole) of 4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (cortisol acetate) was slurried with 122 ml. of natural collidine, and then 370 ml. of dimethylformamide was added. This sequence of addition allows the cortisol acetate to dissolve momentarily and then quickly separate as fine crystals of the dimethylformamide complex. Good stirring is essential to keep the resulting thick slurry mobile. The mixture was cooled to 10° and treated in about 2 min. with 37 ml. of methanesulfonyl chloride containing 3.2% sulfur dioxide. The batch was allowed to stir at 25–35° for 10 min. and then excess reagent was destroyed by the gradual addition (1 min.) of 60 ml. of water. Despite ice-bath cooling the temperature of the reaction mixture rose to 59°. The thin slurry was cooled to room temperature and added gradually to 3700 ml. of hot (80–90°) water with good agitation.[5] This mixture was stirred at 85–90° for 1 hr., cooled to room temperature, and filtered. The product was washed several times with water and dried in air at 60°. There was obtained 56.0 g. (97.7%) of cream-colored powder which melted at 226–228.5°, contained 0.6% water (by Karl Fischer titration), and possessed a specific rotation (c 0.5) in chloroform of +131.8°. Treatment of this product with ten parts of refluxing methanol gave a recovery of about 92% of 11(9)-anhydrocortisol acetate which melted at 234–237°; lit.[1a] m.p. 236–237°, [α]D (c 1, chloroform) +117°; lit.[6] m.p. 231.5–234.5°, [α]D (*c* 1.04, chloroform) +124°; lit.[1g] m.p. 232.5–236.5°.

The above procedure in the absence of sulfur dioxide gave only unchanged starting material.

1,4,9(11)-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate.—A charge of 16.2 g. (0.04 mole) of 1,4-pregnadiene-11β,17α,21-trio.-3,20-dione 21-acetate (prednisolone acetate) was dehydrated by the procedure described for 11(9)-anhydrocortisol acetate. The crude product was obtained in a yield of 15.85 g. (103%), m.p., 154–205°. Paper-strip analysis showed complete dehydration had occurred. Refluxing the product with five parts of acetone permitted a recovery of 46.8% of triene which melted at 220–222°, lit.[7] m.p. 223–226°.

Acknowledgment.—We wish to express our appreciation to Mr. Charles B. Muchmore for the preparation and help in the interpretation of the vapor phase chromatograms. We also wish to thank Dr. Erwin Schoenewaldt of the Merck Sharp and Dohme Research Laboratories for his valuable suggestions and information. It was he who proposed the mechanism which we have described here.

(5) Precipitation of the product by hot water allows the isolation of a partially hydrated material which is easily freed of water at moderate temperatures. Precipitation by cold water furnished the dimethylformamide complex of the product which requires vigorous drying conditions in order to be rid of the solvent or a slurry treatment with hot water, in which case the hydrate is obtained.

(6) R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, *J. Am. Chem. Soc.*, **76**, 4722 (1953).

(7) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. D. Schneider, P. F. Beal, and J. Korman, *ibid.*, **77**, 4438 (1955).

Steroids of Unnatural Configuration. The Absence of Long-Range Conformational Effects in Ring A Modified 20-Ketopregnanes[1a,b]

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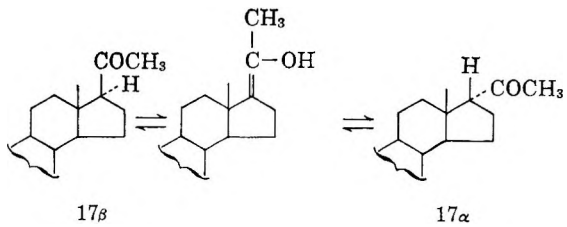
Syntheses of 5α,17α-pregnane-3,20-dione, 5β,17α-pregnane-3,20-dione, and 17α-1-dehydroprogesterone are described. No detectable long-range conformational effects were observed in the n.m.r. spectra or relative stabilities (*vs.* 17β-isomers) of these three compounds as well as 17α-pregnenolone and 17α-progesterone.

A large variety of 20-ketopregnanes, unsubstituted at C-17, have been described. Although the two C-17 isomers of these ketones are interconvertible through a common enol (or enolate ion), only the 17β-epimers are naturally occurring.[3] We have undertaken a systematic study of the unnatural (17α) isomers of these ketones[4a] with the objectives of evaluating the role of C-17 configuration in biological activity and investigating the operation of a variety of steric effects in fused ring systems. This report describes the first stage of this investigation and is concerned with the



(1) (a) This research was supported in part by a Public Health Service Research Grant, A-3943, from the National Institute of Arthritis and Metabolic Diseases; (b) presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) National Institutes of Health Predoctoral Fellow, 1961–1962.

(3) Two exceptions to this generalization have been reported: (a) H. I. Calvin and S. Lieberman [*Biochemistry*, **1**, 639 (1962)] have isolated tritiated IIα from human urine after ingestion of tritiated 16-dehydroprogesterone. Earlier isolations of IIα from human urine were explicable on the basis of isomerization of 17β-isomer during vigorous acid hydrolysis involved in the isolation procedures [S. Lieberman, K. Dobriner, B. R. Hill, L. F. Fieser, and C. P. Rhoads, *J. Biol. Chem.*, **172**, 263 (1948); G. Birke, C. A. Gemzell, L. O. Plantin, and H. Robbe, *Acta Endocrinol.*, **27**, 389 (1958)]; (b) P. D. Meister, D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, and H. M. Leigh [*J. Am. Chem. Soc.*, **75**, 55 (1953)] isolated 25% of 11α-hydroxy-17α-progesterone from incubation of 16-dehydroprogesterone with *Rhizopus nigricans*.

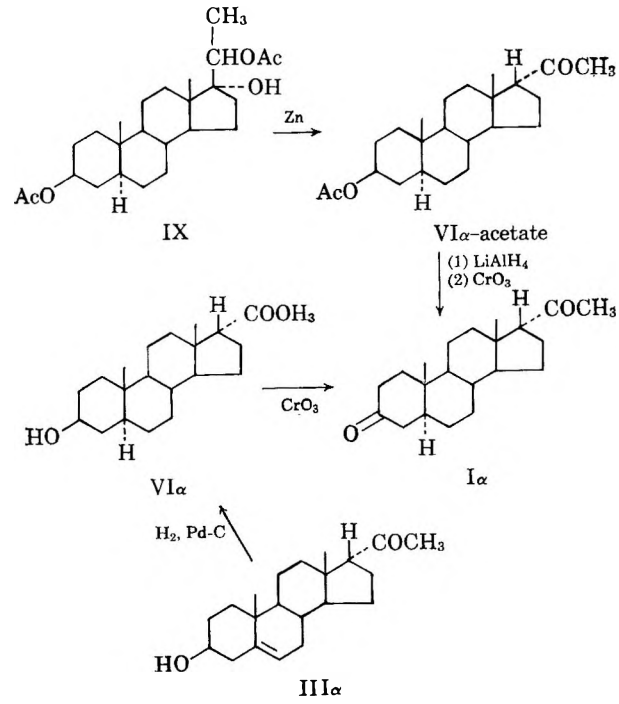
(4) (a) A review of 17α-20-ketopregnanes has recently appeared [M. B. Rubin, *Steroids*, **2**, 561 (1963)]. (b) In this report 20-ketopregnanes (unsubstituted at C-17) are designated by a Roman numeral followed by α or β to indicate the stereochemistry at C-17.

following 17α-20-ketopregnanes[4b] in which the nature of ring A has been varied: 5α,17α-pregnane-3,20-dione (Iα), 5β,17α-pregnane-3,20-dione (IIα), 17α-pregnenolone (IIIα, 17α-Δ⁵-pregnen-3β-ol-20-one), 17α-progesterone (IVα, 17α-Δ⁴-pregnene-3,20-dione), and 17α-1-dehydroprogesterone (Vα, 17α-Δ¹,⁴-pregnadiene-3,20-dione).

Shortly before the inception of this work, Barton and co-workers[5] described a "conformational transmission effect" in 3-keto steroids and 3-ketotriterpenes. They observed variations in the rate of base-catalyzed aldol condensation at C-2 as unsaturation in rings B, C, and D was changed, and attributed these variations to distortions transmitted through the fused ring system to the reaction site.[6] The two extremes of reaction rate differed by a factor of 43. Since Barton's findings were published, other workers have described similar effects on reaction rate as a function of remote structural changes.[7] In an attempt to observe the effect of conformational transmission on equilibrium composition, Allinger and Greenberg[8] examined the mixtures obtained by base-catalyzed equilibration of A-nor-androstane-3,20-dione and A-nor-D-homoandrostane-3,17a-dione but observed no effect of change in size of ring D on composition of equilibrated mixtures. A particular point of interest in the present work lay in the possibility of conformational transmission from ring A to C-17 which might be detected by examination of the variation in relative stabilities of 17α- *vs.* 17β-isomers as a function of ring A structure.

As we have reported recently,[9] modification of the Serini–Logemann reaction provides a convenient entry into the 17α-20-ketopregnane system. Appreciable quantities of IIIα-acetate and IVα could be prepared without difficulty from commercially available 16α,17α-epoxypregnenolone and 17α-hydroxyprogesterone. The hydrolysis of IIIα-acetate to IIIα (without isomerization at C-17) has been described,[10] and proceeded in quantitative yield in our hands. It had been anticipated that IVα would serve as starting material for synthesis of both 5α,17α- and 5β,17α-pregnane-3,20-diones. In model experiments, hydrogenation of progesterone (IVβ) over 10% palladium on charcoal in the presence of a trace of potassium hydroxide[11] yielded a 3:2 mixture of allopregnanedione (Iβ) and pregnanedione (IIβ) which could be separated without difficulty by chromatography on Florisil.[12] However, when the same procedure was applied to IVα, a mixture was obtained from which no pure products could be isolated by repeated chromatography on Florisil or silica gel.[13] In view of these results it was necessary to prepare Iα and IIα by independent procedures.

Two syntheses of Iα in low yield have been described in the literature. In the first of these,[14] 5α,17α-pregnan-3β-ol-20-one (VIα), obtained by base-catalyzed equilibration of the acetate of the 17β-isomer, was oxidized with chromium trioxide in acetic acid to give a mixture of C-17 epimers from which reported Iα, m.p. 134–135°, $[\alpha]_D$ −15°, was isolated. In the second synthesis, Shoppee[15] prepared the 3-acetate of VIα by Serini–Logemann reaction of 5α-pregnane-3β,17α,20-triol 3,20-diacetate (IX), hydrolyzed the acetate with aqueous methanolic potassium bicarbonate, and oxidized the resultant VIα as described by the earlier workers[14] to obtain Iα, m.p. 148–149°, $[\alpha]_D$ −50°. In our hands, the 3-acetate of VIα, obtained in 79% yield by Serini–Logemann reaction of IX, either was not hydrolyzed to VIα (potassium carbonate in aqueous methanol) or yielded a mixture containing appreciable amounts of allopregnanolone (VIβ, 1 *N* potassium hydroxide in methanol). This difficulty could be circumvented by lithium aluminum hydride reduction of VIα-acetate to the 3,20-diol followed by oxidation with chromium trioxide–pyridine complex[16] to yield Iα, m.p. 145–147°, $[\alpha]_D$ −44°, in reasonable agreement with the properties described by Shoppee. A much simpler



procedure which furnished Iα in 81% yield from IIIα consisted of catalytic hydrogenation of IIIα to VIα followed by oxidation with chromic acid in acetone.[17]

Since reductive methods were unpromising, we turned to the Serini–Logemann reaction for the preparation of 5β,17α-pregnanedione (IIα). Lithium aluminum hy-

(5) D. H. R. Barton and A. J. Head, *J. Chem. Soc.*, 932 (1956); D. H. R. Barton, A. J. Head, and P. J. May, *ibid.*, 935 (1957); D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *ibid.*, 1297 (1960).

(6) It should be noted that other possible explanations, such as classical conformational effects or inductive effects, did not explain satisfactorily the observed variations. Theoretical treatments of conformational transmission in simple systems have recently appeared [R. Bucourt, *Bull. soc. chim. France*, 1983 (1962); 1262 (1963)].

(7) T. L. Kim-Phuong and H. B. Kagan, *Compt. rend.*, **256**, 4036 (1963), and references contained therein.

(8) N. L. Allinger and S. Greenberg, *J. Org. Chem.*, **25**, 1399 (1960).

(9) M. B. Rubin and E. C. Blossey, *Steroids*, **1**, 453 (1963).

(10) A. Butenandt, J. Schmidt-Thomé, and H. Paul, *Ber.*, **72**, 1112 (1939).

(11) W. S. Johnson, E. R. Rogier, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister, and H. Wynberg, *J. Am. Chem. Soc.*, **78**, 6289 (1956).

(12) A 2:3 mixture of the same products was obtained by reduction of 1-dehydroprogesterone under the same conditions.

(13) The mild conditions and low concentration of base in the hydrogenation reaction seem to preclude the possibility that purification was complicated by partial conversion to 17β-isomers.

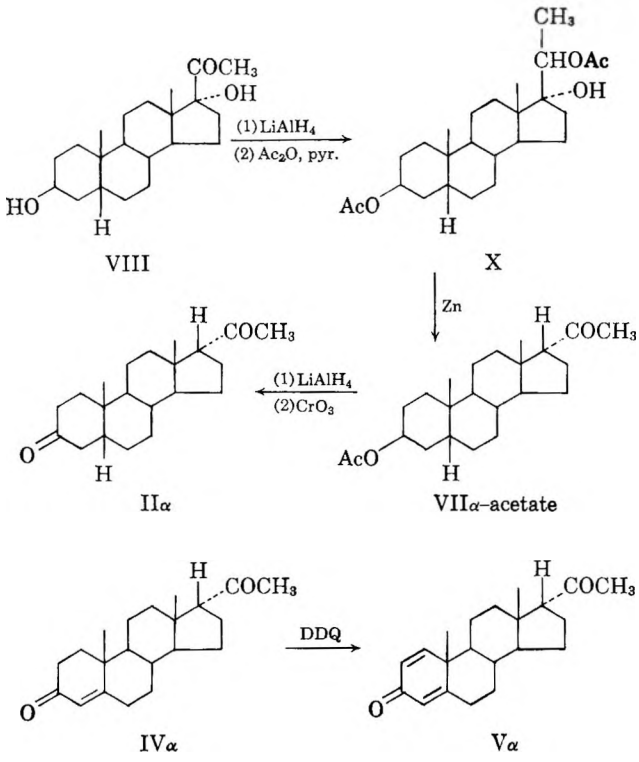
(14) A. Butenandt and L. Mamoli, *Ber.*, **68**, 1847 (1935).

(15) C. W. Shoppee, *J. Chem. Soc.*, 1671 (1949).

(16) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(17) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

dride reduction of commercially available 5β-pregnane-3β,17α-diol-20-one (VIII) followed by acetylation and Serini reaction (86% yield) gave 5β,17α-pregnan-3β-ol-20-one acetate (VIIα-acetate). The difficulties encountered in the hydrolysis of VIα-acetate were also observed with the 5β-epimer necessitating use of the hydride reduction and chromic acid oxidation sequence for conversion of VIIα-acetate to IIα.



VIII X IIα VIIα-acetate IVα Vα

The synthesis of 17α-1-dehydroprogesterone (Vα) was achieved in one step from IVα. After the selenium dioxide dehydrogenation[18] of IVα was shown to yield a difficultly resolvable mixture containing about 50% of the desired product, the use of 2,3-dichloro-5,6-dicyanoquinone[19] (DDQ) was investigated. Reaction of this quinone with IVα in refluxing benzene gave the desired Vα in 79% yield.

Ultraviolet and infrared spectra of the various compounds described were in agreement with the structures proposed. As would be expected, comparisons of infrared spectra of the 17α-ketones with those of the corresponding 17β-isomers showed significant differences in the "fingerprint" region although no assignment of a band characteristic of the 17α-acetyl group could be made.

The standard method[4] for assignment of 17α-configuration to one of a pair of C-17 epimeric 20-ketones has been based on the fact that the 17α-isomer is the more levorotatory of the two. The values for the molecular rotation difference between C-17 epimers ($M_D^{\beta} - M_D^{\alpha}$) obtained in this work were the following: I, 543; II, 563; III, 560; IV, 580; V, 635; VI, 535; and VII-acetate, 570. These are in agreement with the configurations assigned although it might be noted that the values for IV and V, both of which possess a conjugated carbonyl function in ring A, lie outside the range of 550 ± 20 which has been observed[15,20] with a variety of 20-ketopregnanes which are not substituted in the vicinity of the 20-keto group.[21]

More recently, the application of optical rotatory dispersion studies has provided a superior method for assignment of C-17 configuration since both isomers need not be available. In all reported cases, the 17α-20-ketones have exhibited strong negative Cotton effect curves in contrast to the positive Cotton effects observed with their 17β-isomers.[22a-c] The constancy of molecular rotation difference observed at 589 mμ has been shown by Struck and Houtman[22b] to extend throughout the spectrum. These workers derived an "average difference curve" which, by algebraic addition to the curve of a 17β-20-ketopregnane, allowed prediction of the curve of its 17α-isomer. The rotatory dispersion data for Iα–Vα are presented in the Experimental section; in all cases the expected negative Cotton effect was observed. The results for compounds Iα, IIα, and IIIα, which exhibited single Cotton effects, fit the average difference curve reasonably well. However, the steep slope of this curve in the region of 310–380 mμ where the fine structure of the multiple Cotton effect curve of IVα is observed allowed only approximate agreement between calculated and observed values. Interestingly, only single Cotton effect curves were exhibited by Vα and Vβ.

Preliminary comparisons of the n.m.r. spectra of 17α-steroids with spectra of their 17β-isomers indicated appreciable variations in the chemical shifts of methyl protons as a function of C-17 configuration. Accordingly, the spectra were carefully determined on a field-frequency controlled instrument (Varian A-60) and checked on two other instruments[23] (A-60 and HR-60); the maximum observed deviation from the average for three scans of each spectrum was 0.4 c.p.s. The results, expressed in c.p.s. from tetramethylsilane, are presented in Table I.

TABLE I

CHEMICAL SHIFTS OF METHYL PROTONS[a]

	C-18			C-19		
	17β	17α	ΔC-18[b]	3	α	C-21
I	38.1	55.7	17.6	60.9	59.9	
II	38.5	55.8	17.3	62.1	60.2	
III	38.1	55.8	17.7	60.6	60.0	127.8 ± 0.5
IV[c]	40.2	57.8	17.6	71.4	70.6	(τ 8.87)
V	41.9	59.3	17.4	74.2	73.2	

[a] In c.p.s. from tetramethylsilane. Spectra were determined on 0.32 *M* solutions in deuteriochloroform with internal tetramethylsilane using a Varian Associates A-60 spectrometer. Reported values are averages of three scans; maximum observed deviation was 0.4 c.p.s. [b] Chemical shift of 17α-isomer minus shift of 17β. [c] Identical results were obtained with 0.08 and 0.16 *M* solutions.

Comparison of the shift of the C-18 protons for each pair of 17-epimers indicates a marked downfield shift

(18) J. A. Edwards, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 2318 (1960).

(19) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(20) C. W. Marshall and T. F. Gallagher, *J. Biol. Chem.*, **179**, 1265 (1949).

(21) An even larger deviation is observed with the Δ4,6-pregnadiene-3,20-diones where ΔMD = 812 (J. E. Vaux, Jr., unpublished results).

(22) (a) C. Djerassi, *Bull. soc. chim. France*, 741 (1957); *cf.* also C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 52; (b) W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961); (c) P. Crabbé, *Tetrahedron*, **19**, 51 (1963).

(23) We wish to acknowledge the cooperation of Dr. E. Legoff of the Mellon Institute and Mr. P. Yajko of NMR Specialties, Inc., in the determination of these spectra.

for the 17α-isomer in each case.[24] Although the position of the resonance varied from compound to compound in both the 17α- and 17β-series (presumably due to long-range shielding by ring A functionality), the magnitude of the difference between pairs of isomers (ΔC-18) was remarkably constant, the average value being 17.5 ± 0.2 c.p.s. This difference is undoubtedly due to long-range shielding by the 20-ketone; its magnitude must reflect the spatial relationship between the ketone and C-18 methyl groups and might allow calculation of molecular geometry. The constant value of ΔC–18 strongly suggests that changes in ring A do not lead to appreciable change in dihedral angle between C-13 and C-17 substituents.

The chemical shifts of C-19 protons varied as expected[25] with changes in ring A. Interestingly, however, the chemical shifts of C-17 epimers were not identical. A slight upfield change in the position of the resonance of the 17α-isomer, varying from 0.5 c.p.s. for III to 1.9 c.p.s. for II, was observed. This again may be attributed to long-range shielding by the 20-ketone. No variations in chemical shift of the C-21 protons were observed; the value for the ten compounds was 127.8 ± 0.5 c.p.s. (τ 8.87 ± 0.01) independent of C-17 configuration or ring A structure. The remaining features of the n.m.r. spectra were in agreement with the structures assigned.

The fact that 17β is the more stable of the two possible configurations in most 17-substituted steroids has been attributed[26] to the pseudo-equatorial character of the 17β-bond as opposed to the pseudo-axial nature of the 17α-bond. Distortions in the steroid skeleton which lead to changes in conformation at C-17 should then be reflected in changes in the relative stabilities of C-17 epimers. Since acid- or base-catalyzed enolization of the 20-ketone towards C-17 provides a reversible path for interconversion of 17α- and 17β-20-ketopregnanes, their relative stabilities can be determined by measurement of the compositions of equilibrated mixtures. This has been done with each of the 5 pairs of isomers (I–V) available in this work using optical rotation as a convenient method for analysis of mixtures. Preliminary experiments indicated a reduction in the ultraviolet absorption of progesterone upon standing in acid medium, so that equilibration studies were confined to alkaline solution. The standard procedure used in all cases involved measurement of the optical rotation of a 1% solution of an individual steroid in 1 *N* methanolic potassium hydroxide at room temperature in a nitrogen atmosphere until no further change was observed (12–24 hr.).[27] The product mixture then was isolated, its spectra were determined to ensure that no appreciable side reactions had occurred, and the optical rotation was determined in chloroform solution. Since the rotations of the pure 17-epimers were known, the composition of the equilibrated mixture could be calculated by a simple proportionality.[28] In all cases the equilibrium compositions obtained from 17α- and 17β-isomers were in agreement within the estimated error of ±2% composition.

The values for per cent of 17α-isomer at equilibrium were the following: I, 23%; II, 23%; III, 21%; IV, 25%; and V, 22% (average 23 ± 2%). It might be noted that these compositions correspond to free-energy differences of about 1 kcal. per mole. The only other ring A modified 20-ketopregnanes whose base-catalyzed[29] equilibrations have been reported are 5β,17α- and 5β,17β-pregnan-3α-ol-20-one[32] where the value of 23% of 17α-isomer at equilibrium[33] is in agreement with the results obtained in this work. The commonly accepted value of 30% of 17α-isomer at equilibrium[34] is based on the results of Moffett and Hoehn[32] and of Butenandt, *et al.*,[14,35] whose 17α-20-ketones were later[15,20] shown to have been impure.

The equilibration results described above suggest no appreciable conformational change at C-17 upon introduction of unsaturation in ring A. Combined with the interpretation of n.m.r. spectra suggesting no change in the C-13, C-17 dihedral angle, the results lead to the conclusion that no significant conformational transmission effect is operative from ring A to ring D. The possibility that variations in the steroid molecule closer to C-17 might produce an observable effect is being investigated.

The five 17α-20-ketopregnanes were examined in a general endocrine screening program and were uniformly inactive[36] in contrast to some of the 17β-epimers.

Experimental[37]

5α-Pregnane-3β,17α,20-triol 3,20-Diacetate.—Hydrogenation of 1.20 g. of Δ⁵-pregnene-3β,17α,20-triol 3,20-diacetate[9] in 50 ml. of ethyl acetate over 0.12 g. of 10% palladium on charcoal at atmospheric pressure, followed by filtration and concentration, afforded an oil, $[\alpha]^{30}D$ −3 ± 2°. Crystallization from isopropyl ether gave 0.66 g. (55%) of mixed C-20 epimers, m.p. 147–195°, $[\alpha]^{30}D$ −3 ± 2°; $\lambda_{max}^{CH_2Cl_2}$ 2.75, 5.75, 8.1 μ [lit.[15] for 20β-isomer,

(24) This shift provides a convenient method for establishing configuration of the side chain; *cf.* also W. J. Wechter and H. C. Murray, *J. Org. Chem.*, **28**, 755 (1963).

(25) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); G. Slomp and B. R. McGarvey, *ibid.*, **81**, 2200 (1959); J. S. G. Cox, E. O. Bishop, and R. E. Richards, *J. Chem. Soc.*, 5118 (1960).

(26) D. H. R. Barton, *Experientia*, **6**, 316 (1950); L. J. Chinn, *J. Org. Chem.*, **27**, 54 (1962).

(27) It is noteworthy that half-lives were approximately 2 hr. under these mild conditions. Similar reaction times have been observed in equilibrations of 16β-methyl-5α-Δ⁹⁽¹¹⁾-pregnen-3β-ol-20-ones (17α and 17β) by E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton [*J. Chem. Soc.*, 1578 (1962)].

(28) Partial resolution of synthetic mixtures of Iα and Iβ, IIIα- and IIIβ-acetates, and IVα and IVβ could be achieved by gas chromatography (50-μg. samples, 1.5% SE-30 on silanized Chromosorb W, 225°, 75 ml. of He/min.); in these instances the 17α-isomer had the shorter retention time [*cf.* W. J. Wechter and H. C. Murray, *J. Org. Chem.*, **28**, 755 (1963)]. Because of the considerable overlap of the two peaks, unsatisfactory results were obtained upon attempted analysis of synthetic mixtures of known composition. No appreciable amounts of impurities were detected by gas chromatographic examination of equilibrated mixtures. Modifications which might afford improved resolution are being investigated for application in future work.

(29) Acid-catalyzed equilibrations of pregnenolones[30] (18% of 17α) and pregnenolone methyl ethers[31] (15% of 17α) have been reported. The reasons for the slightly lower per cent of 17α-isomer at equilibrium are not clear.

(30) J.-F. Biellman, D. Kucan, and G. Ourisson, *Bull. soc. chim. France*, 337 (1962).

(31) O. R. Rodig, P. Brown, and P. Zaffaroni, *J. Org. Chem.*, **26**, 2431 (1961).

(32) R. B. Moffett and W. M. Hoehn, *J. Am. Chem. Soc.*, **66**, 2098 (1944).

(33) The original workers reported 29% of 17α-isomer. It was later shown[20] that their 17α-steroid was impure; the value of 23% presented above has been recalculated from the original data using $[\alpha]D$ −50° instead of $[\alpha]D$ −41° for the 17α-isomer.

(34) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 566.

(35) A. Butenandt and G. Fleischer, *Ber.*, **70**, 96 (1937).

(36) These tests were performed under the supervision of Dr. L. J. Lerner at the Squibb Institute for Medical Research.

(37) Melting points are corrected. Optical rotations were determined in 1% chloroform solutions and ultraviolet spectra were determined in 95% ethanol.

m.p. 161–162°, $[\alpha]^{19}D$ −25 ± 1 (acetone); for 20α-isomer, m.p. 250–251°, $[\alpha]^{20}D$ −39° (acetone)].

5α,17α-Pregnan-3β-ol-20-one Acetate (VIα-Acetate).—Reaction of 0.64 g. of mixed C-20 epimers described above for 26 hr. under the standard Serini–Logemann reaction conditions[9] furnished 0.61 g. of oil, $[\alpha]^{29}D$ −64 ± 1°. Crystallization from isopropyl ether furnished, in two crops, 0.43 g. (79%) of product, m.p. 97–112°, $[\alpha]^{20}D$ −75 ± 2°. Recrystallization from methanol raised the m.p. to 113–114°, $[\alpha]^{30}D$ −75 ± 1°; lit.[15] m.p. 119–122°, $[\alpha]^{21}D$ −75° (alcohol).

Attempted Hydrolyses of VIα-Acetate. A.—A solution of 0.9 g. of potassium carbonate in 25 ml. of water was added to a solution of 173 mg. of VIα-acetate in 50 ml. of methanol. After 1 hr. at room temperature, the pH was adjusted to 2 by addition of concentrated hydrochloric acid and the solution was concentrated under reduced pressure. The residue was taken up in ethyl acetate, washed with water and saturated salt solution, dried over anhydrous sodium sulfate, and concentrated to give 136 mg. of solid, m.p. 95–123°. The infrared spectrum showed weak absorption at 2.75 μ and strong absorption at 5.76, 5.85, and 8.09 μ.

B.—Twenty milliliters of 1 *N* methanolic potassium hydroxide containing 104 mg. of VIα-acetate was stirred at room temperature for 1 hr. After work-up as described in A, 103 mg. of solid, m.p. 105–133°, was obtained. This was chromatographed on Florisil. Elution with 1 and 2% ethyl acetate in benzene gave 25 mg. (24%) of VIα, m.p. 115–134°, $[\alpha]^{30}D$ −73 ± 1°; lit.[15] m.p. 139°, $[\alpha]^{22}D$ −78° (alcohol). Elution with 2, 3, and 4% ethyl acetate in benzene gave 28 mg. (28%) of VIβ, m.p. 145–187°, $[\alpha]^{30}D$ 87 ± 1°; lit.[35] m.p. 194.5°, $[\alpha]D$ 91° (alcohol).

5α,17α-Pregnane-3β,20-diol.—A solution of 0.53 g. of VIα-acetate in 20 ml. of anhydrous ether was added to 0.3 g. of lithium aluminum hydride in 20 ml. of ether. After refluxing for 1.5 hr. the solution was cooled, excess hydride was decomposed with wet ether, and the solid was filtered. The filtrate, after washing with water, drying over anhydrous sodium sulfate, and concentration, yielded 0.46 g. of white solid, m.p. 120–160°, $\lambda_{max}^{CH_2Cl_2}$ 2.75–3.0 μ. This was used without further purification.

5α,17α-Pregnane-3,20-dione (Iα). A. From 17α-Pregnenolone.—Hydrogenation of 1.18 g. of 17α-pregnenolone, $[\alpha]^{31}D$ −149° (*c* 1, $CHCl_3$), over 0.10 g. of 10% palladium on charcoal in 50 ml. of ethyl acetate at atmosphere pressure and room temperature resulted in absorption of 1.0 equiv. of hydrogen after 2 hr. when reaction ceased. Filtration and evaporation afforded 1.13 g. (95%) of 5α,17α-pregnan-3β-ol-20-one (VIα), m.p. 120–136°, $[\alpha]^{29}D$ −74°; lit.[15] m.p. 139°, $[\alpha]D$ −78° (alcohol).

A solution of 1.00 g. of the above in 100 ml. of acetone under nitrogen was treated with 0.91 ml. of 8 *N* chromic acid solution[17] at 10–14° for 5 min. with stirring. The mixture was poured into 500 ml. of water and the precipitated solid was filtered to give 0.85 g. (85%) of Iα as glistening plates, m.p. 140–146°, $[\alpha]^{29}D$ −45°, λ_{max}^{KBr} 5.85 μ; lit.[15] m.p. 148–149°, $[\alpha]^{21}D$ −49.5° (alcohol). Crystallization from petroleum ether (b.p. 68–75°) raised the m.p. to 145–147°, specific rotation unchanged.

B. **From 5α,17α-Pregnane-3β,20-diol.**—A solution of 0.45 g. of the crude diol in 5 ml. of dry pyridine was added to the reagent[16] prepared from 0.85 g. of chromium trioxide and 9 ml. of pyridine. After 17 hr. at room temperature the mixture was worked up in the usual manner to give 382 mg. of solid which was chromatographed on 37 g. of silica gel. Elution with 3 to 5% ethyl acetate in benzene gave 189 mg. (41% over-all from VIα-acetate) of material, m.p. 120–148°. The infrared spectrum was identical with that of the product obtained by procedure A.

5β-Pregnane-3β,17α,20-triol 3,20-Diacetate.—A solution of 4.00 g. of 5β-pregnane-3β,17α-diol-20-one[38] in 100 ml. of tetrahydrofuran (THF) was added slowly with stirring to a slurry of 1.4 g. of lithium aluminum hydride in 200 ml. of THF at 0°. After 1.5 hr. at reflux, the solution was cooled in an ice bath and excess hydride decomposed by careful addition of a solution of 5 ml. of water in 5 ml. of THF. Anhydrous sodium sulfate then was added, the supernatant was decanted, the solid was washed with THF, and the combined solutions were evaporated to give 4.00 g. of 5β-pregnane-3β,17α,20-triol as a white solid, m.p. 180–190°. Repeated crystallization from acetone–petroleum ether afforded the analytical sample as needles which melted at 170° and resolidified to fine needles melting at 190°, $[\alpha]^{30}D$ −15°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.22; H, 10.72.

(38) Intermediates Incorporated, Joliet, Ill.

Reaction of 2.58 g. of the triol with 10 ml. of acetic anhydride and 20 ml. of pyridine overnight at room temperature afforded, after the usual work-up procedure, 3.66 g. of oil which was chromatographed on 183 g. of Florisil. Elution with 1 through 5% ethyl acetate in benzene gave a total of 3.28 g. of white solid. The analytical sample of triol-diacetate X was obtained by crystallization from petroleum ether as white needles, m.p. 146–148°, changing to plates, m.p. 164°; λ_{max}^{KBr} 2.80, 5.78, 5.87, 8.00 μ; $[\alpha]^{29}D$ 36 ± 1°.

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 71.39; H, 9.59. Found: C, 71.28; H, 9.52.

5β,17α-Pregnan-3β-ol-20-one Acetate (VIIα-Acetate).—Reaction of 4.54 g. of triol-diacetate X described above for 20 hr. using the standard Serini–Logemann reaction procedure[9] afforded 3.69 g. of oil, $[\alpha]^{31}D$ −42°, which was chromatographed on 185 g. of Florisil collecting 2-l. fractions. Elution with 1 and 2% ethyl acetate in benzene gave 1.953 g. (49%) of crude VIIα-acetate. Crystallization of 1.14 g. from petroleum ether gave 0.76 g. of white plates, m.p. 119–123°. The analytical sample was obtained by crystallization from methanol as white plates, m.p. 120–123°; λ_{max}^{KBr} 5.77, 5.85, 8.00 μ; $[\alpha]^{31}D$ −78 ± 1°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 75.62; H, 10.07. Found: C, 76.54; H, 9.91.

Further elution of the column with 2, 3, 4, and 5% ethyl acetate in benzene gave 1.24 g. (37%) of VIIα, m.p. 155–171°; $\lambda_{max}^{CH_2Cl_2}$ 2.71, 2.84, and 5.87 μ; $[\alpha]^{31}D$ −70 ± 1°. Acetylation with acetic anhydride and pyridine at room temperature yielded material identical with the acetate obtained from the earlier fractions.

5β,17α-Pregnane-3,20-dione (IIα).—A solution of 1.03 g. of VIIα-acetate in 50 ml. of dry ether was added with stirring to a slurry of 0.87 g. of lithium aluminum hydride in 50 ml. of ether at 0°. After 1 hr. at room temperature, the excess hydride was decomposed with wet ether and anhydrous sodium sulfate. The solvent was evaporated after filtration and washing, the residue was taken up in ethyl acetate, washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated to give 0.87 g. (100%) of white solid, m.p. 100–120°, λ_{max}^{KBr} 2.85 μ. This diol was oxidized without further characterization.

A solution of 0.80 g. of diol in 110 ml. of acetone under nitrogen was treated with 1.41 ml. of 8 *N* chromic acid solution[17] at 10° for 5 min. The mixture was poured into water which then was extracted with ethyl acetate, and the extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to give 0.75 g. (94%) of faintly yellow crystals, m.p. 85–100°, $\alpha^{29}D$ −46°. This was chromatographed on 21 g. of Florisil collecting 200-ml. fractions. Elution with benzene and 1% ethyl acetate benzene gave 0.63 g. of solid, m.p. 80–104°, which crystallized from petroleum ether to yield 0.33 g. (41%) of IIα, m.p. 107°. The analytical sample crystallized from petroleum ether as prisms, m.p. 107°, $[\alpha]^{32}D$ −65°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 80.02; H, 10.08.

17α-Δ^{1,4}-Pregnadiene-3,20-dione (Vα).—A solution of 1.26 g. of 17α-progesterone and 1.22 g. of freshly crystallized DDQ[19] in 200 ml. of dry benzene was refluxed with stirring under nitrogen for 18 hr. The solution was cooled, filtered, and evaporated to dryness. The red residue was dissolved in ethyl acetate, washed with 5% sodium hydroxide solution and water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure on the steam bath to give 1.02 g. of red tar. This was washed through 20 g. of alumina with 200 ml. of benzene to yield 1.00 g. (79%) of white solid, m.p. 113–136°. Recrystallization from isopropyl ether and then acetone–petroleum ether gave the analytical sample as white needles, m.p. 146–147°, λ_{max} 244 mμ (ε 18,600); (KBr) 5.85, 6.00, 6.13, 6.22 μ; $[\alpha]^{30}D$ −60°.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.88; H, 9.48.

Rotatory dispersions, in methanol, gave the following results: Iα, methanol (*c* 0.147), $[\alpha]_{400}$ −180, $[\alpha]_{305}$ −1000, $[\alpha]_{255}$ +710, $[\alpha]_{245}$ +530; IIα, methanol (*c* 0.147), $[\alpha]_{400}$ −240, $[\alpha]_{309}$ −1990, $[\alpha]_{261}$ +2160, $[\alpha]_{240}$ +1550; IIIα-acetate, methanol (*c* 0.084), $[\alpha]_{400}$ −400, $[\alpha]_{308}$ −1790, $[\alpha]_{261}$ +7.0, $[\alpha]_{250}$ +500. In dioxane, the values were IVα, dioxane (*c* 0.145), $[\alpha]_{400}$ −160, $[\alpha]_{367}$ −593, $[\alpha]_{364}$ −578; (*c* 0.0483), $[\alpha]_{354}$ −694, $[\alpha]_{344}$ −383, $[\alpha]_{338}$ −472, $[\alpha]_{328}$ −74, $[\alpha]_{332}$ −203, $[\alpha]_{310}$ −20 (inflection); (*c* 0.029), $[\alpha]_{250}$ +4500; Vα, dioxane (*c* 0.115), $[\alpha]_{400}$ −450, $[\alpha]_{310}$ −1900, $[\alpha]_{265}$ +660, $[\alpha]_{250}$ +210; Vβ, dioxane (*c* 0.26), $[\alpha]_{400}$ +320, $[\alpha]_{325}$ +1900; (*c* 0.087), $[\alpha]_{310}$ +3000; (*c* 0.029), $[\alpha]_{276}$ −240, $[\alpha]_{225}$ +2100°.

Base-Catalyzed Equilibrations.—A 1% solution of each ketone in 1 *N* methanolic potassium hydroxide was introduced into a polarimeter tube of appropriate capacity which was then flushed with nitrogen and sealed. Optical rotations were measured periodically until no further change was observed. The solution then was recovered from the tube and neutralized with acetic acid, and the solvent was removed by evaporation under reduced pressure. The residue was taken up in ethyl acetate, washed twice with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The specific rotation of the residue was then determined in 1% chloroform solution and the infrared and ultraviolet (for IV and V) spectra were determined. The following rotational values were observed.

5α-Pregnane-3,20-diones (I): Iβ, $[\alpha]^{32}D$ 113° ($CHCl_3$); after 2 hr. in 1 *N* methanolic potassium hydroxide, 92°; 12 hr., 80°; Iα, $[\alpha]^{30}D$ −45° ($CHCl_3$); after 2 hr., −7°; 24 hr., +76°; recovered product, $[\alpha]^{32}D$ +77° ($CHCl_3$).

5β-Pregnane-3,20-diones (II): IIβ, $[\alpha]^{32}D$ 116° ($CHCl_3$); after 2 hr., 103°; 24 hr., 80°; IIα, $[\alpha]^{32}D$ −64°; after 2 hr., −2°; 24 hr., 79°; recovered product, $[\alpha]^{34}D$ +75° ($CHCl_3$).

Pregnenolones (III): IIIβ, $[\alpha]^{32}D$ 24° ($CHCl_3$); after 2 hr., 14°; after 12 hr., −3°; IIIα, $[\alpha]^{32}D$ −150° ($CHCl_3$); after 2 hr., −70°; 12 hr., −4°; recovered product, $[\alpha]^{34}D$ −10° ($CHCl_3$).

Progesterones (IV): IVβ, $[\alpha]^{30}D$ 192° ($CHCl_3$); after 4 hr., 151°; 22 hr., 142°; IVα, $[\alpha]^{30}D$ 10° ($CHCl_3$); after 4 hr., 107°; 22 hr., 144°; recovered product $[\alpha]^{32}D$ 140° ($CHCl_3$), λ_{max} 242 mμ (ε 16,000).

1-Dehydroprogesterones (V): Vβ, $[\alpha]^{36}D$ +131 ($CHCl_3$); after 2 hr., 107°; 22 hr., 92°; 17α, $[\alpha]^{36}D$ −60 ($CHCl_3$); after 2 hr., +41°; 22 hr., +86°; recovered product, $[\alpha]^{32}D$ +87 ($CHCl_3$), λ_{max} 244 mμ (ε 18,000).

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A Study of Isobutylene–Nitric Oxide Reaction Products

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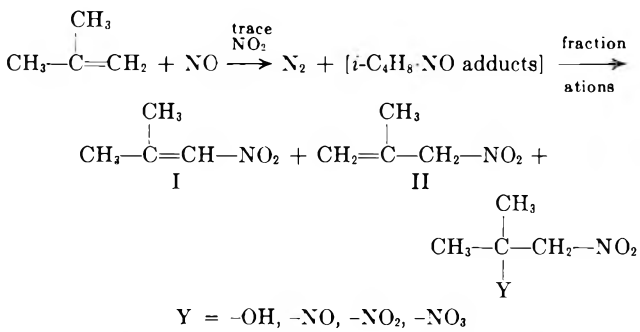
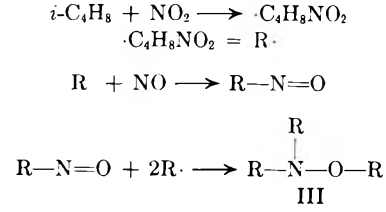
The products of the reaction of nitric oxide with isobutylene were investigated and a synthesis of methyl methacrylate precursors was developed. A previously unreported compound, tris(nitro-*t*-butyl)hydroxylamine, was found to be a major component of the isobutylene–nitric oxide reaction product. This compound decomposed readily to O,N-bis(nitro-*t*-butyl)hydroxylamine and a mixture of α- and β-nitroisobutylene. The α- and β-nitroisobutylenes were found to equilibrate in the presence of a variety of basic catalysts.

A previous investigation[1] has shown that nitric oxide reacts with liquid isobutylene in the presence of traces of nitrogen dioxide to give nitrogen and an unstable liquid mixture of nitro compounds. A series of fractionations of the liquid product under mild conditions was reported to yield a mixture of α-nitroisobutylene (I), β-nitroisobutylene (II), and small quantities of substances having nitro-*t*-butyl structures.



In addition to the products reported earlier,[1] we have found that the isobutylene–nitric oxide reaction product contains 34–45% by weight of crystalline tris(nitro-*t*-butyl)hydroxylamine (III). This new compound probably arises through formation of nitro-*t*-butyl radicals, as described by Brown,[1] followed by their reaction with nitric oxide. Hoffmann and coworkers[2] recently reported a similar preparation of tris-*t*-butylhydroxylamine by reaction of *t*-butyl radicals with *t*-nitrosobutane. (See col. 2.)

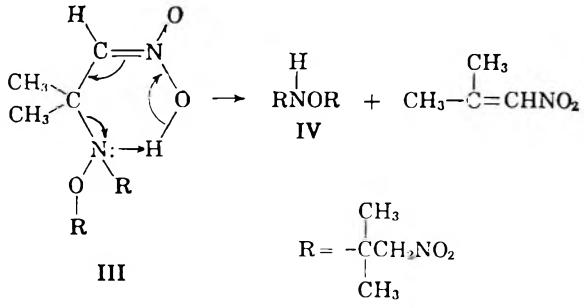
We were able to isolate pure tris(nitro-*t*-butyl)-hydroxylamine only by recrystallization below room temperature. The trishydroxylamine was found to decompose rapidly at moderate temperatures to form O,N-bis(nitro-*t*-butyl)hydroxylamine (IV), and a mixture of nitroisobutylenes accompanied by trace quantities of acetone, nitromethane, and O-(nitro-*t*-butyl)-acetoxime. Crude or solvent-wet tris(nitro-*t*-butyl)-hydroxylamine decomposes completely at room temperature within a few days. O,N-Bis(nitro-*t*-butyl)-hydroxylamine decomposes slowly upon heating to give a mixture of nitroisobutylenes, nitromethane, acetoxime, and O-(nitro-*t*-butyl)acetoxime. N-(Nitro-*t*-butyl)hydroxylamine decomposes rapidly to acetoxime and nitromethane under similar conditions. These decomposition products suggest that O,N-bis(nitro-*t*-butyl)hydroxylamine first decomposes to nitroisobutylenes and N-(nitro-*t*-butyl)hydroxylamine, which then immediately undergoes decomposition to acetone and nitromethane.



It appears likely that thermal decomposition of the three nitro-*t*-butylhydroxylamines is promoted by transition states involving quasi six-membered ring intermediates. According to this mechanism, the nitro groups of the tris and bis compounds would be in the *aci* form, and the nitro group of the mono compound in the normal form. A representative structure for decomposition of tris(nitro-*t*-butyl)hydroxylamine is illustrated.

(1) J. F. Brown, Jr., *J. Am. Chem. Soc.*, **79**, 2480 (1957).

(2) (a) A. K. Hoffmann and A. T. Henderson, *ibid.*, **83**, 4671 (1961); (b) A. K. Hoffmann, W. G. Hodgson, and W. H. Jura, *ibid.*, **83**, 4675 (1961).



III IV

A portion of the α-nitroisobutylene probably isomerizes to produce the observed quantities of β-nitroisobutylene.

Thermal decompositions of the crude isobutylene–nitric oxide adducts under a variety of conditions gave nitroisobutylenes as the major product in the approximate ratio of one part of β-nitroisobutylene to four parts of α-nitroisobutylene. Decompositions in benzene or in the absence of a solvent resulted in 73–85% conversions to the mixture of nitroisobutylenes and only minor quantities of nitro-*t*-butyl alcohol. When decompositions were carried out in methanol or water, however, side reactions occurred. Thus, decompositions in methanol gave in high conversions mixtures of nitroisobutylenes which also contained about 17% by weight of methyl nitro-*t*-butyl ether. The products from a similar decomposition in water contained 21% nitro-*t*-butyl alcohol.

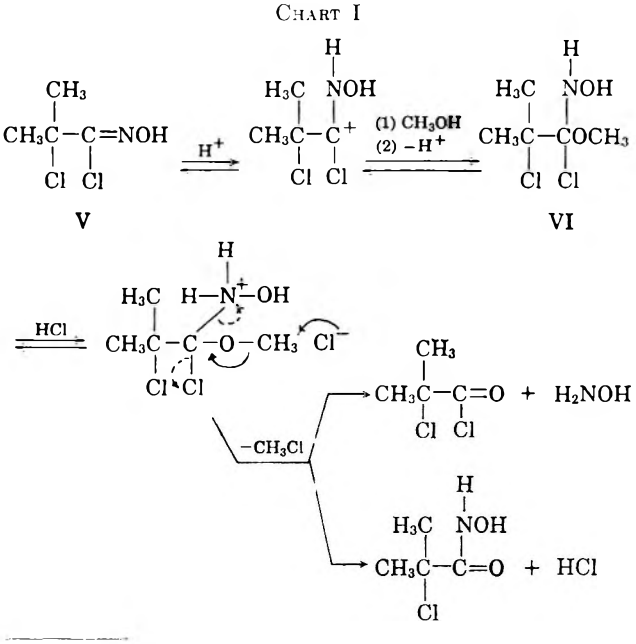
The ready availability of the nitroisobutylenes prompted a search for practical methods of isomer interconversion. Shechter and Shepherd[3] reported that long standing of either isomer in the presence of methanolic potassium hydroxide at room temperature yields an equilibrium mixture of 18–19% β-nitroisobutylene and 81–82% α-nitroisobutylene. We found that α-nitroisobutylene isomerizes rapidly in the presence of potassium hydroxide catalyst at moderately elevated temperatures. By removing the lower boiling β-nitroisobutylene from the reaction mixture by continuous distillation this isomer can be prepared in good yields from the α-isomer. Passage of β-nitroisobutylene through a warm column of Amberlite IR-45, a weak base ion-exchange resin, causes rapid isomerization to an equilibrium mixture which contains 78% α-nitroisobutylene and 22% β-nitroisobutylene. A number of organic bases such as triethylamine, pyridine, and 2,5-dimethylpiperazine were found to be extremely effective isomerization catalysts for both isomers. Reagents such as sodium acetate, dimethylaniline, and mono- and bis(nitro-*t*-butyl)hydroxylamine appear to have little catalytic activity.

The conversion of isobutylene–nitric oxide adducts and their thermal decomposition products to methyl methacrylate precursors was studied extensively. The crude isobutylene–nitric oxide adducts or their thermal decomposition products were treated with hydrogen chloride and methanol to produce mixtures of methyl esters and hydroxylamine hydrochloride. These esters were chiefly methyl α-chloroisobutyrate and methyl α-methoxyisobutyrate together with smaller quantities of methyl β-chloroisobutyrate, methyl α-hydroxyisobutyrate, and methyl methacrylate. Methanolysis of the crude isobutylene–nitric oxide adducts gave the mixture of esters in only 22% yield. Significant improvements to yields as high as 82% were obtained when the crude adducts were first decomposed to a mixture of nitroisobutylenes or when only α-nitroisobutylene was employed. Reaction of β-nitroisobutylene with hydrogen chloride and methanol gave methyl methacrylate precursors in only 24% yield, but in this instance the major product was methyl methacrylate. Methanolysis or hydrolysis of α-nitroisobutylene, β-nitroisobutylene, or isobutylene–nitric oxide adducts in the presence of acids other than hydrogen chloride generally gave only low yields of esters or carboxylic acids. In such systems, decompositions to gaseous products and acetoxime seem to be the main reactions.

Solvolyses of the pure nitroisobutylenes appeared to be particularly promising, and further attention was directed toward finding better methods of converting these compounds to methyl methacrylate precursors. A modification of the procedure of Heath and Rose[4] permitted the preparation of α-chloroisobutyrohydroxamyl chloride (V) in yields greater than 87% by reaction of anhydrous hydrogen chloride with α-nitroisobutylene. β-Nitroisobutylene failed to react with hydrogen chloride under the same conditions, and this isomer could be recovered unchanged from reactions carried out with mixtures of nitroisobutylenes.

Methanolysis of α-chloroisobutyrohydroxamyl chloride in the presence of hydrogen chloride gave a mixture of methyl methacrylate precursors, hydroxylamine hydrochloride, and methyl chloride in high yields. In this instance, the methyl methacrylate precursors consisted chiefly of methyl α-chloroisobutyrate and methyl α-methoxyisobutyrate in the approximate mole ratio of 2:1, respectively. Reaction of α-chloroisobutyrohydroxamyl chloride with methanol in the absence of hydrogen chloride resulted in the formation of 1-methoxy-2-chloro-2-methylpropionaldehyde oxime, methyl α-methoxyisobutyrate, and methyl chloride. Only a trace of methyl α-chloroisobutyrate was detected. Subsequent reaction of 1-methoxy-2-chloro-2-methylpropionaldehyde oxime with methanolic hydrogen chloride gave methyl α-methoxyisobutyrate, hydroxyl-

CHART I

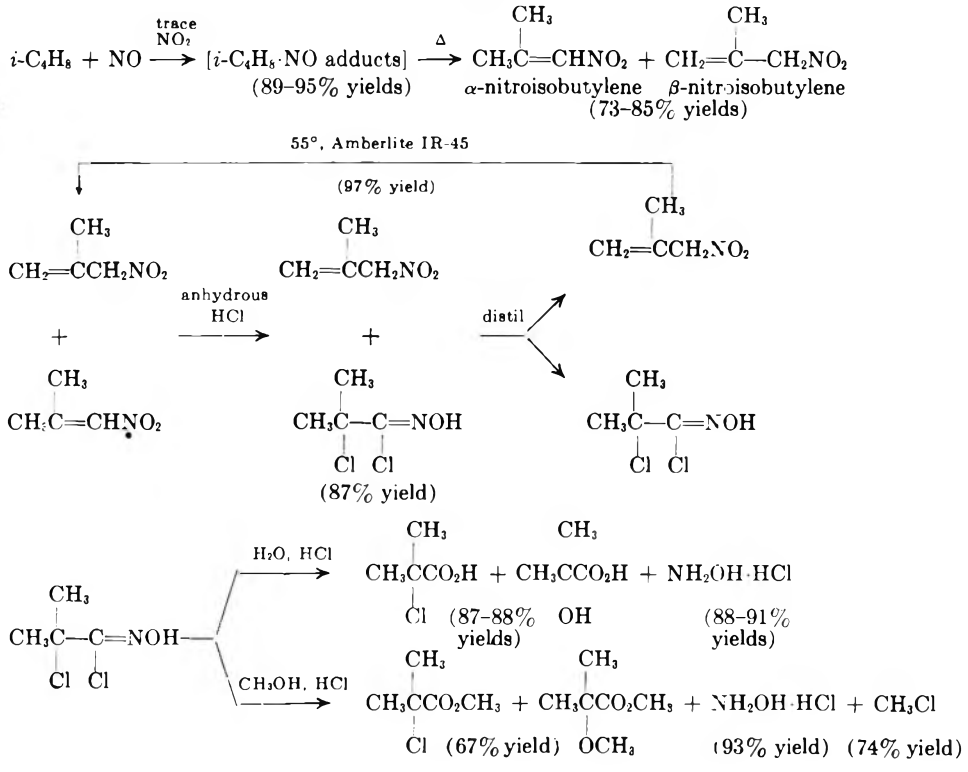


V VI

(3) H. Shechter and J. W. Shepherd, *J. Am. Chem. Soc.*, **76**, 3617 (1954).

(4) R. L. Heath and J. D. Rose, *J. Chem. Soc.*, 1485 (1947).

CHART II



amine hydrochloride, and methyl chloride but no detectable quantity of methyl α-chloroisobutyrate. 1-Methoxy-2-chloro-2-methylpropionaldehyde oxime failed to react with hydrogen chloride in the absence of methanol. Methyl α-chloroisobutyrate and methyl α-methoxyisobutyrate could not be interconverted by treatment with methanolic hydrogen chloride, and the amount of methyl chloride produced during the methanolysis reactions was shown to be much greater than that produced by reaction of hydrogen chloride upon methanol under similar reaction conditions.

Based on these observations, a reaction mechanism is proposed for the methanolysis of α-chloroisobutyrohydroxamyl chloride (see Chart I) and proceeds through a protonated intermediate *via* a path similar to that suggested by Speziale and Freeman[5] for the formation of alkyl halides from trichlorovinylamines. The hydrolysis of α-chloroisobutyrohydroxamyl chloride was investigated also. Heath and Rose[4] had reported that hydrolysis of the hydroxamyl chloride in refluxing hydrochloric acid over long reaction times gave only α-hydroxyisobutyric acid in 30–50% yields. We found that when hydrolysis was carried out at more moderate temperatures and short reaction times, a mixture of α-chloroisobutyric acid and α-hydroxyisobutyric acid was obtained in 87–88% yields. Hydrolysis in the absence of hydrochloric acid produced the mixture of organic acids in only 35% yield.

The ability to produce the α-chloro- and α-hydroxyisobutyric acid in high yields provides a feasible route to methacrylic acid from isobutylene and nitric oxide. As summarized above, this synthetic route can be employed to produce mixtures of either acids or esters. These products are all readily converted to methacrylic acid over known vapor phase dehydration or dehydrohalogenation catalysts.

(5) A. J. Speziale and R. C. Freeman, *J. Am. Chem. Soc.*, **82**, 909 (1960).

Experimental

Gas Chromatography of Nitro-*t*-butyl Compounds and Their Reaction Products.—An Aerograph Model A-100-C gas chromatograph with a Varian 2-mv. recorder was employed. Samples in 10-μl. quantities were analyzed on a 6-ft. column of dinonyl phthalate on Chromasorb B (25:75 ratio, respectively) at 110–115° with a flow rate of 60–65 cc. of hydrogen/min. and with a current of 250 mamp. to the detector. The retention times of compounds analyzed under these conditions are listed in Table I.

TABLE I

RETENTION TIMES OF COMPOUNDS ANALYZED ON DINONYL PHTHALATE COLUMN

Compound	Retention time, min.
Acetone	1.2
Nitromethane	2.4
Methyl methacrylate	3.3
Acetoxime	4.0
Methyl α-hydroxyisobutyrate	5.4
Methyl α-chloroisobutyrate and methyl α-methoxyisobutyrate	7.0
β-Nitroisobutylene	9.1
Methyl α-chloroisobutyrate	13.0
α-Nitroisobutylene	18.1
Nitro-*t*-butyl alcohol	27.0
Methyl nitro-*t*-butyl ether	30.8
O-(Nitro-*t*-butyl)acetoxime	58.0

The compounds were positively identified by comparison of their retention times with those of authentic materials and by isolating the individual components from the gas chromatograph and comparing their infrared spectra with the spectra of authentic compounds. Compounds such as N-(nitro-*t*-butyl)hydroxylamine and O,N-bis-(nitro-*t*-butyl)hydroxylamine could not be detected under the conditions employed. Isobutylene pseudonitrosite decomposed on the column to give two unidentified peaks at 2 sec. and 3.6 sec. The quantity of isobutylene pseudonitrosite could be approximated by comparing the area of the decomposition peak at 3.6 sec. with a graph of known concentrations of isobutylene pseudo-nitrosite *vs.* the corresponding areas of the peak at 3.6 sec. Nitro-*t*-butyl alcohol decomposed

to acetone and nitromethane to a small extent during analysis. This was verified by isolating a sample of the alcohol from the gas chromatograph and reinjecting this sample. Methyl α-chloroisobutyrate and methyl α-methoxyisobutyrate could not be separated on the dinonyl phthalate column under the conditions described. Partial separation was obtained on a 6-ft. column of Carbowax 20 M on Celite 545 (25:75 ratio, respectively) at 110–115° with a flow rate of 35 cc. of hydrogen/min.

Preparation of Isobutylene–Nitric Oxide Adducts.—The following procedure is a minor modification of that employed by Brown.[1] A 1-l. Magne-Dash reactor was equipped with a dip tube, cooling jacket, cold acetone condenser, and a Grove stainless steel back-pressure regulator which contained a Teflon diaphragm. The back-pressure regulator was set to maintain a pressure of 150 p.s.i.g. Nitric oxide was metered through a Fisher-Porter 1/16-20-G-5/81 flowmeter equipped with a tantalum ball float. The amount of nitric oxide charged during the reaction was measured by difference in weight of the nitric oxide cylinder before and after reaction.

The following system was employed to collect the liquid and gaseous products of the reaction. The reactor vent was led through a vacuum adapter into a 500-ml. round-bottomed flask; this flask was connected to a 300-ml. round-bottomed flask which was connected to two vapor traps; the outlet from the back-pressure regulator was attached to a gas collection bag which was also connected to the vapor traps described above by means of a three-way stopcock. The collecting flasks and vapor traps were cooled in ice baths.

The reaction and collection systems were swept with argon and evacuated with a vacuum pump. The reactor, which had been cooled to −15 to −20°, was charged with 207.1 g. of isobutylene, then warmed to 0°. Nitric oxide, 195.5 g., was added through the dip tube with agitation during the course of 83 min. while the temperature was maintained below 29°. The reactor was then cooled to 10°, vented slowly, and flushed with argon. During venting, 273.8 g. of green oil was forced out of the reactor, and the remainder of the product was washed out of the reactor with acetone. The main fraction was pumped at room temperature and 50–60-mm. pressure to leave 253 g. of oil. Removal of acetone from the washings gave an additional 35.19 g. of oil. Duplicate carbon, hydrogen, and nitrogen analyses were obtained for each of the liquid fractions. The loss in weight of the main fraction was assumed to represent unchanged isobutylene. On the assumption that the acetone washings contained the same proportion of dissolved isobutylene, a total of 22.64 g. of isobutylene would have been recovered.

The gaseous products of the reaction were forced through a scrubbing system, which contained acidified ferrous sulfate for removal of nitric oxide, then measured volumetrically by a wet-test meter. Duplicate samples of the scrubbed off-gases were analyzed quantitatively by mass spectroscopy and were found to consist mostly of nitrogen and isobutylene with small amounts of carbon dioxide, nitrous oxide, and nitric oxide in addition to argon.

Samples of the isobutylene, nitric oxide, and argon employed for the reaction were analyzed quantitatively by gas–solid chromatography.

Under the conditions employed, 6.4 moles of nitric oxide reacted with 2.8 moles of isobutylene to form 289.1 g. of liquid product, 1.76 moles of nitrogen, and extremely small amounts of nitrous oxide and carbon dioxide. Thus, the reaction required 2.29 moles of nitric oxide/mole of isobutylene and evolved 0.63 mole of nitrogen/mole of isobutylene or 0.28 mole of nitrogen/mole of nitric oxide. Based upon the amounts of recovered starting materials, the conversions of isobutylene and nitric oxide to adducts were 76% and 99%, respectively. The carbon balance was 95.5% and the nitrogen balance was 104.5%. The yields of adducts which were based upon isobutylene and an assumed molecular weight of 114 for the adducts varied from 89–95% for a number of runs. These adducts were stored at Dry Ice temperature.

Isolation and Identification of Tris(nitro-*t*-butyl)hydroxylamine.—A 94.2-g. portion of isobutylene–nitric oxide adducts partially crystallized after standing at Dry Ice temperature for 2 days. The mixture was filtered to give 20.4 g. of a crude solid and 73.8 g. of green oil filtrate. A portion of the filtrate, 20 g., was dissolved in ether; then pentane was added to cause separation of layers. The top solvent layer was removed by decantation, and the bottom layer was dissolved in an equal volume of benzene. Twice the original volume of ethanol was added, hexane was added to the cloud point at room temperature, then the solution was cooled in an ice bath. Seeding with a small amount of the solid isolated earlier caused separation of 5.9 g. of crystalline material. In all, the amount of solid recovered represents 45% by weight of the reaction product. The solid adduct was purified by dissolving it in benzene at room temperature, adding twice the volume of ethanol or hexane to the cloud point, then chilling and filtering immediately to minimize decomposition in solution. After being pumped at 1 mm. for 20 hr. at room temperature, the white, well-formed crystals melted at 70–71°.

Anal. Calcd. for $C_{12}H_{24}N_4O_7$: C, 42.85; H, 7.19; N, 16.66; mol. wt., 336.3. Found: C, 42.89; H, 7.12; N, 16.51; mol. wt. (cryoscopic in benzene), 334, 338.

The infrared spectrum showed strong bands of a primary nitro group at 6.45 and 7.3 μ. Other characteristic bands were the following: a strong band at 7.98; medium bands at 6.7, 6.85, 7.0, 8.3, 8.7, 8.8, 10.95, 13.3, 13.52, and 14.05; and weak bands at 9.8, 10.65, 11.22, 11.73, and 12.7 μ. Perhaps the most distinguished feature of the spectrum was a group of three bands, a medium band at 10.95 between two weak bands of approximately equal intensity at 10.65 and 11.22 μ.

Thermal Decomposition of Tris(nitro-*t*-butyl)hydroxylamine.—An analytically pure sample of the solid isobutylene–nitric oxide adduct, 3.21 g. (0.0095 mole), was heated under nitrogen at 85° for 3 hr. The sample was then pumped at room temperature and 1 mm. pressure to leave 1.84 g. (0.008 mole) of O,N-bis(nitro-*t*-butyl)hydroxylamine. The volatile materials, which had been collected in a Dry Ice trap, weighed 1.29 g. A gas chromatographic analysis indicated the following composition: 0.0002 mole of acetone, 0.0017 mole of nitromethane, 0.011 mole of nitroisobutylenes, and 0.0004 mole of O-nitro-*t*-butylacetoxime.

A qualitative gas chromatogram which had been obtained immediately after the reaction indicated the presence of acetoxime. After the volatiles had stood overnight, the acetoxime peak had disappeared and the O-nitro-*t*-butylacetoxime peak increase in area. This indicates that the acetoxime had reacted with α-nitroisobutylene.

Thermal Decomposition of N-(Nitro-*t*-butyl)hydroxylamine.—N-(Nitro-*t*-butyl)hydroxylamine,[1] 1 g., was heated at a bath temperature of 120° for 1 hr. The reaction mixture crystallized when cooled to room temperature. Enough ether was added to completely dissolve the solid, and this solution was analyzed by gas chromatography. The major products were acetoxime and nitromethane, with very small quantities of nitroisobutylenes and O-(nitro-*t*-butyl)acetoxime.

Thermal Decomposition of Isobutylene–Nitric Oxide Adducts.—Isobutylene–nitric oxide adducts in 45–50-g. quantities were heated with stirring at reflux if a solvent was employed. In the absence of a solvent, the temperature was maintained at 85° for 3 hr., then slowly raised to 95–100°. In most cases, a mild exothermic decomposition (fume-off) occurred at about 95°. Although no violent decompositions occurred, suitable safety precautions were always exercised. The reaction mixtures were distilled by slowly reducing the pressure to 10 mm. and raising the bath temperature to 120°. The distillates were collected in Dry Ice-cooled receivers. The residue which remained was transferred to a smaller distillation apparatus with the aid of ether and further distilled at 1 mm. and bath temperatures no higher than 120°. In each experiment about 10% by weight of the initial charge of adducts remained as an intractable tar. All distillates were analyzed by gas chromatography. Representative experiments are summarized in Table II. In all experiments minute quantities of isobutylene pseudo-nitrosite, acetone, and nitromethane were observed in addition to the compounds listed in the table. Conversions were based on an assumed average molecular weight of 114 for the isobutylene–nitric oxide adducts.

Isomerizations of α- and β-Nitroisobutylene.—α-Nitroisobutylene, $n^{25}D$ 1.4679, and β-nitroisobutylene, $n^{25}D$ 1.4300, were obtained by two distillations of each isomer through an 18-in. spinning band column.

A. Evaluation of Catalysts.—A 2-g. sample of α-nitroisobutylene was mixed with 1–2% by weight of the base to be tested. The mixture was heated at 80–90° for 2 hr., then the extent of isomerization was determined by gas chromatography. Effective catalysts included 2,5-dimethylpiperazine, 2-picoline, triethylamine, 1,2,3,4-tetrahydroquinoline, N,N-dimethyl-*p*-phenylenediamine, Amberlite IR-45 (weak base ion-exchange resin), and alcoholic potassium hydroxide. Basic compounds such as sodium acetate, dimethylaniline, N-nitro-*t*-butyl-hy-

TABLE II

THERMAL DECOMPOSITION OF ISOBUTYLENE–NITRIC OXIDE ADDUCTS

Solvent	Amt. of adducts, g.	Reaction temp., °C.	Time, hr.	Prod. wt., g.	Conversion, %	Nitro-*t*-butyl compounds, normalized product composition, %				
						α[a]	β[b]	Alcohol[c]	Ether[d]	Oxime[e]
None	50	85–95	4	39.5	85	77	17	6		
Benzene	50	89	7	33.1	74	70	27	3		
Methanol	50	70	16	38.4	83	71	12	3	12	2
Water	50	85–90	6	34.1	72	54	19	21		6

[a] α-Nitroisobutylene. [b] β-Nitroisobutylene. [c] Nitro-*t*-butyl alcohol. [d] Methyl nitro-*t*-butyl ether. [e] O-(Nitro-*t*-butyl)acetoxime.

droxylamine, and O,N-bis(nitro-*t*-butyl)hydroxylamine caused no detectable isomerism.

B. Preparation of β-Nitroisobutylene from α-Nitroisobutylene.—α-Nitroisobutylene and 1–2% by weight of potassium hydroxide dissolved in a minimum of alcohol were allowed to stand at room temperature for 45 min. The mixture then was distilled slowly at 25–40 mm. through a 12-in. column packed with stainless steel so that the lower boiling β-isomer was removed as it formed. By this procedure β-nitroisobutylene was obtained in yields of 60–64%. The use of other catalysts such as triethanolamine was unsatisfactory. It appeared that some codistillation of the catalyst occurred, thereby causing a large amount of α-nitroisobutylene to re-form in the distillate.

Isomerization of β-Nitroisobutylene.—A 1-cm. i.d. glass column which was surrounded by a water jacket was equipped at the top with a small dropping funnel, a thermometer, and an argon inlet. The column was packed with 20 cm. of analytical grade Amberlite IR-45. The thermometer extended into the resin about one quarter the total length of the resin column. A three-necked flask equipped with a Dry Ice condenser was attached to the bottom of the column. The column was pumped for 2 hr. at 70° and 1 mm., then flushed with argon. While the column was maintained at the desired temperature by circulation of water from a constant temperature bath, a slow stream of argon was passed through the system, and a 5–10-g. charge of β-nitroisobutylene was added dropwise during the course of 30 min. After addition had been completed, the column was swept with argon for 20 min., the fraction which had been collected was removed, and the addition of another charge was begun. The fractions were analyzed by gas chromatography. The products from the first five charges contained progressively decreasing amounts of acetone and nitromethane by-products, and the sixth charge contained only trace quantities. These compounds were probably caused by insufficient drying of the resin and reaction of water with the nitroisobutylenes to give nitro-*t*-butyl alcohol which decomposed. At a column temperature of 55°, β-nitroisobutylene was converted in a continuous operation to a mixture of 75% α-nitroisobutylene and 24% β-nitroisobutylene with nearly quantitative recovery. The equilibrium concentration of α- and β-nitroisobutylene was determined by recycling the isomerized products through the column three times. After the first recycle at 55°, a constant ratio of 78% α- to 22% β-nitroisobutylene was reached.

Preparation of α-Chloroisobutyrohydroxamyl Chloride.—A modification of the procedure of Heath and Rose[4] was employed. Anhydrous ether, 200 ml., was saturated with hydrogen chloride at 0°, 40 g. of silica gel was added, then 30 g. (0.297 mole) of α-nitroisobutylene was added slowly. The reaction mixture was stirred at 0° for 4 hr. then allowed to stand at room temperature overnight. After filtration, the ether was removed to leave 45 g. of yellow oil which was distilled to give 40.1 g. (87% yield) of α-chloroisobutyrohydroxamyl chloride, b.p. 46–48° (1 mm.), $n^{21}D$ 1.4901; lit.[4] b.p. 64–65° (3 mm.), $n^{20}D$ 1.4910.

Reaction of α-Chloroisobutyrohydroxamyl Chloride with Methanolic Hydrogen Chloride.—A solution of 7.0 g. (0.045 mole) of α-chloroisobutyrohydroxamyl chloride, 7.2 g. (0.225 mole) of methanol, and 3.3 g. (0.09 mole) of hydrogen chloride was allowed to stand at room temperature overnight then refluxed for 2 hr. Off-gases, 2.6 g., were collected in a Dry Ice trap. After the reaction mixture had cooled, 20 ml. of ether was added, the mixture was chilled, and then 2.5 g. (80% yield) of hydroxylamine hydrochloride was removed by filtration. The filtrate was dried over magnesium sulfate, then pumped at 1 mm. at a bath temperature of 30–35°; volatile materials were collected in a Dry Ice-cooled receiver. There remained 1 g. (15% yield) of residue which was identified as 2-chloro-1-methoxy-2-methylpropionaldehyde oxime by infrared analysis. A portion of the ether was removed from the volatile fraction to leave 5.0 g. of solution. Quantitative gas chromatography (dinonyl phthalate column) showed the presence of 2.9 g. (47% yield) of a mixture of methyl α-chloroisobutyrate and methyl α-methoxyisobutyrate. Infrared analysis and gas chromatography on the Carbowax column indicated that the mixture of esters consisted of 2 moles of chloro ester/mole of methoxy ester.

A solution of 3.3 g. (0.09 mole) of hydrogen chloride and 7.2 g. (0.225 mole) of methanol was allowed to stand overnight at room temperature, then refluxed for 2 hr. During this time 0.8 g. of off-gases was collected in a Dry Ice trap. The condensed gases were allowed to volatilize into a gas-collection bag, then pulled into an evacuated gas sample bottle. Infrared analysis indicated the presence of 44.8% methyl chloride or 0.36 g. of methyl chloride in the sample.

Infrared analysis of the off-gases obtained in the methanolysis of α-chloroisobutyrohydroxamyl chloride indicated the presence of 77.5% methyl chloride. After correction for the amount of methyl chloride formed by reaction of hydrogen chloride with methanol, 1.7 g. (74% yield) of methyl chloride was estimated to have been obtained.

Reaction of α-Chloroisobutyrohydroxamyl Chloride with Methanol.—A solution of 7.0 g. (0.045 mole) of α-chloroisobutyrohydroxamyl chloride and 7.2 g. (0.225 mole) of methanol was allowed to stand overnight, then refluxed for 2 hr. The reaction was worked up as described in the previous experiment. An infrared spectrum of the ester fraction which was isolated by gas chromatography indicated the presence of methyl α-methoxyisobutyrate with only a trace of methyl α-chloroisobutyrate. The reaction products consisted of 2.3 g. (39% yield) of methyl α-methoxyisobutyrate, 3.0 g. (44% yield) of 2-chloro-1-methoxy-2-methylpropionaldehyde oxime, 1.7 g. (54% yield) of hydroxylamine hydrochloride, and 0.67 g. (29% yield) of methyl chloride.

Reaction of 2-Chloro-1-methoxy-2-methylpropionaldehyde Oxime with Methanolic Hydrogen Chloride.—A mixture of 2.0 g. (0.0132 mole) of 2-chloro-1-methoxy-2-methylpropionaldehyde oxime, 3.5 g. (0.094 mole) of methanol, and 1 g. (0.0274 mole) of hydrogen chloride was refluxed for 2 hr., then worked up as described previously. Infrared analysis of the ester portion which was isolated by gas chromatography indicated the presence of methyl α-methoxyisobutyrate only. The reaction products consisted of 1.02 g. (58% yield) of methyl α-methoxyisobutyrate, 0.6 g. (66% yield) of hydroxylamine hydrochloride, and 0.4 g. (60% yield) of methyl chloride.

Reaction of Methyl α-Chloroisobutyrate with Methanolic Hydrogen Chloride.—A solution of 1.0 g. (0.0073 mole) of methyl α-chloroisobutyrate, 0.5 g. (0.0137 mole) of hydrogen chloride, and 1.5 g. (0.0469 mole) of methanol was refluxed for 2 hr. A large portion of the methanol was removed by distillation. The material at the retention time for methyl α-chloroisobutyrate and methyl α-methoxyisobutyrate was isolated by gas chromatography and analyzed by infrared spectroscopy. The spectrum indicated the presence of methyl α-chloroisobutyrate and the absence of methyl α-methoxyisobutyrate.

Reaction of Methanolic Hydrogen Chloride with Methyl α-Methoxyisobutyrate. A.—A solution of 2 g. (0.015 mole) of methyl α-methoxyisobutyrate, 1.1 g. (0.031 mole) of hydrogen chloride, and 1.07 g. (0.034 mole) of methanol was refluxed for 8 hr.; then a large portion of the methanol was removed by distillation. The portion of the residue at the retention time of methyl α-chloroisobutyrate and methyl α-methoxyisobutyrate was isolated by gas chromatography. An infrared analysis of this material indicated the presence of methyl α-methoxyisobutyrate and the absence of methyl α-chloroisobutyrate.

B.—A mixture of 1 g. (0.0075 mole) of methyl α-methoxyisobutyrate, 0.57 g. (0.015 mole) of hydrogen chloride, 0.53 g. (0.017 mole) of methanol, and 0.52 g. (0.0075 mole) of hydroxylamine

hydrochloride was refluxed for 8 hr. A large portion of the methanol was removed by distillation, then the portion of the residue at the retention time for methyl α-chloroisobutyrate and methyl α-methoxyisobutyrate was isolated by gas chromatography. An infrared analysis indicated the presence of methyl α-methoxyisobutyrate and the absence of methyl α-chloroisobutyrate.

Attempted Reaction of Hydrogen Chloride with 2-Chloro-1-methoxy-2-methylpropionaldehyde Oxime.—Hydrogen chloride was passed into a solution of 6 g. (0.0396 mole) of 2-chloro-1-methoxy-2-methylpropionaldehyde oxime and 36 g. of benzene at room temperature for 1 hr. Very little absorption of hydrogen chloride occurred and no observable quantity of methyl chloride was formed during this treatment. A solution of 2 g. of ether and 2 drops of methanol was added, and hydrogen chloride was bubbled through the mixture at 70–75° for 4 hr. No methyl chloride formation was observed. The solvents were removed under reduced pressure to leave 5.9 g. of unchanged 2-chloro-1-methoxy-2-methylpropionaldehyde oxime.

Preparation of Authentic 2-Chloro-1-methoxy-2-methylpropionaldehyde Oxime.—This material was prepared by the reaction of α-chloroisobutyrohydroxamyl chloride with methanol in the presence of calcium carbonate as described by Ogloblin.[6]

Hydrochloric Acid Hydrolysis of α-Chloroisobutyrohydroxamyl Chloride.—A mixture of 20 g. (0.128 mole) of freshly distilled α-chloroisobutyrohydroxamyl chloride and 14 ml. (0.168 mole) of concentrated hydrochloric acid was stirred at 55–60° for 3 hr. During this time the two-phase system changed to a single phase. The solution was cooled to room temperature, an equal volume of ether was added, and the mixture was filtered to give 7.3 g. of hydroxylamine hydrochloride. The aqueous phase of the filtrate was extracted with several small portions of ether which were added to the organic phase; then the aqueous phase was evaporated to dryness to leave 2.7 g. of solid residue. This residue was triturated with ether to leave 0.5 g. of hydroxylamine hydrochloride. Evaporation of the ether extract gave 2 g. of α-hydroxyisobutyric acid.

The combined organic solutions were dried over magnesium sulfate, then distilled to give 9.3 g. (59% yield) of α-chloroisobutyric acid, b.p. 43–48° (1 mm.), and 1.8 g. of α-hydroxyisobuytric acid, b.p. 48–53° (1 mm.). In all, α-hydroxyisobutyric acid was obtained in 29% yield and hydroxylamine hydrochloride in 87% yield.

(6) K. A. Ogloblin, *Zh. Obshch. Khim.*, **29**, 1752 (1959); *Chem. Abstr.*, **54**, 8617 (1960).

The Reaction of *sec*-Alkyl Sulfides with *p*-Toluenesulfinic Acid[1]

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The reaction of several *sec*-alkyl sulfides with *p*-toluenesulfinic acid has been investigated. As with their primary counterparts, the principal reaction involves cleavage of the sulfide, the products being *p*-tolyl *p*-toluenethiolsulfonate, the *sec*-alkyl *p*-toluenethiolsulfonate, and the ketone derived from oxidation of the *sec*-alkyl group. However, with 2-octyl sulfide the reaction appears to be somewhat more complex than usual, since some of the sulfide is also oxidized to the sulfoxide. The reactivity of *sec*-alkyl sulfides is distinctly lower than expected from the reactivity of primary alkyl sulfides. Evidence is presented that this is due to the influence of steric hindrance on the initial equilibrium (eq. 4) involving sulfinic acid and sulfide.

Previous papers[2,3] have described a new reaction between primary alkyl sulfides and *p*-toluenesulfinic acid, which leads to the cleavage of the sulfide and the oxidation of one of its alkyl groups to the corresponding aldehyde. The other products are the *p*-tolyl and alkyl *p*-toluenethiolsulfonates, the over-all stoichiometry presumably being as shown in eq. 1. Consideration of

$$5ArSO_2H + (RCH_2)_2S \longrightarrow 2ArSO_2SAr + ArSO_2SCH_2R + RCHO + 3H_2O \quad (1)$$

the mechanism[3] of the reaction suggests no reason why secondary alkyl sulfides should not react in comparable fashion, one of their alkyl groups being oxidized to the corresponding ketone.

The present paper examines the reactions of several typical secondary alkyl sulfides with *p*-toluenesulfinic acid. In the main, the predictions above about the course of the reactions are borne out, although with 2-octyl sulfide one additional interesting new facet becomes apparent. Kinetic studies allow the reactivity of *sec*-alkyl sulfides to be compared with that of closely related primary alkyl sulfides.

Results and Discussion

Products of the Reaction of *sec*-Alkyl Sulfides with *p*-Toluenesulfinic Acid.—The reaction was studied with two typical *sec*-alkyl sulfides—isopropyl sulfide and 2-octyl sulfide. In both cases the three products expected by analogy to eq. 1 were found: (1) the appropriate ketone (acetone or 2-octanone), (2) *p*-tolyl *p*-toluenethiolsulfonate, and (3) the *sec*-alkyl *p*-toluenethiolsulfonate. For both sulfides the yield of the *p*-tolyl ester was 0.29–0.30 mole/mole of sulfinic acid reacting, and that of the appropriate *sec*-alkyl *p*-toluenethiolsulfonate was 0.15–0.17 mole/mole of sulfinic acid. The yield of 2-octanone from the 2-octyl sulfide reaction, as determined by conversion of the crude 2-octanone fraction to the semicarbazone, was 0.10–0.11 mole/mole of sulfinic acid. In the isopropyl sulfide reaction, experimental difficulties precluded an accurate quantitative estimate of the amount of acetone formed.

In the 2-octyl sulfide reaction one further product was isolated, 2-octyl sulfoxide, in an amount equal to approximately 0.10 mole/mole of sulfinic acid consumed. On the other hand, no isopropyl sulfoxide was obtained from the isopropyl sulfide reaction, although it is conceivable the work-up procedure employed may have been responsible for its apparent absence. In this connection it is also worth noting that in our early studies[2] of the *n*-butyl sulfide–*p*-toluenesulfinic acid reaction we considered that *n*-butyl sulfoxide might be a possible product, and accordingly, made a careful search for it. None could be detected. The formation of sulfoxides would therefore appear to be limited to sulfide–sulfinic acid reactions involving secondary sulfides.

(1) Paper VII: Mechanisms of Reactions of Sulfinic Acids. This research was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research, under Grant AFOSR-106-63.

(2) J. L. Kice and K. W. Bowers, *J. Am. Chem. Soc.*, **84**, 2390 (1962).

(3) J. L. Kice and E. H. Morkved, *ibid.*, **85**, 3472 (1963).

At first glance, the simplest way to explain the formation of the sulfoxide seems to be to assume that in the case in question the reaction proceeds in part by the usual path (eq. 2) and in part by the path shown in eq. 3. One can even present some not unreasonable

$$5ArSO_2H + (RR'CH)_2S \longrightarrow 2ArSO_2SAr + ArSO_2SCHRR' + \begin{matrix} R' \\ \diagdown \\ CO \\ \diagup \\ R \end{matrix} + 3H_2O \quad (2)$$

$$2ArSO_2H + (RR'CH)_2S \longrightarrow ArSO_2SAr + (RR'CH)_2S{\rightarrow}O + H_2O \quad (3)$$

arguments[4] why reaction 3 should play a more important role in the 2-octyl sulfide case than in the other sulfide–sulfinic acid reactions so far examined. This explanation, however, also leads one to expect that the ratio of *p*-tolyl to alkyl *p*-toluenethiolsulfonate should be significantly larger than has been found[3] in the other alkyl sulfide–*p*-toluenesulfinic acid reactions. This is not the case. Indeed, if anything, the ratio (1.8:1) is slightly smaller than normally observed. This, coupled with the fact that the total yields of both thiolsulfonates, although a bit lower, are still closely comparable to those obtained in earlier[3] *p*-toluenesulfinic acid–primary alkyl sulfide reactions, tends to cast considerable doubt on this otherwise attractive explanation.

At present we have no simple alternative explanation for the formation of the sulfoxide. However, the results of some experiments we carried out to obtain further information relevant to this point are worth noting. Heating 2-octyl sulfide alone in the acetic acid–water–sulfuric acid medium used for the sulfide–sulfinic acid reactions yielded, as expected, no sulfoxide. However, heating it with 2-octanone in the same solvent, either in the presence or absence of *p*-tolyl *p*-toluenethiolsulfonate, led to the formation of a small amount of material, which from its infrared spectrum and point of elution from a chromatographic column must have consisted chiefly of 2-octyl sulfoxide. The amount of sulfoxide so formed was less than the amount isolated from the sulfide–sulfinic acid reaction, but the fact that some was formed raises the possibility that in the presence of sulfinic acid one might have a more efficient reaction involving ketone and sulfide, which would consume some of the ketone, oxidize some of the sulfide to the sulfoxide, and convert a small amount of sulfinic acid to indeterminate products.

We might then summarize the present state of our knowledge by saying that, although most of the reaction between *sec*-alkyl sulfides and the sulfinic acid seems to follow the expected course outlined in eq. 2, with at least some secondary sulfides additional complexities give rise to the formation of some *sec*-alkyl sulfoxide, apparently principally at the expense of some of the ketone expected from eq. 2.

Reactivity of Secondary Alkyl Sulfides in the Sulfide–Sulfinic Acid Reaction.—The kinetics of the reaction of several *sec*-alkyl sulfides with *p*-toluenesulfinic acid were examined in acetic acid–0.56 *M* water–0.6 *M* sulfuric acid using the techniques outlined in previous publications.[2,3] In each case the reactions were found to be first order in both sulfinic acid and sulfide. The rate contants, k_s, calculated from the equation

$$-d(ArSO_2H)/dt = k_s(ArSO_2H)(R_2S)$$

are shown in Table I, along with selected data on primary alkyl sulfides from earlier work.[3]

TABLE I

RATE CONSTANTS FOR REACTION OF *sec*-ALKYL SULFIDES WITH *p*-TOLUENESULFINIC ACID

Alkyl sulfide	$k_S \times 10^3$, M^{-1} sec.$^{-1}$
Isopropyl	2.6
sec-Butyl	2.8
2-Octyl	2.4
n-Butyl[b]	17.5
Ethyl[b]	10.2

[a] All data are at 70° with acetic acid–0.56 *M* water–0.6 *M* sulfuric acid as the reaction medium. [b] Data of ref. 3.

The primary alkyl sulfides are seen to be four to seven times as reactive as the corresponding secondary alkyl sulfides. Since previous work[3] with selected primary alkyl sulfides has shown that the rate of the sulfide–sulfinic acid reaction is subject to inductive acceleration by an increase in the electron-donating character of the alkyl group ($\rho^* = -1.85$), the decreased reactivity of the *sec*-alkyl sulfides is certainly not due to an inductive effect. Consideration of the kinetically important steps[3] of the usual sulfide–sulfinic acid reaction (eq. 4 and 5) suggests two possible

$$ArSO_2H + (RR'CH)_2S + H^+ \underset{}{\overset{K_e}{\rightleftharpoons}} Ar{-}\overset{+}{S}{-}\underset{\underset{O}{\downarrow}}{S}(CHRR')_2 + H_2O \quad (4)$$

I

$$Ar{-}\overset{+}{S}{-}\underset{\underset{O}{\downarrow}}{S}(CHRR')_2 \xrightarrow{k_d} ArSOH + \begin{matrix} R' \\ \diagdown \\ C{=}\overset{+}{S}{-}CHRR' \\ \diagup \\ R \end{matrix} \quad (5)$$

I

causes for the lower reactivity of the secondary sulfides. First, steric factors could cause the first equilibrium to be less favorable for the formation of I. Second, elimination of ArSOH from I might occur with greater difficulty than elimination of the same species from $ArS(O)S(CH_2R)_2$, the equivalent ion formed from a primary sulfide. Preliminary results[5] of a study of the preferred direction of elimination in unsymmetrical alkyl sulfides indicate that the first factor is the important one, since comparable amounts of ethyl and isopropyl *p*-toluenethiolsulfonates are formed in the reaction of ethyl isopropyl sulfide with *p*-toluenesulfinic acid. It thus appears that the increased steric require-

(4) The normal initial equilibrium between sulfinic acid and sulfide (eq. 4) leads to the ion I which then decomposes as shown in eq. 5.[3] One can argue that with increasing steric requirements of the alkyl groups of the sulfide an alternate equilibrium to give ion II may assume some importance, and that ion II will undergo decomposition as indicated below. This leads to the over-all stoichiometry shown in eq. 3. Clearly, if steric considerations tend to promote II at the expense of I, reaction 3 should be more important with 2-octyl sulfide than with the other sulfides that have been studied.

$$ArSO_2H + H^+ \rightleftharpoons ArSO^+ + H_2O$$

$$Ar{-}\overset{+}{S}{=}O + S(CHRR')_2 \longrightarrow Ar{-}S{-}O{-}\overset{+}{S}(CHRR')_2$$

II

$$II \longrightarrow (RR'CH)_2S{\rightarrow}O + ArS^+ \xrightarrow{ArSO_2H} ArSO_2SAr$$

(5) B. Toth, unpublished results.

ments of the *sec*-alkyl sulfides cause the equilibrium in eq. 4 to be less favorable than for primary alkyl sulfides.

Experimental

Materials.—*p*-Toluenesulfinic acid was prepared and purified as previously described.[3] Isopropyl and *sec*-butyl sulfides (Aldrich Chemical Co.) were purified by fractional distillation. Acetic acid–0.56 *M* water solutions and stock solutions of sulfuric acid in the same solvent were prepared from purified acetic acid in the manner outlined previously.[3]

2-Octyl Sulfide.—2-Octyl mercaptan[6] (10.4 g.), b.p. 87–89° (28 mm.), was dissolved in 30 ml. of methanol. The solution was kept under nitrogen, and 4 g. of potassium hydroxide in 25 ml. of methanol was added. To this was then added dropwise with good stirring 13.7 g. of 2-octyl bromide. The mixture was refluxed for 10 hr. After cooling the solution, the precipitated potassium bromide was filtered off, and the filtrate was poured into water and extracted with ether. The ether extracts were dried and the ether was removed by distillation. Distillation of the residue gave 11.2 g. (61%) of 2-octyl sulfide, b.p. 129–131° (2 mm.), lit.[7] b.p. 175° (20 mm.).

Anal. Calcd. for $C_{16}H_{34}S$: C, 74.45; H, 13.22. Found: C, 74.22; H, 13.22.

Kinetic Runs.—These were carried out using the methods described in an earlier paper.[3]

Products of the *sec*-Alkyl Sulfide–*p*-Toluenesulfinic Acid Reactions.—The same general procedure was used for both sulfides studied. A solution of 5.00 mmoles of *p*-toluenesulfinic acid and 15.0 mmoles of the *sec*-alkyl sulfide in 100 ml. of acetic acid–0.56 *M* water–0.6 *M* sulfuric acid was deaerated at room temperature and then heated under nitrogen at 70° for 2 hr. At the end of that time a small aliquot was removed, and the residual sulfinic acid content was determined by nitrite titration.[3] This was 0.28 mmole for the isopropyl sulfide reaction and 0.44 mmole in the 2-octyl sulfide case.

The reaction mixture was then poured into ten times its volume of water, and the mixture was extracted several times with ether. The ether extracts were washed with aqueous 5% sodium bicarbonate until neutral, then with water, and were finally dried over anhydrous sodium sulfate. The ether was removed by careful fractional distillation, and the residue was subjected to chromatography on acid-washed alumina.

In the isopropyl case successive elution with hexane and benzene allowed the separation of the unchanged sulfide from a mixture of *p*-tolyl and isopropyl[8] *p*-toluenethiolsulfonates. The relative amounts of the two thiolsulfonates in the mixture was then determined by an n.m.r. analytical method already outlined.[8] The results indicated the amounts of the two thiolsulfonates formed in the reaction were *p*-tolyl *p*-toluenethiolsulfonate, 1.37 mmoles, and isopropyl *p*-toluenethiolsulfonate, 0.74 mmole.

The formation of acetone as an additional reaction product was demonstrated in a separate experiment. In it the final reaction solution was distilled through a short Vigreux column until about 4 ml. of distillate was obtained. The distillate was treated with an alcohol solution of 2,4-dinitrophenylhydrazine in the usual manner, and the acetone 2,4-dinitrophenylhydrazone which precipitated was recrystallized and identified.

For the 2-octyl sulfide reaction, the chromatographic column was eluted much more gradually, using successively hexane, 10% benzene–hexane, 25% benzene–hexane, 50% benzene–hexane, pure benzene, and finally ether. After the unchanged sulfide there were eluted, in order, essentially pure fractions of 2-octanone, 2-octyl *p*-toluenethiolsulfonate, and *p*-tolyl *p*-toluenethiolsulfonate. The identity of the ketone was confirmed by comparison of the infrared spectrum of the crude product with that of a known sample of 2-octanone and by conversion of the crude ketone to its semicarbazone, m.p. 125–126°. The yield, as estimated from the amount of semicarbazone obtained, was 0.42 mmole. Experiments with pure 2-octanone samples indicated that under our conditions the formation of the semicarbazone from the ketone was only about 85% quantitative. On this basis the probable true yield of 2-octanone from the reaction would be about 0.49 mmole.

The yields of the two thiolsulfonates were determined from the weights of the respective fractions, n.m.r. analyses having shown that each was essentially uncontaminated by the other ester: *p*-tolyl *p*-toluenethiolsulfonate, 1.35 mmoles, and **2-octoyl *p*-toluenethiolsulfonate**, 0.76 mmole. The identity of the latter ester was established by elemental analysis and infrared and n.m.r. spectral data on the appropriate chromatographic fractions. It is a liquid, but too high boiling to allow distillation without decomposition.

Anal. Calcd. for $C_{15}H_{24}O_2S_2$: C, 59.95; H, 8.05. Found: C, 60.16; H, 7.94.

In the isopropyl sulfide runs, elution of the chromatographic column with ether gave no products. The ether fractions from the 2-octyl sulfide runs, on the other hand, contained a significant amount of material. Its principal component was shown to be 2-octyl sulfoxide.

2-Octyl Sulfoxide.—The ether fractions from the chromatogram were subjected to molecular distillation. The distillate had an infrared spectrum which showed a very strong band at 1025 $cm.^{-1}$, as would be expected for a sulfoxide.

Anal. Calcd. for $C_{16}H_{34}OS$: C, 70.01; H, 12.48; S, 11.68. Found: C, 70.12; H, 12.65; S, 11.78.

A known sample of 2-octyl sulfide was allowed to react in acetone solution with an equimolar amount of hydrogen peroxide for 1 week at room temperature. After standard work-up procedures there was isolated an 80% yield of a substance having an infrared spectrum identical with the compound isolated from the sulfide–sulfinic acid reaction.

2-Octyl Sulfone.—A sample of 2-octyl sulfide was oxidized in hot acetic acid with sufficient hydrogen peroxide to convert it to the sulfone. There was obtained a 98% yield of crude 2-octyl sulfone. Its infrared spectrum showed the expected strong absorption at 1300 and 1125 $cm.^{-1}$. It was further purified by molecular distillation at 10^{-4} mm. in a small Hickman still.

Anal. Calcd. for $C_{16}H_{34}O_2S$: C, 66.15; H, 11.80; S, 11.04. Found: C, 66.28; H, 12.04; S, 11.30.

A portion of the presumed 2-octyl sulfoxide from the sulfide–sulfinic acid reaction was treated with an equimolar amount of hydrogen peroxide in hot acetic acid. On work-up there was obtained an 80% yield of a substance having an infrared spectrum identical with that of the known 2-octyl sulfone, prepared above from the sulfide. There is thus no doubt that the compound formed in the 2-octyl sulfide-*p*-toluenesulfinic acid reaction is 2-octyl sulfoxide.

Interaction of 2-Octanone and 2-Octyl Sulfide.—2-Octyl sulfide (15 mmoles), 2-octanone (5 mmoles), and *p*-tolyl *p*-toluenethiolsulfonate (2 mmoles) were heated at 70° for 2 hr. in 100 ml. of acetic acid–0.56 *M* water–0.6 *M* sulfuric acid. The reaction mixture was poured into water and worked up in just the same way as the 2-octyl sulfide–*p*-toluenesulfinic acid reaction. The ether fraction from the chromatography had an infrared spectrum which indicated it consisted chiefly of 2-octyl sulfoxide. It weighed 0.025 g. Similar results were obtained in the absence of *p*-tolyl *p*-toluenethiolsulfonate. However, heating the sulfide alone under the same conditions gave no detectable sulfoxide on work-up.

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(7) S. O. Jones and E. E. Reid, *ibid.*, **60**, 2452 (1938).
(8) J. L. Kice and E. H. Morkved, *ibid.*, **86**, 2270 (1964).

The Analysis of t-Butyl Sulfides[1]

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t-Butyl sulfides, like trityl sulfides but unlike other alkyl sulfides, consume 6 equiv. of bromine when titrated by the Siggia–Edsberg procedure. This behavior is attributed to solvolysis of intermediate bromosulfonium ions to yield *t*-butyl carbonium ions and sulfenyl bromides, the latter materials being oxidized subsequently to sulfonyl bromides. The results obtained indicate that the Siggia–Edsberg procedure may be used for the quantitative analysis of tertiary sulfides.

Organic sulfides generally are determined by bromimetric or bromometric procedures in which the sulfide becomes oxidized to a sulfoxide.[2] In such analyses, the sulfide usually consumes 2 equiv. of bromine, but care must be taken to prevent subsequent oxidation of the sulfoxide to sulfone, particularly when alkyl sulfides are being analyzed. Thus, bromometric procedures are suitable for the analysis of aryl and heterocyclic sulfides,[3] but only bromimetric methods can be utilized for the analysis of strictly aliphatic sulfides. Of the available bromimetric procedures, the method of Siggia and Edsberg[4] seems the most attractive from the standpoint of reagent stability, convenience, and reliability. In this procedure, an acidic solution of the sulfide is titrated with a standard potassium bromide–potassium bromate solution. Bromine is liberated *in situ* and the end point of the titration is signaled by the appearance of a permanent bromine color.

$$BrO_3^- + 5Br^- + 6H^+ \longrightarrow 3Br_2 + 3H_2O$$

$$R_2S + Br_2 \xrightarrow{H_2O} R_2SO + 2HBr$$

Although many sulfides have been analyzed satisfactorily by the Siggia–Edsberg and other procedures, the limitations of such bromination techniques have not been defined and one must be cautious in the application of such techniques to the characterization of new sulfides. For example, Gregg and Blood[5] noted that triphenylmethyl (trityl) sulfides consume 6 equiv. of bromine when analyzed by the Siggia–Edsberg procedure. Primary and secondary alkyl sulfides have been analyzed satisfactorily by bromimetric procedures, but no studies have been reported on the determination of tertiary alkyl sulfides.

Results

In the course of other studies, we had occasion to analyze a number of *t*-butyl sulfides by the Siggia–Edsberg procedure. As is shown in Table I, these sulfides consumed three times as much reagent (6 equiv. of reagent per sulfur atom) as would be expected on the basis of the titration behavior of primary and secondary alkyl sulfides. A study of analysis conditions did not lead to any significant change in the results obtained. The water content of the titration mixtures did not influence the results, provided the mixtures were homogeneous. Titrations conducted at elevated temperatures gave better results than those conducted at room temperature, but the general stoichiometry of the titrations was not affected by temperature. The use of sulfuric or nitric acid instead of hydrochloric acid in these analyses caused premature oxidation of the samples.

TABLE I

TITRATION OF ALKYL SULFIDES BY THE SIGGIA–EDSBERG PROCEDURE

Sulfide	Equiv. of bromine consumed per sulfur atom
$(CH_3)_2S$	1.93
$(n\text{-}C_3H_7)_2S$	1.98
$(n\text{-}C_4H_9)_2S$	1.98
$t\text{-BuSCH}_2CH_2S(t\text{-Bu})$	5.93
$t\text{-BuSCH}_2CH_2OH$	5.85
$t\text{-BuSCH}_2CH_2Cl$	5.87
$t\text{-BuSCH}_2CH_2CH_2CH_3$	5.67
$(t\text{-Bu})_2S$	7.31
$t\text{-BuSC}_6H_5$	5.64
$t\text{-BuSCH}_2C_6H_5$	5.84

The similar stoichiometry noted for the bromination of *t*-butyl sulfides and for trityl sulfides[5] suggested that the brominations might have yielded similar products. Since Gregg and Blood reported that trityl aryl sulfides yield arenesulfonyl bromides and triphenylcarbinol on bromination, attempts were made to identify similar products from the *t*-butyl sulfide brominations.

In a study of products formed in the bromimetric titration of 1,2-bis(*t*-butylthio)ethane, 1,2-ethanedisulfonic acid was isolated in 53% yield. The acid was identified through its aniline and S-benzylisothiouronium salts. In addition, vapor phase chromatography (v.p.c.) established that *t*-butyl alcohol was formed during the titration in at least 20% yield.

The products formed in the bromimetric titration of *t*-butyl phenyl sulfide also were investigated. In this study, the oxidation was conducted stepwise. Reaction of the sulfide with 1 equiv. of oxidizing agent produced diphenyl disulfide in 73% yield; subsequent oxidation of the disulfide with 5 equiv. of bromide–bromate reagent per sulfur atom led to the formation of benzenesulfonyl bromide. This latter product was characterized by conversion to the corresponding amide, the derivative being isolated in 62% yield, based on the starting disulfide. The identity of the amide was established by melting point and by comparing its infrared spectrum with that of authentic benzenesulfonamide. Vapor phase chromatography established that *t*-butyl alcohol was present in the reaction mixture, in about 20% yield, after 2 equiv. of

(1) (a) Abstracted from M.S. theses submitted by C. R. Strauss, 1963, and H. G. Guay, 1961, to the University of Akron; (b) presented before the Division of Analytical Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1951.

(3) W. H. Houff and R. D. Scheutz, *Anal. Chem.*, **25**, 1258 (1953).

(4) S. Siggia and R. L. Edsberg, *ibid.*, **20**, 938 (1948).

(5) D. C. Gregg and C. A. Blood, Jr., *J. Org. Chem.*, **16**, 1255 (1951).

the bromide–bromate reagent had reacted with the sulfide.

In addition, the products from the titration of di(*t*-butyl) sulfide consumed nearly 8 equiv. of bromide–bromate reagent. Sulfuric acid was found to be a major product in this case. The sulfuric acid was converted to barium sulfate, and the latter product was identified by X-ray diffraction. Based on the starting sulfide, barium sulfate was obtained in 68.8% yield.

Discussion

The results obtained in this study indicate the bromination of *t*-butyl sulfides proceeds similarly to that of trityl sulfides according to the following reactions.

$$2t\text{-BuSR} + Br_2 \longrightarrow RS\text{–}SR + (2t\text{-BuBr})$$

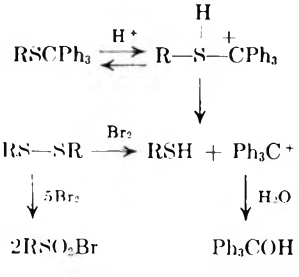
$$RS\text{–}SR + 5Br_2 + 4H_2O \longrightarrow 2RSO_2Br + 8HBr$$

$$RSO_2Br + H_2O \longrightarrow RSO_3H + HBr$$

Although aryl *t*-butyl sulfides yield arenesulfonyl bromides and alkyl *t*-butyl sulfides yield alkanesulfonic acids when brominated under the conditions of the Siggia–Edsberg procedure, this difference in behavior is probably not a result of the bromination reaction. Instead, it is believed that alkanesulfonyl bromides are intermediates in the formation of the sulfonic acids. Whether sulfonyl bromides or sulfonic acids are isolated from the bromination experiments would, of course, depend on the stability of the sulfonyl bromide. Since Johnson and Sprague[6] already have commented on the limited stability of alkanesulfonyl bromides in water, it is not surprising that an alkanesulfonic acid was obtained from the alkyl *t*-butyl sulfide experiment.

The inclination of *t*-butyl and trityl sulfides to consume 6 equiv. of bromine in the Siggia–Edsberg procedure, yielding sulfonyl bromides or sulfonic acids, is attributed to the tendency of *t*-butyl and trityl groups to form relatively stable carbonium ions in ionizing solvents. Thus, if solvolytic forces can facilitate the formation of such ions during the bromimetric titration of tertiary sulfides, then the remaining sulfur fragment is free to undergo advanced oxidation.

Gregg and Blood concluded that aryl trityl sulfides were not stable to the conditions of the Siggia–Edsberg procedure; their conjugate acids solvolyzed in dilute acetic acid, yielding mercaptans and triphenylcarbinol. Subsequent oxidation of the mercaptan to sulfonyl bromide required 6 equiv. of bromine. The instability of tertiary sulfides in acid media has been reported by Harnish and Tarbell[7,8] and one is tempted to assume that the oxidation of *t*-butyl sulfides proceeds by the same path as that of trityl sulfides. However, considerable evidence is available to indicate that *t*-butyl sulfides are more stable to acid than are trityl sulfides. Thus, the cleavage of *t*-butyl phenyl sulfide with aluminum bromide in chlorobenzene, while observable, is still considerably slower than that of trityl phenyl sulfide; *t*-butyl phenyl sulfide does not react with iodine under conditions in which trityl phenyl sulfide is rapidly converted to diphenyl disulfide; and all attempts[9,10] to prepare trityl sulfoxides or sulfones have failed, whereas *t*-butyl sulfones are easily prepared from corresponding sulfides by reaction with hydrogen peroxide.[11]



In addition, results obtained in our own work and that of others[12] indicate that *t*-butyl sulfides do not solvolyze fast enough in acetic acid–hydrogen chloride solutions to account for the results obtained in the bromimetric titration. For example, the concentration of *t*-butyl alcohol in the titration mixtures is considerably greater at the end of a bromimetric titration than it is at the beginning, regardless of how long the mixture has been allowed to stand prior to titration. Also, 1,2-bis(*t*-butylthio)ethane has been oxidized to the corresponding disulfone in about 60% yield using hydrogen peroxide in either acetic acid solution or in

$$t\text{-BuSCH}_2\text{CH}_2\text{S}(t\text{-Bu}) \xrightarrow[\text{HOAc}]{H_2O_2} t\text{-BuSO}_2\text{CH}_2\text{CH}_2\text{SO}_2(t\text{-Bu})$$

acetic acid containing a small amount of hydrogen chloride. Had the disulfide solvolyzed in the presence of strong acid, the yield of disulfone would have been considerably different in the two cases.

It therefore seems most reasonable to assume that the solvolysis process occurring in the *t*-butyl sulfide titrations involves bromosulfonium ions, as is illustrated in the following scheme.

$$t\text{-BuSR} + Br_2 \longrightarrow \left[t\text{-Bu}\!-\!\overset{+}{S}(Br)\!-\!R\right]Br^- \longrightarrow RSBr + t\text{-Bu}^+ + Br^-$$

$$t\text{-BuSR} + RSBr \longrightarrow \left[t\text{-Bu}\!-\!\overset{+}{S}(SR)\!-\!R\right]Br^- \longrightarrow RSSR + t\text{-Bu}^+ + Br^-$$

Bromosulfonium bromides are considered to be intermediates in the bromination of sulfides[13] and similar intermediates are known to be unstable when tertiary alkyl groups are bonded to sulfur.[14] Furthermore, a number of reactions related to those proposed have been reviewed by Tarbell and Harnish.[15] Most interesting of these are studies on the chlorination of aryl alkyl sulfides, in which chlorosulfonium chlorides are obtained in nonpolar solvents, but in which arenesulfonyl chlorides are obtained in ionizing solvents.[16,17] In certain cases, the chlorosulfonium chlorides were observed to decompose to alkyl chlorides and arene-

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(13) R. C. Fuson, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 576.
(14) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 424.
(15) D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 31 (1951).
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sulfenyl chlorides. The chlorosulfonium chlorides also were demonstrated to be intermediates in the conversion of sulfides to sulfonyl chlorides in ionizing media.

Although tertiary sulfides do not behave like primary and secondary sulfides in the Siggia–Edsberg procedure, their reactions with bromine are rapid and they seem to involve rather exact stoichiometry. With the exception of di(*t*-butyl) sulfide, all the tertiary sulfides listed in Table I consumed approximately 6 equiv. of bromine per atom of sulfur. Assuming the titration of *t*-alkyl sulfides to require 6 equiv. of reagent per atom of sulfur, the determinations summarized in Table I accounted for 97–99% of the sulfide analyzed in most cases. Di(*t*-butyl) sulfide, a a compound containing two *t*-butyl groups, might have been expected to consume 8 equiv. of reagent, yielding sulfuric acid as a final product. The amount of sulfuric acid formed in this titration correlated very nicely with the amount of bromine consumed.

In conclusion, two types of behavior are observed in the bromimetric determination of sulfides. Primary and secondary sulfides are oxidized to the corresponding sulfoxides through the consumption of 2 equiv. of bromine; tertiary alkyl sulfides are oxidized to sulfonyl bromides through the consumption of 6 equiv. of bromine. Thus far, the sulfides studied have cleanly followed only one course of reaction and their analysis by bromimetric procedures has been possible. However, it is certainly possible that sulfides will eventually be encountered which undergo both oxidations simultaneously. The analysis of such sulfides will be very sensitive to experimental conditions and will most likely be unsuccessful by this particular procedure.

Experimental

Materials.—Dimethyl sulfide, di-*n*-propyl sulfide, di-*n*-butyl sulfide, and di-*t*-butyl sulfide were obtained from commercial sources and were used as received. Benzyl *t*-butyl sulfide, *t*-butyl phenyl sulfide, *t*-butyl β-chloroethyl sulfide, and *t*-butyl β-hydroxyethyl sulfide were prepared by literature procedures. The properties of the purified materials are summarized: *t*-BuS–$CH_2C_6H_5$, b.p. 81–83° (1.5 mm.), $n^{20}D$ 1.5305 [lit.[11] b.p., 129–131° (21 mm.)]; *t*-BuS–C_6H_5, b.p. 69–72° (5 mm.), $n^{20}D$ 1.5218 [lit.[18] b.p. 73° (5 mm.), $n^{20}D$ 1.5335]; *t*-BuS–CH_2CH_2Cl, b.p. 82.0–83.0° (30 mm.), $n^{20}D$ 1.4822 [lit.[19] b.p. 81–82° (30 mm.)]; *t*-BuS–CH_2CH_2OH, b.p. 101.5°–102.5° (27 mm.), $n^{20}D$ 1.4748 [lit.[9] b.p. 111–114° (45 mm.), $n^{24}D$ 1.4742].

In addition, the following sulfides, which were synthesized by conventional Williamson procedures, were characterized before being studied further: *t*-BuS–CH_2CH_2S–(*t*-Bu), b.p. 133–135° (30 mm.), $n^{20}D$ 1.4698, d^{20}_4 0.9247 [*Anal.* Calcd. for $C_{10}H_{22}S_2$: C, 58.16; H, 10.75; S, 31.08. Found: C, 58.92; H, 10.74; S, 30.61.]; *t*-BuS–$CH_2CH_2CH_2CH_3$, b.p. 96.5–98.0°, $n^{20}D$ 1.4483 [*Anal.* Calcd. for $C_8H_{18}S$: C, 65.67; H, 12.39; S, 21.91. Found: C, 65.46; H, 12.61; S, 22.61.].

Analytical Procedure.—A sample containing 1–2 mmoles of sulfide was weighed into a 250 ml. erlenmeyer flask and dissolved in a mixture of glacial acetic acid (40 ml.) and water (10 ml.). After being acidified by the addition of 3 ml. of concentrated hydrochloric acid, the solution was titrated with standard bromide–bromate reagent until a stable bromine color, lasting at least 5–10 sec. was noted. A solvent blank was determined to correct for the amount of reagent required to give a visible bromine color.

A study of titration variables showed that the best results were obtained when the titration was conducted at elevated temperatures and when hydrochloric acid was used as the acidifying agent.

(18) V. N. Ipatieff, H. Pines, and B. S. Friedman, *J. Am. Chem. Soc.*, **60**, 73 (1939).

(19) C. D. Hurd and K. Wilkenson, *ibid.*, **71**, 3429 (1949).

TABLE II

EFFECT OF WATER CONTENT ON THE TITRATION OF 1,2-BIS(*t*-BUTYLTHIO)ETHANE WITH BROMATE–BROMIDE REAGENT

Ml. of water/g. of sulfide	Equiv. of bromine consumed per sulfur atom
38.8[a]	0.81
15.2	6.08
4.4	6.19
0.0	6.12

[a] Corresponds to the titration conditions recommended by Siggia and Edsberg.

TABLE III

EFFECT OF MINERAL ACIDS ON THE TITRATION OF 1,2-BIS(*t*-BUTYLTHIO)ETHANE WITH BROMIDE–BORATE REAGENT

Acid used	Ml. of water/g. of sulfide	Equiv. of bromine per sulfur atom
HCl	4.4	6.19
H_2SO_4	2.2	0.21
HNO_3	3.2	0.28

TABLE IV

EFFECT OF TEMPERATURE ON THE TITRATION OF *t*-BUTYL SULFIDES

Sulfide	Temp., °C.	Equiv. of bromine consumed per sulfur atom
$(t\text{-BuSCH}_2)_2$	25	6.19
	60	6.00
$t\text{-BuSCH}_2CH_2OH$	25	6.15
	80	5.86
	80	5.82
$t\text{-BuSCH}_2CH_2Cl$	80	5.85
$(n\text{-Bu})_2S$	25	2.11
	80	1.98

The water content of the titration medium did not influence the results provided it was not high enough to make the titration mixture heterogeneous. The results of these studies are summarized in Tables II–IV.

Reaction of 1,2-Bis(*t*-butylthio)ethane with Bromide–Bromate Reagent.—A solution of 1,2-bis(*t*-butylthio)ethane (3.00 g., 14.5 mmoles) in a mixture of glacial acetic acid (150 ml.), water (5 ml.), and concentrated hydrochloric acid (5 ml.) was titrated at 80° with 1.00 *N* bromide–bromate reagent until a bromine color lasting 10 sec. was noted. This macrotitration required 174.5 ml. of the reagent, and this corresponded to the consumption of 12.0 equiv. of bromine per mole of the disulfide. The reaction mixture was concentrated to about 100 ml. and then passed through a Dowex 50 ion-exchange bed to remove inorganic salts. The solution was then concentrated further to yield 1.7 g. (53%) of 1,2-ethanedisulfonic acid in the form of white crystals. The crystals were sensitive to air and were best stored in a moist condition. The acid was identified through its aniline salt (m.p. 270–280° dec., lit.[20] m.p. 270° dec.) and S-benzylisothiouronium salt (m.p. 196–199°, lit.[21] m.p. 199–202°) derivatives. The infrared spectrum of the aniline salt was identical with that of authentic material and a mixture melting point of the S-benzylisothiouronium salt with authentic material was undepressed.

In another experiment, the titration mixture was made alkaline and extracted with ether. Examination of the ether extract *via* v.p.c. indicated the presence of *t*-butyl alcohol in approximately 20% of the theoretical amount.

Reaction of *t*-Butyl Phenyl Sulfide with Bromide–Bromate Reagent.—A solution of *t*-butyl phenyl sulfide (2.82 g., 0.169 mmole) in a mixture of glacial acetic acid (200 ml.), water (12 ml.), and concentrated hydrochloric acid (12 ml.) was treated with 2 equiv. of bromide–bromate reagent at 60° during 5 min. The reaction mixture was poured into 800 ml. of distilled water and

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(21) W. E. Truce and M. M. Boudakian, *J. Am. Chem. Soc.*, **78**, 2755 (1956).

the resulting solution was cooled in ice. White crystals of diphenyl disulfide separated almost immediately. These were washed with dilute alkali, filtered, and dried in a desiccator. The yield was 1.35 g. (73%), m.p. 60.4–60.9°, lit.[22] m.p. 61.5°. A mixture melting point was undepressed. In another experiment, the titration mixture was made alkaline and extracted with ether. Examination of the ether extract *via* v.p.c. indicated the presence of *t*-butyl alcohol in about 20% of the theoretical amount.

Reaction of Diphenyl Disulfide with Bromide–Bromate Reagent.—Diphenyl disulfide (0.3 g., 1.37 mmoles) was dissolved in a mixture of glacial acetic acid (50 ml.) and concentrated hydrochloric acid (2 ml.), and the solution was heated to 80°. With stirring, 13.8 ml. of 1.0 *N* bromide–bromate (13.8 mequiv.) was added to the hot solution. The reaction mixture was then quickly cooled to room temperature, diluted with 100 ml. of distilled water, and extracted twice with 20-ml. portions of benzene. Concentrated ammonia solution was then added to the benzene extract and the mixture was momentarily brought to reflux. After cooling, the aqueous phase was separated and allowed to evaporate at room temperature. Crystals of benzenesulfonamide (0.262 g. 61.6%) which separated overnight were filtered and dried in a desiccator, m.p. 151–152°, lit.[23] m.p. 150–151°. The infrared spectra of the product was identical with that of authentic benzenesulfonamide.

Reaction of Di(*t*-butyl) Sulfide with Bromide–Bromate Reagent.—A solution of di(*t*-butyl) sulfide (0.2390 g., 1.632 mmoles) in a mixture of glacial acetic acid (50 ml.) and concentrated hydrochloric acid (4 ml.) was treated with 116.5 ml. of 0.0995 *N* bromide–bromate reagent for 5 min. at room temperature. The pH of the reaction mixture was then adjusted to 6.5 with 25% sodium hydroxide solution.

An aqueous solution containing barium chloride (0.5 g.) was added to the reaction mixture and a white precipitate immediately appeared. The reaction mixture was digested for 0.5 hr. at about 60°. The precipitate was washed by decantation using distilled water. The precipitate was separated from the last traces of water by drying at 110°, after which it was heated to 1000° for 1 hr. in an open crucible suspended above a Fisher burner. The weight of the sample remained essentiallly constant during this latter treatment. The product, 0.2621 g. (1.12 mmoles), was identified as barium sulfate by its X-ray diffraction pattern.

Oxidation of 1,2-Bis(*t*-butylthio)ethane with Hydrogen Peroxide.—A solution of 1,2-bis(*t*-butylthio)ethane (1.006 g., 4.39 mmoles) in glacial acetic acid (50 ml.) was allowed to stand for 24 hr. The solution was then heated to 60° and a 10% excess of 30% hydrogen peroxide (2.5 ml.) was added dropwise. After the addition was complete, the mixture was heated an additional 0.5 hr. at 60°. The solution was then carefully evaporated to dryness at 40–60° and the residue was recrystallized from 95% ethanol to yield white crystals of 1,2-bis(*t*-butylsulfonyl)ethane, 0.8485 g. (64.6%), m.p. 228–230°, lit.[24] m.p. 230–231°.

Anal. Calcd. for $C_{10}H_{22}O_4S_2$: C, 44.42; H, 8.21; S, 23.70. Found: C, 44.72; H, 7.82; S, 22.96.

When this experiment was repeated in the presence of concentrated hydrochloric acid (6 ml.), the yield of recrystallized sulfone was 54.7%.

(22) W. Steinkopf, I. Schubart, and S. Schmidt, *Ber.*, **61**, 680 (1928).
(23) H. F. Whalen and L. W. Jones, *J. Am. Chem. Soc.*, **47**, 1356 (1925).
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The Reduction of Sulfur-Containing Functional Groups with Triphenyltin Hydride

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The reducing action of triphenyltin hydride on a variety of sulfur-containing functional groups has been studied. Aryl disulfides are cleaved at the S–S bond to give triphenyltin aryl sulfide, $(C_6H_5)_3SnSAr$. The allyl C–S bond in $(C_6H_5CH_2)_2S$, dibenzyl sulfide, and $(C_6H_5CH_2S)_2$, benzyl disulfide, is cleaved to give toluene. Thiophenols and methyl mercaptan evolve hydrogen and give the mixed sulfides. Thiobenzophenone is decolorized in the cold and on heating produces diphenylmethane. Benzenesulfonic acid gives hydrogen and triphenyltin benzenesulfonate. Benzenesulfinic acid and benzenesulfonyl chloride both give triphenyltin benzenesulfinate, hydrogen, and triphenyltin chloride, respectively. The aryl C–S bond is not reduced (Ph_2S, thianthrene) and diphenyl sulfone and diphenyl sulfoxide are not reduced. Catalytic effects of 2,2′-azobis(2-methylpropionitrile) and of triphenylborine were studied.

The purpose of this investigation is to report on the use of triphenyltin hydride as a reducing agent for sulfur functions. Only three previous reports in this area have been made: J. G. Noltes and G. J. M. van der Kerk have reported that allyl mercaptan is converted to propylene while triphenyltin hydride is converted to bis(triphenyltin) sulfide[5] and also that vinyl sulfone and sulfoxide[6] are reduced; Lorenz and Becker have reported that 1-naphthyl and phenyl isothiocyanates are converted to the corresponding aryl isocyanide and N-methylarylamine.[7] The reductions attempted here include aromatic and aliphatic mercaptans and related compounds, a sulfone and a sulfoxide, a sulfinic acid and a sulfonic acid and certain of their derivatives, and carbon disulfide and hydrogen sulfide.

The Aromatic C–S Bond.—No aromatic C–S bond was cleaved by triphenyltin hydride. Thus, neither diphenyl sulfide nor thianthrene reacted. Phenyl disulfide did react, but only to give triphenyltin phenyl sulfide, reduction having taken place only at the S–S bond (eq. 1). Thiophenol and 2-thionaphthol reacted,

$$C_6H_5SSC_6H_5 + 2(C_6H_5)_3SnH \longrightarrow 2(C_6H_5)_3SnSC_6H_5 + H_2 \quad (1)$$

but only at the S–H bond, producing the corresponding triphenyltin aryl sulfide and hydrogen (eq. 2).

$$ArSH + (C_6H_5)_3SnH \longrightarrow ArSSn(C_6H_5)_3 + H_2 \quad (2)$$

$$Ar = C_6H_5, \text{ 2-naphthyl}$$

Benzenesulfenyl chloride reacted spontaneously to give triphenyltin phenyl sulfide in yields as high as 95% (eq. 3).

$$C_6H_5SCl + 2(C_6H_5)_3SnH \longrightarrow (C_6H_5)_3SnCl + (C_6H_5)_3SnSC_6H_5 + H_2 \quad (3)$$

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(4) To whom inquiries should be directed.
(5) Reports of Tin Research Institute, "Functionally Substituted Organotin Compounds," 1958, pp. 73, 115.
(6) J. G. Noltes and G. J. M. van der Kerk, *Chem. Ind.* (London), 294 (1959). In this report the products of the reduction were not established.
(7) D. H. Lorenz and E. I. Becker, *J. Org. Chem.*, **28**, 1707 (1963).

In comparison with these results, lithium aluminum hydride ($LiAlH_4$) cleaves disulfides, but also does not hydrogenolyze the aromatic C–S bond.[8,9] In contrast to the reactions cited for thiophenol and 2-thionaphthol, lithium aluminum hydride does not react. *p*-Toluenesulfenyl chloride reacts with lithium aluminum hydride to give the disulfide in 89% yield.[10]

The Aliphatic C–S Bond.—Benzyl disulfide reacted with triphenyltin hydride to give bis(triphenyltin) sulfide, toluene, hydrogen sulfide, and benzyl mercaptan, thus demonstrating that the benzyl C–S bond was cleaved (eq. 4).

$$(C_6H_5CH_2S)_2 + (C_6H_5)_3SnH \longrightarrow (C_6H_5)_3SnSSn(C_6H_5)_3 + C_6H_5CH_3 + C_6H_5CH_2SH + H_2S \quad (4)$$
(trace)

Benzyl mercaptan reacted to give toluene, hydrogen sulfide, and bis(triphenyltin) sulfide (eq. 5). The

$$2C_6H_5CH_2SH + 2(C_6H_5)_3SnH \longrightarrow (C_6H_5)_3SnSSn(C_6H_5)_3 + 2C_6H_5CH_3 + H_2S \quad (5)$$

C–S bond of benzyl sulfide also was cleaved to give toluene and bis(triphenyltin) sulfide (eq. 6). Thio-

$$C_6H_5CH_2SCH_2C_6H_5 + (C_6H_5)_3SnH \longrightarrow (C_6H_5)_3SnSSn(C_6H_5)_3 + C_6H_5CH_3 \quad (6)$$

benzophenone was decolorized at room temperature and then, after heating at 145° for 4 hr., was converted to diphenylmethane (eq. 7).

$$C_6H_5\overset{\overset{S}{\|}}{C}C_6H_5 + 2(C_6H_5)_3SnH \longrightarrow (C_6H_5)_2CH_2 + (C_6H_5)_3SnSSn(C_6H_5)_3 \quad (7)$$

Carbon disulfide reacted to give bis(triphenyltin) sulfide, but in poor yield (13%). Other products were not identified. The S–H bond of methyl mercaptan was not cleaved even at 160°.

$$CS_2 + (C_6H_5)_3SnH \longrightarrow (C_6H_5)_3SnSSn(C_6H_5)_3 \quad (8)$$

Acids and Their Derivatives.—The reaction of triphenyltin hydride and benzenesulfonic acid takes place rapidly to give triphenyltin benzenesulfonate (89%) and hydrogen (eq. 9). The product was characterized

$$C_6H_5SO_3H + (C_6H_5)_3SnH \longrightarrow C_6H_5SO_3Sn(C_6H_5)_3 + H_2 \quad (9)$$

by saponification which produced hexaphenylstannoxane and sodium benzenesulfonate (eq. 10 and 11).

$$C_6H_5SO_3Sn(C_6H_5)_3 + NaOH \longrightarrow C_6H_5SO_3Na + (C_6H_5)_3SnOH \quad (10)$$

$$2(C_6H_5)_3SnOH \overset{\text{heat}}{\rightleftharpoons} (C_6H_5)_3SnOSn(C_6H_5)_3 + H_2O \quad (11)$$

With benzenesulfinic acid, triphenyltin hydride produced triphenyltin benzenesulfinate in a vigorous exothermic reaction when no solvent was employed; in benzene as solvent the cessation of effervescence (hydrogen) was used visually to mark the end of the reaction (eq. 12). The yield varied from 75–85%.

$$C_6H_5SO_2H + (C_6H_5)_3SnH \longrightarrow C_6H_5SO_2Sn(C_6H_5)_3 + H_2 \quad (12)$$

The same product was obtained in 85% yield from the reaction of triphenyltin hydride with benzenesulfonyl chloride (eq. 13). In the latter reaction hydrogen and triphenyltin chloride were obtained.

$$C_6H_5SO_2Cl + 2(C_6H_5)_3SnH \longrightarrow C_6H_5SO_2Sn(C_6H_5)_3 + (C_6H_5)_3SnCl + H_2 \quad (13)$$

The question whether the tin is attached to oxygen or to sulfur in triphenyltin benzenesulfinate arose. Spectral evidence was not satisfactory because of the absence of suitable models. The argument that it is formed from either benzenesulfinic acid or benzenesulfonyl chloride loses effectiveness since benzenesulfinic acid may be an intermediate in the reaction. However, sodium hydroxide saponifies the product producing hexaphenylstannoxane and sodium benzenesulfinate, which facts point to a Sn–O rather than a Sn–S bond (eq. 14).

$$2C_6H_5SO_2Sn(C_6H_5)_3 - 2NaOH \longrightarrow 2C_6H_5SO_2Na + [(C_6H_5)_3Sn]_2O + H_2O \quad (14)$$

For comparison, it is of interest that lithium aluminum hydride reduces sulfonyl halides to the corresponding sulfinic acids, or disulfides, or mercaptans depending upon the conditions of the reaction.[8,10]

Miscellaneous Compounds.—Diphenyl sulfone, diphenyl sulfoxide, and methyl *p*-toluenesulfonate were not reduced. In contrast, lithium aluminum hydride is known to convert sulfones and sulfoxides to the corresponding sulfides[11,12]; sulfonate esters are displaced on the alcohol C–O bond to give the hydrocarbon derived from the alcohol and the sulfonic acid.[8]

Recently Kuivila, Menapace, and Warner have reported that 2,2′-azobis(2-methylpropionitrile) catalyzes the hydrogenation of halides.[13] Lorenz, *et al.*,[14] have shown that dibenzoyl peroxide and triphenylborine can also catalyze the hydrogenolysis. A study of the effect of triphenylborine and of 2,2′-azobis(2-methylpropionitrile) was made here as well.

The results are summarized in Table I. With thiophenol, benzyl mercaptan, carbon disulfide, phenyl disulfide, and benzyl disulfide, the yields were appreciably improved using either 2,2′-azobis(2-methylpropionitrile) or triphenylborine. With benzyl disulfide, triphenylborine was more effective than with 2,2′-azobis(2-methylpropionitrile). With methyl mercaptan, reaction took place to give triphenyltin methyl sulfide and hydrogen. Neither catalyst caused the unreactive diphenyl sulfone, diphenyl sulfoxide, methyl *p*-toluenesulfonate, thianthrene, or diphenyl sulfide to react. In considering the positive results, it may again be inferred that, as for the halides,[13,14] the hydrogenolysis reaction with sulfur functions may be catalyzed by cationic or radical catalysts (see below).

Mechanism.—The mechanism of the hydrogenolysis reaction has been examined.[13,14] Kuivila, Menapace, and Warner have claimed a free-radical reaction for catalysis with 2,2′-azobis(2-methylpropionitrile) and have presented a mechanism. Recently,[14] benzoyl peroxide also was shown to catalyze the hydrogenolysis reaction. As an example of a Lewis acid catalyst, triphenylborine was shown to catalyze the reaction for

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(9) T. L. Cairns, G. L. Evans, A. W. Larcher, and B. C. McKusick, *J. Am. Chem. Soc.*, **74**, 3982 (1952).

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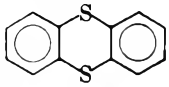
(12) F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.*, **73**, 2251 (1951).

(13) H. G. Kuivila, L. W. Menapace, and C. R. Warner, *ibid.*, **84**, 3584 (1962).

(14) D. H. Lorenz, P. Shapiro, A. Stern, and E. J. Becker, *J. Org. Chem.*, **28**, 2332 (1963).

TABLE I

HYDROGENOLYSIS WITH TRIPHENYLTIN HYDRIDE

Reactants	Conditions: Temp., °C.	Conditions: Time, hr.	Products	M.p. or B.p., °C.	% yield: No catalyst	% yield: AIBN[a] catalyst	% yield: $(Ph)_3B$[b] catalyst
C_6H_5SH	85	2	$(C_6H_5)_3SnSC_6H_5$, H_2	99.4–100.5	67.5	78.9	85.0
$C_6H_5SSC_6H_5$	90	1	$(C_6H_5)_3SnSC_6H_5$, H_2	...	88.0	83.5	91.0
$2C_{10}H_7SH$	120	3	$2C_{10}H_7SSn(C_6H_5)_3$, H_2	74.5–76.0	68.0	72.2	78.7
$C_6H_5CH_2SSCH_2C_6H_5$	130	2	$(C_6H_5)_3SnSSn(C_6H_5)_3$, H_2S, $C_6H_5CH_3$	144.0–144.6	11.6	16.8	78.8
CH_3SH	160	3	$(C_6H_5)_3SnSCH_3$, H_2	94.6–95.4	0	46.6	32.8
$C_6H_5CH_2SH$	85	5	$(C_6H_5)_3SnSSn(C_6H_5)_3$, H_2S, $C_6H_5CH_3$	144.0–144.6	0	54.7	60.0
$C_6H_5CH_2SCH_2C_6H_5$	130	3	$(C_6H_5)_3SnSSn(C_6H_5)_3$, $C_6H_5CH_3$	...	27.3	38.2	41.6
CS_2	155	6	$(C_6H_5)_3SnSSn(C_6H_5)_3$	...	13.0	45.6	54.0
$(C_6H_5)_2SO_2$	130	5			0	0	0
$(C_6H_5)_2SO$	130	5			0	0	0
	130	3			0	0	0
$C_6H_5SC_6H_5$	150	9			0	0	0
$C_6H_5CSC_6H_5$	145	4	$C_6H_5CH_2C_6H_5$	264.5	68.0		
			$(C_6H_5)_3SnSSn(C_6H_5)_2$	114.0–144.6	58.5		
H_2S	130	5	...	...	25.7		
	150	0.5					
$C_6H_5SO_3H$	Spontaneous		$(C_6H_5)_3SnOSO_2C_6H_5$, H_2	253.0–255.0	88.7		
$C_6H_5SO_2H$	...		$(C_6H_5)_3SnOSOC_6H_5$, H_2	228.5–230.5	99.6		
$C_6H_5SO_2Cl$	...		$(C_6H_5)_3SnCl$, H_2	103–104	100		
C_6H_5SCl	...		$(C_6H_5)_3SnCl$, H_2	...	78		
			$(C_6H_5)_3SnSC_6H_5$	99.4–100.5	60		

[a] 2,2′-Azobis(2-methylpropionitrile). [b] Triphenylborine.

halides[14] and, in the present work, for sulfur functions. However, certain new considerations make the assumption of Lewis acid catalysis suspect.

When triphenylborine was first prepared by Krause and Nitsche,[15] it was reported to react rapidly with oxygen. Recently, Kolesnikov,[16-18] Ashikari,[19-21] Welch,[22] Furukawa,[23,24] and Fordham and Sturm[25] have reported that triethylborine or tributylborine will polymerize vinyl monomers and that the reaction is most likely free radical. If the same considerations hold by analogy with triphenylborine, then the catalytic effect we have observed may indeed be simply another free-radical reaction to add to those reported by Kuivila[13] and also by Lorenz and Becker.[14] This point is under further investigation.

Experimental

Phenyl Sulfide.—A mixture of phenyl sulfide (1.8 g., 9.67 mmoles) and triphenyltin hydride (7.5 g., 0.0214 mole) in an ampoule which was sealed *in vacuo* was heated at 150° for 9 hr. Distillation of the reaction mixture afforded only phenyl sulfide, b.p. 296°.

Thianthrene.—Triphenyltin hydride (3.51 g., 0.0100 mole) and thianthrene (1.08 g., 5.00 mmoles) were allowed to react at 130° for 3 hr. with stirring and under nitrogen atmosphere. Thianthrene was isolated quantitatively.

Phenyl Disulfide.—A mixture of triphenyltin hydride (7.0 g., 0.0199 mole) and phenyl disulfide (2.0 g., 9.16 mmoles) was allowed to react in nitrogen atmosphere with stirring at 90° and 1 hr. The mixture solidified when cooled. After recrystallization from *n*-hexane, triphenyltin phenyl sulfide was isolated, m.p. 98.0–99.5°, 7.4 g. (0.0162 mole, 88%).

Thiophenol. 1.—Triphenyltin hydride (7.5 g., 0.0214 mole) and thiophenol (4.0 g., 0.0366 mole) were allowed to react under nitrogen at 85° for 6 hr. Hydrogen was given off during the reaction, and the reaction mixture solidified on cooling. Two recrystallizations from petroleum ether and one from a 1:1 mixture of dioxane–petroleum ether (b.p. 60–70°) gave colorless triphenyltin phenyl sulfide, melting at 92.2–93.0°. After drying *in vacuo* at 80°, it melted at 99.4–100.5° (8.0 g., 0.0174 mole, 81.3%).

Anal. Calcd. for $C_{24}H_{20}SSn$: C, 62.78; H, 4.39; S, 6.98; Sn, 25.85; mol. wt., 459.2. Found: C, 62.80; H, 4.41; S, 6.98; Sn, 25.8; mol. wt., 462 (cryoscopic in benzene).

Thiophenol. 2.—When the above reaction was run at 140° for 3 hr., beginning with triphenyltin hydride (14.0 g., 0.040 mole) and thiophenol (4.0 g., 0.0366 mole), triphenyltin phenyl sulfide was isolated, m.p. 99.4–100.5° (14.0 g., 0.0320 mole, 87%). When the reaction was run at 85° for 2 hr., the yield was 67.5% (12.40 g., 0.0270 mole).

(15) F. Krause and R. Nitsche, *Ber.*, **55**, 1262 (1922).
(16) G. S. Kolesnikov and L. S. Fedorova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 236 (1957); *Chem. Abstr.*, **51**, 11,291 (1957).
(17) G. S. Kolesnikov and L. S. Fedorova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 906 (1958); *Chem. Abstr.*, **52**, 21,216 (1958).
(18) G. S. Kolesnikov and N. V. Klimentova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 652 (1957); *Chem. Abstr.*, **51**, 15,458 (1957).
(19) J. N. Ashikari and A. Nishimura, *J. Polymer Sci.*, **31**, 247 (1958).
(20) J. N. Ashikari, *ibid.*, **31**, 250 (1958).
(21) J. N. Ashikari, *ibid.*, **31**, 641 (1958).
(22) E. J. Welch, *ibid.*, **61**, 243 (1962).
(23) J. Furukawa and T. Tsuruta, *ibid.*, **28**, 227 (1958).
(24) J. Furukawa, T. Tsuruta, R. Sokata, and K. Ito, *Makromol. Chem.*, **30**, 109 (1959).
(25) J. W. L. Fordham and C. L. Sturm, *J. Polymer Sci.*, **33**, 503 (1958).

2-Naphthalenethiol.—Triphenyltin hydride (7.0 g., 0.0199 mole) and 2-naphthalenethiol (3.2 g., 0.020 mole) in 10 ml. of benzene were heated at 120° for 3 hr. Hydrogen was given off during the reaction. After 15 ml. of *n*-hexane was added to the cooled reaction mixture, triphenyltin 2-naphthyl sulfide precipitated. After recrystallization from *n*-hexane, it melted at 74.5–76.0° (6.92 g., 0.0136 mole, 68%).

Anal. Calcd. for $C_{28}H_{22}SSn$: C, 66.04; H, 4.36; S, 6.30; Sn, 23.3; mol. wt., 509.3. Found: C, 66.00; H, 4.47; S, 6.39; Sn, 23.2; mol. wt., 515 (ebullioscopic with benzene).

Benzenesulfenyl Chloride.—Benzenesulfenyl chloride[26] was prepared as reported. Triphenyltin hydride (3.2 g., 9.12 mmoles) was added dropwise to a stirred, ice-cooled solution of benzenesulfenyl chloride (1.25 g., 8.64 mmoles) in 10 ml. of *n*-hexane. Hydrogen was given off violently and the red color discharged. At this point there was no observable change when another drop of triphenyltin hydride was added. A small sample indicated thiophenol by vapor phase chromatography (v.p.c.). An infrared band at 2550 cm.$^{-1}$ also indicated the presence of thiophenol. Evaporation of another sample to dryness afforded triphenyltin chloride. Another portion of triphenyltin hydride (5.3 g., 0.0151 mole) was added to the above reaction mixture which was heated in an oil bath at 130° for 1 hr. Hydrogen was given off during the reaction. When the mixture cooled, a precipitate was formed. The filtered solid was extracted with ethanol and the residue recrystallized from *n*-hexane to give triphenyltin phenyl sulfide, m.p. 99.4–100.6° (3.1 g., 6.74 mmoles, 78%). Evaporation of the ethanolic extract *in vacuo* yielded triphenyltin chloride, m.p. 103–104° (2.0 g., 5.2 mmoles, 60%). Other runs gave up to 95% of the sulfide.

α-Tolyl Disulfide.—Triphenyltin hydride (15.0 g., 0.0427 mole) and α-tolyl disulfide (2.46 g., 0.0100 mole) were sealed into an evacuated ampoule and heated at 160° for 3 hr. The cooled product mixture was extracted with 5 ml. of *n*-hexane. Toluene and benzyl mercaptan were found in the hexane extract by infrared spectrum and v.p.c. analysis. Hydrogen sulfide odor was detected and confirmed by acidified lead acetate test. The residual solid, which remained after the hexane extraction, was dissolved in ethyl ether, then filtered by suction, and evaporated to dryness. A white crystalline material was obtained. After two recrystallizations from a 1:3 mixture of benzene–*n*-hexane, bis(triphenyltin) sulfide was obtained (6.0 g., 8.20 mmoles, 82%), m.p. 144.0–144.6°. When a similar reaction was run at 130° for 2 hr., the yield was 11.6%.

Benzyl Mercaptan.—At 85° triphenyltin hydride did not reduce benzyl mercaptan. When triphenyltin hydride (14.0 g., 0.0399 mole) and benzyl mercaptan (4.9 g., 0.394 mole) were held at 160° for 3 hr. with stirring, hydrogen sulfide was evolved. Toluene was identified by its vapor phase chromatogram from a sample of the reaction mixture injected into the v.p.c. unit and by its infrared spectrum. Upon cooling, the reaction mixture solidified and the solid was recrystallized three times from petroleum ether. Bis(triphenyltin) sulfide was isolated (3.0 g., 4.1 mmoles, 20.8%), m.p. 144.0–144.5° (lit.[27] m.p. 141.5–143°).

Benzyl Sulfide.—A mixture of benzyl sulfide (2.14 g., 0.0100 mole) and triphenyltin hydride (3.51 g., 0.0100 mole) was heated at 130° for 3 hr. *n*-Hexane was added and crystallization took place when cooled. Bis(triphenyltin) sulfide was isolated (1.00 g., 1.365 mmoles, 27.3%), m.p. 144.0–144.5°.

Thiobenzophenone.—A mixture of triphenyltin hydride (8.0 g., 0.0228 mole) and thiobenzophenone[28] (1.4 g., 7.0 mmoles) was heated at 145° for 4 hr. It was extracted with *n*-pentane which yielded diphenylmethane (0.80 g., 4.76 mmoles, 68%) on evaporation of the pentane *in vacuo*. Recrystallization of the residue afforded bis(triphenyltin) sulfide (3.0 g., 4.1 mmoles, 58.5%), m.p. 144.0–144.5°.

Carbon Disulfide.—A mixture of triphenyltin hydride (14.0 g., 0.0300 mole) and carbon disulfide (25.0 g., 0.3283 mole) was refluxed at 155° for 6 hr. The mixture turned brown. When cooled, it solidified after 15 ml. of *n*-hexane was added. Bis(triphenyltin) sulfide was isolated, and, after recrystallization with *n*-hexane, had m.p. 144.0–145.0° (2.85 g., 3.89 mmoles, 13%).

Methanethiol.—A mixture of triphenyltin hydride (3.5 g., 0.0100 mole) and methanethiol (1.28 g., 0.0400 mole) in an evacuated ampoule was heated at 160° for 3 hr. Methyl mercaptan was left unchanged.

Benzenesulfonic Acid.—Triphenyltin hydride (3.51 g., 0.0100 mole) in 10 ml. of benzene was added with stirring to benzenesulfonic acid (1.76 g., 0.0100 mole) in an ice bath. No apparent change was observed for 25 min. When the mixture was allowed to warm to room temperature, hydrogen bubbled out and a white curdy precipitate formed. A total of 30 ml. of benzene was added during the reaction in order to ease stirring. The product on filtration by suction afforded a solid, which, after recrystallization with dioxane, melted at 253.0–255.0° (4.52 g., 8.87 mmoles, 88.7%).

Anal. Calcd. for $C_{24}H_{20}O_3SSn$: C, 56.77; H, 3.97, S, 6.43; Sn, 23.38. Found: C, 56.68; H, 4.04; S, 6.54; Sn, 22.85.

Chemical Analysis.—Two grams (3.94 mmoles) of the above product was heated with stirring with 35 ml. of 25% sodium hydroxide at 100° for 2 hr. After the solution cooled, it was filtered by suction, and the hexaphenylstannoxane collected was recrystallized from ether, m.p. 120–122° dec. (1.3 g., 1.82 mmoles 92.4%). The alkaline filtrate was acidified with 1:1 aqueous sulfuric acid, then titrated with 25% sodium hydroxide until the solution was just basic, and evaporated to dryness *in vacuo*. The white solid, which remained, was extracted with ethanol. Evaporation of the ethanol gave a solid whose infrared spectrum was superimposable on that of sodium benzenesulfonate.

Benzenesulfinic Acid. 1.—Triphenyltin hydride (3.51 g., 0.0100 mole) and benzenesulfinic acid (1.42 g., 0.0100 mole) were mixed in a 25-ml. flask. A vigorous and exothermic reaction accompanied by hydrogen evolution was observed. The reaction mixture solidified and was recrystallized twice from 1:1 mixture of chloroform–ethanol to afford 3.9 g. (7.94 mmoles, 79.4%) of colorless product, m.p. 228.5–230.5°.

Benzenesulfinic Acid. 2.—Triphenyltin hydride (1.540 g., 4.490 mmoles) was injected through a syringe to a solution of benzenesulfinic acid (0.3280 g., 2.310 mmoles) in 20 ml. of benzene with stirring. Hydrogen, 53.4 ml. (cor.) (calcd.[29] 52.65 ml.) was collected. Triphenyltin benzenesulfinate (1.1296 g., 2.300 mmoles, 99.6%) was isolated.

Anal. Calcd. for $C_{24}H_{20}O_2SSn$: C, 58.69; H, 4.10; S, 6.53; Sn, 24.16. Found: C, 58.67; H, 4.04; S, 6.40; Sn, 24.50.

Degradation of Triphenyltin Benzenesulfinate.—Triphenyltin benzenesulfinate (3.0 g., 6.12 mmoles) of 30 ml. of 25% sodium hydroxide solution were allowed to stand with stirring at 100° in an open flask for 2 hr. Bis(triphenyltin) oxide was obtained on suction filtration of the reaction mixture. After recrystallization twice from ether, it melted at 120–122° dec. (lit.[30] m.p. 124° for hexaphenylstannoxane) (1.8 g., 2.51 mmoles, 82.3%). The filtrate from above was acidified with dilute (1:1) hydrochloric acid, and then extracted twice with ether. The ethereal extract, after being washed with water, was evaporated to dryness *in vacuo* giving benzenesulfinic acid, m.p. 79.5–81.7° (lit. m.p. 82.5° for benzenesulfinic acid) (0.210 g., 15 mmoles, 15%).

Benzenesulfonyl Chloride. 1.—Triphenyltin hydride (7.0 g., 0.0200 mole) was added dropwise to benzenesulfonyl chloride (1.76 g., 0.0100 mole). Within 2 min. after the addition, violent effervescence occurred and the temperature of the reaction mixture rose to 120°. The effluent gas did not redden wet litmus paper but gave a "pop" test. When it had cooled to room temperature, 1.02 g. (2.91 mmoles) of triphenyltin hydride was added, and no further reaction was noted. About 10 ml. of *n*-pentane was added and the mixture was filtered by suction to give, after washing the solid with 5 ml. of *n*-pentane, 8.1 g. of crystalline solid starting to melt at 95°. There was no observable solubility of the solid in hot water. The crystalline product was extracted with ether and evaporation of the extract to dryness yielded triphenyltin chloride (3.50 g., 9.10 mmoles, 91%), m.p. 103–104° (recrystallized with *n*-hexane). The residue after washing with ethanol afforded triphenyltin benzenesulfinate (4.20 g., 8.56 mmoles, 85%), m.p. 228.5–230.5° (recrystallized).

Benzenesulfonyl Chloride. 2.—Triphenyltin hydride (3.0800 g., 8.600 mmoles) was injected through a syringe to a solution of benzenesulfonyl chloride (0.5142 g., 2.900 mmoles) in 10 ml. of benzene with stirring. Hydrogen,[31] 66.8 ml. (cor.) (calcd.[32]

(26) H. Lecher and F. Holschneider [*Ber.*, **57**, 757 (1924)] report b.p. 58–60° (3 mm.), $n^{30}D$ 1.6132, red liquid.

(27) J. G. Noltes and G. J. M. van der Kerk, *Chem. Ind.* (London), 294 (1959).

(28) F. H. Westheimer, R. H. Abeles, and R. F. Hutton, *J. Am. Chem. Soc.*, **79**, 712 (1957).

(29) This value is obtained by reaction 12.

(30) H. Gilman and L. A. Gist, Jr., *J. Org. Chem.*, **22**, 250 (1957).

(31) The absence of hydrogen chloride was tested by wet litmus paper.

(32) Value is based on reaction 13.

TABLE II

Phenyl sulfone, g.	Phenyl sulfone, mmoles	Triphenyltin hydride, g.	Triphenyltin hydride, mmoles	Temp., °C.	Time, hr.	Other conditions
2.0	9.16	5.0	14.2	135	3	Under nitrogen
...	...	6.5	18.5	160	2	...
...	...	...	...	130	1	...
1.5	6.87	4.8	13.7	130	5	*in vacuo*
1.48	6.78	11.9	34.0	130	1	*in vacuo*
				180	0.5	...

65.2 ml.) was collected. Triphenyltin chloride (1.120 g., 2.910 mmoles; theoretical, 1.118 g., 2.900 mmoles) and triphenyltin benzenesulfinate (1.412 g., 2.88 mmoles; theoretical, 1.424 g., 2.900 mmoles) were isolated separately.

Phenyl Sulfone.—A mixture of phenyl sulfone and triphenyltin hydride was heated in an evacuated ampoule as shown in Table II. To the cooled product, 25 ml. of ether was added and then filtered by suction. The filtrate on evaporation to dryness afforded a white solid which, after recrystallization with *n*-hexane, melted at 124.5–125.5° (lit. m.p. 125° for phenyl sulfone). The amount of phenyl sulfone reisolated was nearly 100% in all cases.

Phenyl Sulfoxide.—A mixture of triphenyltin hydride (7.0 g., 0.020 mole) and phenyl sulfoxide (2.0 g., 9.9 mmoles) was sealed in an evacuated ampoule and was heated at 130° for 5 hr. To the cooled product, 20 ml. of *n*-hexane was added and the mixture was filtered by suction immediately. The filtrate on standing yielded phenyl sulfoxide (2.0 g., 9.9 mmoles), m.p. 69.0–70.4°.

Methyl *p*-Toluenesulfonate.—The title compound was not reduced at 80° for 1 hr. using a ratio of 4:1 triphenyltin hydride–ester. When 11.6 g. (0.0330 mole) of triphenyltin hydride and 0.87 g. (4.72 mmoles) of methyl *p*-toluenesulfonate (7:1) were heated at 150° for 7 hr. and then at 180° for 0.5 hr. in a sealed evacuated ampoule, again there was no hydrogenation.

Reactions Catalyzed by 2,2′-Azobis(2-methylpropionitrile) or Triphenylborine Thiophenol.—Triphenyltin hydride (3.51 g., 0.0100 mole), thiophenol (1.10 g., 0.0100 mole), and 2,2′-azobis-(2-methylpropionitrile) (1.6 mg., 0.10 mmole) were mixed, then heated at 85° for 2 hr. under nitrogen. Triphenyltin phenyl sulfide (3.62 g., 7.89 mmoles, 78.9%) was isolated. When using triphenylborine as catalyst the above reaction under similar conditions yielded phenyl triphenyltin sulfide (3.90 g., 8.50 mmoles, 85.0%).

Benzyl Mercaptan.—A mixture of triphenyltin hydride (3.51 g., 0.0100 mole), benzyl mercaptan (1.24 g., 0.0100 mole), and 2,2′-azobis(2-methylpropionitrile) (1.6 mg., 0.100 mmole) was heated at 85° for 5 hr. under nitrogen. Bis(triphenyltin) sulfide (2.00 g., 2.733 mmoles, 54.7%) was isolated. When using triphenylborine as catalyst the above reaction under similar conditions yielded bis(triphenyltin) sulfide (2.20 g., 3.00 mmoles, 60%).

Benzyl Sulfide.—Triphenyltin hydride (3.51 g., 0.0100 mole), benzyl sulfide (2.14 g., 0.0100 mole), and 2,2′-azobis(2-methylpropionitrile) (1.6 mg., 0.100 mmole) were allowed to react at 130° for 3 hr. under nitrogen. Bis(triphenyltin) sulfide (1.40 g., 1.912 mmoles, 38.2%) was isolated. When using triphenylborine as catalyst the above reaction under similar conditions yielded bis(triphenyltin) sulfide (1.52 g., 2.078 mmoles, 41.6%).

Phenyl Disulfide.—A mixture of triphenyltin hydride (7.50 g., 0.0213 mole), phenyl disulfide (2.18 g., 0.0100 mole), and 2,2′-azobis(2-methylpropionitrile) (3.2 mg., 0.200 mmole) was heated at 90° for 1 hr. under nitrogen. Triphenyltin phenyl sulfide (7.66 g., 0.0167 mole, 83.5%) was isolated. When the above reaction was run under similar conditions using triphenylborine as catalyst, phenyl triphenyltin sulfide (8.38 g., 0.0182 mole, 91.0%) was isolated.

Carbon Disulfide.—A mixture of triphenyltin hydride (3.51 g., 0.0100 mole), carbon disulfide (7.60 g., 0.1000 mole), and 2,2′-azobis(2-methylpropionitrile) (1.6 mg., 0.100 mmole) was heated at 155° for 6 hr. Bis(triphenyltin) sulfide (1.67 g., 2.280 mmoles, 45.6%) was isolated. When the above reaction using triphenylborine as catalyst was run under similar conditions, bis(triphenyltin) sulfide (2.00 g., 2.730 mmoles, 54.6%) was obtained.

Benzyl Disulfide.—Triphenyltin hydride (7.01 g., 0.0200 mole), benzyl disulfide (1.23 g., 5.000 mmoles), and 2,2′-azobis-(2-methylpropionitrile) (2.3 mg., 0.2000 mmole) were heated at 130° for 2 hr. under nitrogen. Bis(triphenyltin) sulfide (1.20 g., 1.64 mmoles, 16.8%) was isolated. When the above reaction using triphenylborine as catalyst was run under similar conditions, bis(triphenyl) sulfide (5.62 g., 7.88 mmoles, 78.8%) was isolated.

Methyl Mercaptan.—A mixture of triphenyltin hydride (3.51 g., 0.0100 mole), methyl mercaptan (1.28 g., 0.0400 mole), and 2,2′-azobis(2-methylpropionitrile) (1.6 mg., 0.100 mmole) in a sealed evacuated Carius tube was heated at 160° for 3 hr. Triphenyltin methyl sulfide (1.85 g., 4.660 mmoles, 46.6%), m.p. 94.6–95.4° was isolated. When the above reaction was run using triphenylborine as catalyst under similar conditions triphenyltin methyl sulfide (1.30 g., 3.280 mmoles, 32.8%) was obtained.

Anal. Calcd. for $C_{19}H_{18}SSn$: C, 57.45; H, 4.58; S, 8.07; Sn, 29.90; mol. wt., 397.1. Found: C, 57.23; H, 4.77; S, 7.88; Sn, 30.03; mol. wt., 423 (ebullioscopic in CCl_4).

Diphenyl Sulfone, Diphenyl Sulfoxide, Methyl *p*-Toluenesulfonate, Thianthrene, and Diphenyl Sulfide.—Their reactions with triphenyltin hydride were repeated as described in the preceding reactions with the exception of using 2,2′-azobis(2-methylpropionitrile) or triphenylborine as catalyst. Neither catalyst had any effect on the reaction as described previously.

Configurational Relationships among Some Sulfoxides[1]

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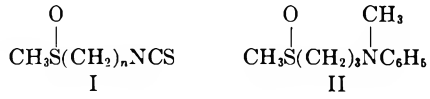
The configuration of sulfur in (−)-N-methyl-N-[3-(methylsulfinyl)propyl]aniline relative to some alkyl aryl sulfoxides and some (−)-menthyl (−)-arylsulfinates was determined using a synthetic procedure which should have general applicability. (−)-N-Methyl-N-[3-(methylsulfinyl)propyl]aniline was chosen as an optical analog of some naturally occurring levorotatory (−)-ω-(methylsulfinyl)alkyl isothiocyanates in an attempt to determine the latter's absolute configuration. While the relative configuration of these compounds was established, their absolute configuration remains uncertain.

Numerous naturally occurring sulfoxides have been isolated in recent years; most of these have in common an optically active methylsulfinyl group.[2a] The absolute configuration about sulfur was established for one of these sulfoxides, (+)-3-(methylsulfinyl)-alanine,[2b] using X-ray methods; in all of the other cases, the configuration is unknown. This article reports the results of experiments designed to determine the configuration of some isothiocyanate sulfoxides (I), where n varies from 3 to 10, which have been investigated very extensively by Kjaer and coworkers. Klyne, Day, and Kjaer[3] demonstrated that

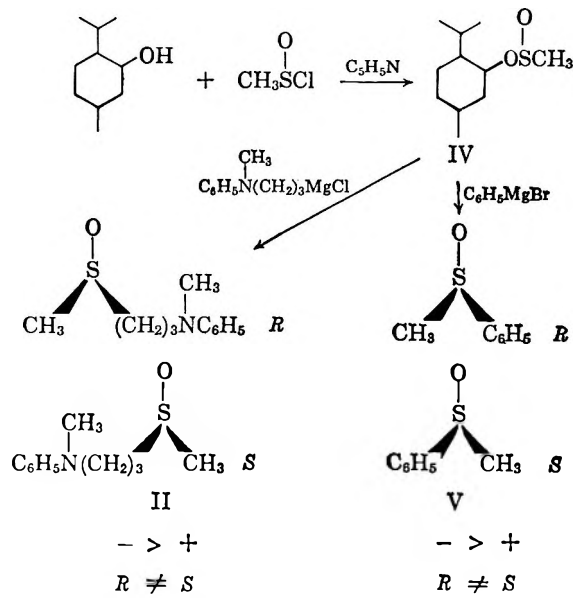


I

II

various phenylurea, phenylthiourea, and thiourea derivatives of these naturally occurring sulfoxides all gave negative plain optical rotatory dispersion (O.R.D.) curves between 600 and 300 mμ which were very similar and in some cases almost superimposable. This was interpreted to mean that the absolute configurations were identical for all of these compounds. Since a change in the value of n does not affect the sign and scarcely affects the shape of the O.R.D. curves, the functional groups at the terminal position of the alkyl chain must have very little if any influence on the sulfoxide chromophore. N-Methyl-N-[3-(methylsulfinyl)propyl]aniline (II), for this reason, should be a suitable optical analog of these naturally occurring sulfoxides. If the absolute configuration of II could be determined, a comparison of its O.R.D. curve with those obtained by Klyne, Day, and Kjaer would permit an assignment of configuration to the (−)-ω-(methylsulfinyl)alkyl isothiocyanates (I).

In order to determine the absolute configuration of the model compound II, its configuration was related to that of (−)-menthyl (−)-*p*-toluenesulfinate (III). In one of a series of important articles, Herbrandson[4] tentatively assigned the *S*-configuration[5] to sulfur in (−)-menthyl (−)-*p*-iodobenzenesulfinate. Both of these sulfinate esters should have the same absolute configurations. The validity of Herbrandson's assignment will be assumed for the moment. The synthetic procedure used to relate the N-methyl-N-[3-(methylsulfinyl)propyl]aniline (II) to (−)-menthyl (−)-*p*-toluenesulfinate (III) is shown below.



An epimeric mixture of (−)-menthyl (±)-methanesulfinate (IV) was prepared from (−)-menthol and racemic methanesulfinyl chloride. The equilibrium ratio of the amounts of the two epimers, which differ in configuration at sulfur, is not known, but probably is only a few per cent from unity. Herbrandson[4] found a 59:41 equilibrium epimer ratio for the (−)-menthyl (±)-*p*-iodobenzenesulfinates in nitrobenzene. The n.m.r. spectrum of the ester mixture included two partially separated, very sharp signals of about equal intensity. These were assigned to the protons of the two methanesulfinyl groups although long-range splitting by the axial proton has not been ruled out. This point is being investigated. Attempts to separate the two epimers by fractional distillation and by vapor phase chromatography were unsuccessful.

Addition of catalytic amounts of hydrogen chloride to the epimeric mixture should lead to equilibration of the two epimers as described by Herbrandson[4] for similar compounds. When this was done, scarcely

(1) This research was supported in part by the Public Health Service under Grant No. GM 10800.

(2) (a) B. W. Christensen and A. Kjaer, *Acta Chem. Scand.*, **17**, 846 (1963), and references cited therein; (b) R. Hine, *Acta Cryst.*, **15**, 635 (1962).

(3) W. Klyne, J. Day, and A. Kjaer, *Acta Chem. Scand.*, **14**, 215 (1960).

(4) H. F. Herbrandson and C. M. Cusano, *J. Am. Chem. Soc.*, **83**, 2124 (1961).

(5) A referee has suggested that the sulfinyl oxygen in sulfinate esters be assigned a sequence number of 32 rather than 16 since the SO bond presumably has partial double bond character. We do not agree with such a change. Both the author[6] and C. J. M. Stirling [*J. Chem. Soc.*, 5741 (1963)] have followed Herbrandson's original assignment[4] based on the concept of octet valency structures. Any change at this point would lead to confusion in the literature. In addition, configurational assignment to molecules such as sulfinyl fluorides, RS(O)F, would be confusing. Conceivably oxygen could be assigned a value of 16 or 32 and fluorine values of 19 or 38 depending on the amount of double-bonded character. We strongly urge future authors to assign configurations to tri- and tetrasubstituted sulfur on the basis of the most stable octet valency structure and not on the basis of structures involving an expanded octet for sulfur.

any change in rotation was observed. Apparently, the esters were already at or close to equilibrium. An attempt to enrich the ester mixture in the concentration of one of the epimers was undertaken successfully by adding a menthol–pyridine solution in ether to a 3 *M* excess of methanesulfinyl chloride. The ester rotation became less negative indicating enrichment in the concentration of the epimer containing the dextrorotatory sulfinate group. Mutarotation occurred, however, and over a period of a few days the equilibrium rotation was attained. This mutarotation was probably catalyzed by chloride on the laboratory glassware.[4]

The important point, however, is that the addition of an ether solution of phenylmagnesium bromide to an equilibrium mixture of esters or to a mixture slightly more dextrorotatory than the equilibrium rotation always gave methyl phenyl sulfoxide (V) in which the dextrorotatory isomer predominated over the levorotatory isomer.[6,7] Addition of the Grignard reagent prepared from N-methyl-N-(3-chloropropyl)aniline to the ester mixture always resulted in N-methyl-N-[3-methylsulfinyl)propyl]aniline (II) in which the levorotatory isomer predominated over the dextrorotatory isomer.

The reaction of the Grignard reagent with the esters is rapid compared with the rate of addition of the Grignard solution to the ester solution. A Gilman test[8] on the reaction mixture immediately after the addition of some Grignard reagent was negative; this means that a drop of added Grignard reagent was consumed before the next drop was added. The Grignard reagent possibly could react more rapidly with one epimer than another, although both epimers react rapidly compared with the rate of addition of the Grignard solution.

If the more stable epimer (present in largest concentration) reacts most rapidly, then the per cent of ester mixture which reacts has no influence on the sign of rotation of the product. If the least stable epimer reacts most rapidly, the sign of rotation of the product would depend on the per cent of reaction completed. After a certain per cent of the ester mixture had reacted, one sulfoxide enantiomer could predominate while further along toward 100% reaction the concentration of the other enantiomer formed from the less reactive but predominant epimer could overtake the originally predominant sulfoxide. Perhaps, although this seems unlikely, the relative reactivity of the epimeric esters is reversed depending on the Grignard reagent used.

Reactions in which the esters were added to the Grignard reagent rule out the last two possibilities. As each drop of ester solution was added to the Grignard solution, it reacted before the next drop was added. The configuration of the sulfoxide enantiomer predominating in the product isolated reflects the configuration of the predominant ester in the epimeric starting material. Significantly, the specific rotation at the sodium D-line of the methyl phenyl sulfoxide (V) formed in this way was +19° compared to +23° when formed by addition of the Grignard reagent to the esters. The specific rotation of II prepared in this way was −11° compared to −12° when formed by addition of the Grignard reagent to the esters.

An estimate of the optical purity of the products II and V is possible. The almost superimposable O.R.D. curves[3] give the value of 250° for the molecular rotations at the sodium D-line for a series of sulfoxides structurally analogous to II. Sulfoxide II is estimated to be 10% optically pure. An estimate of the optical purity of V is somewhat more speculative in the absence of extensive data. A comparison of the molecular rotation of V with that of optically pure ethyl *p*-tolyl sulfoxide[9] gives a value of 9% optical purity for V.

Thus, the configuration of the two predominating enantiomers, (+)-methyl phenyl sulfoxide and (−)-N-methyl-N-[3-(methylsulfinyl)propyl]aniline, must be the same since they both result from the predominant epimer of the ester mixture.

In an earlier paper,[6] the *R*-configuration was assigned to (+)-ethyl *p*-tolyl sulfoxide prepared from optically pure (−)-menthyl (−)-*p*-toluenesulfinate (III). Mislow, Ternay, and Melillo[10] demonstrated that several alkyl *p*-tolyl sulfoxides prepared from III were all dextrorotatory and gave similar O.R.D. curves; therefore, all (+)-alkyl *p*-tolyl sulfoxides are expected to have the same configuration. This means that (+)-methyl phenyl sulfoxide has the same configuration as the (+)-alkyl *p*-tolyl sulfoxides; the absence of the *para* methyl group should not influence the sign of rotation. Assuming the validity of the *S*-configurational assignment to sulfur in (−)-menthyl (−)-*p*-toluenesulfinate (III), then both (+)-methyl phenyl sulfoxide and (−)-N-methyl-N-[3-(methylsulfinyl)propyl]aniline should be of configuration *R*.

A plain O.R.D. curve between 700 and 300 mμ was obtained for N-methyl-N-[3-(methylsulfinyl)propyl]-aniline (II). If the choice of II as a model compound for the (−)-ω-(methylsulfinyl)alkyl isothiocyanates (I) was a good one, then their configurations should also be *R*.

Several of the assumptions made in this argument should now be examined since Mislow, Ternay, and Melillo[10] pointed out that recent work by Cram and Pine[11] is in conflict with an *R* assignment to (+)-ethyl *p*-tolyl sulfoxide. Cram and Pine assigned the *S*-configuration to sulfur in (+)-2-octyl phenyl sulfoxide. The first assumption concerns the validity of Herbrandson's tentative assignment while the second assumption concerns the validity of supposing that inversion at sulfur occurs when a Grignard reagent reacts with a sulfinate ester. Johnson's[12] elegant work on the inversion of sulfoxides *via* intermediate alkoxysulfonium salts is additional evidence, besides that cited earlier,[6,10] for inversion in the Grignard reaction. This leaves the first assumption as the most probable source of the conflict. While one could make

(6) K. K. Andersen, *Tetrahedron Letters*, **No. 3**, 93 (1962).

(7) H. Gilman, J. Robinson, and N. H. Beaber, *J. Am. Chem. Soc.*, **48**, 2715 (1926); H. Gilman and J. D. Robinson, *Bull. soc. chim. France*, [4]**45**, 636 (1929).

(8) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(9) Unpublished results of N. Papanikolaou and J. W. Foley indicate that the method in ref. 6 leads to optically pure sulfoxides, if optically pure sulfinate esters are used as starting materials.

(10) K. Mislow, A. L. Ternay, Jr., and J. T. Melillo, *J. Am. Chem. Soc.*, **85**, 2329 (1963).

(11) D. J. Cram and S. H. Pine, *ibid.*, **85**, 1096 (1963).

(12) C. R. Johnson, and J. B. Sapp, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 23Q; C. R. Johnson, *J. Am. Chem. Soc.*, **85**, 1020 (1963).

a choice between Herbrandson's assignment and Cram and Pine's assignment by contemplating molecular models, the uncertainty in bond angles, bond lengths, and van der Waals radii make such an endeavor speculative. For this reason, the configurational relationships assigned in this paper must be considered relative.

It should be noted that Hine[2b] assigned the *S*-configuration to the dextrorotatory methylsulfinyl group in (+)-3-(methylsulfinyl)alanine.[13] The assignment of the *R*-configuration to (−)-N-methyl-N-[3-(methylsulfinyl)propyl]aniline is consistent with Hine's assignment, and then, of course, with Herbrandson's assignment, but such a configurational comparison is based on the very questionable assumption that the asymmetric carbon atom and its attached functional groups do not greatly influence the more powerfully rotating asymmetrically perturbed sulfoxide chromophore in this amino acid.

On the other hand, the work of Phillips[14] on the inversion of sulfinate esters seems to favor Cram's assignment. When 1 mole of racemic ethyl *p*-toluenesulfinate was treated with 0.5 mole of (−)-(*R*)-2-octanol, 2-octyl *p*-toluenesulfinate predominating in the levorotatory epimer was formed. The unchanged portion of the ethyl ester was also levorotatory. Similar results were obtained using *n*-butyl *p*-toluenesulfinate; a levorotatory ester predominated in the unchanged enantiomeric ester mixture. Upon treatment with *n*-butyl alcohol, the levorotatory ethyl ester was converted to the *n*-butyl ester in which the dextrorotatory isomer predominated. These ester interchange reactions are best explained as proceeding by nucleophilic attack by the alcohol on the sulfur atom with inversion and displacement of an alkoxy group. Application of Cram's rule[15] to SN2-type transition states involving the (−)-(*R*)-2-octanol and the (*R*)- and (*S*)-alkyl *p*-toluenesulfinates leads one to predict that the transition state involving the octanol and the (*S*)-ester has a lower energy than the transition state involving the octanol and the (*R*)-ester. In these transition states, the CO bonds of entering and leaving alkoxy groups are considered to lie on a line passing through the sulfur atom and perpendicular to a plane containing the *p*-toluenesulfinyl group. Arrangement of the *p*-tolyl group of the ester is considered to be *trans* or *anti* to the *n*-hexyl group of the 2-octanol. The levorotatory ethyl and *n*-butyl esters which predominate in the unchanged portion of the esters should be the least reactive ones and so of configuration *R*. It is significant that Phillips' work suggests that alkyl *p*-toluenesulfinates of the same sign of rotation have the same configuration. This is supported by Mislow's conclusion that the *p*-toluenesulfinyl group is a dissymmetric chromophore whose sign of rotation is not changed by alkyl groups as in alkyl *p*-tolyl sulfoxides. Neither do alkoxy groups seem to influence this chromophore's sign of rotation. To be consistent with the previous argument, (−)-menthyl (−)-*p*-toluenesulfinate should also be of configuration *R* about sulfur and not *S* as tentatively suggested by Herbrandson. It should be emphasized that this application of Cram's rule is speculative; further research is needed to establish the validity of the preceding analysis.

In spite of the present confusion concerning their absolute configurations, the relative configurations of several sulfoxides have been assigned using a method capable of extension to other sulfoxides and sulfinate esters.

(13) C. J. Morris and J. F. Thompson, *Chem. Ind.* (London), 951 (1955).
(14) H. Phillips, *J. Chem. Soc.*, **127**, 2552 (1925).
(15) F. Q. Abd Elhafez and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 339 (1953); D. J. Cram and F. Q. Abd Elhafez, *ibid.*, **74**, 5828 (1952).

Experimental

(−)-Menthyl (±)-Methanesulfinate (IV).—A solution of methanesulfinyl chloride[16] (50.2 g., 0.510 mole) in anhydrous ether (150 ml.) was added dropwise with stirring and cooling in an ice bath to a solution of U.S.P. (−)-menthol (78.1 g., 0.500 mole) and pyridine (40.3 g., 0.510 mole) in ether (50 ml).. After the mixture stood overnight in an ice bath, ether (100 ml.) was added. The mixture was extracted with cold water, cold 10% hydrochloric acid, cold aqueous sodium bicarbonate, and again with cold water, in that order. After drying over sodium sulfate and subsequent removal of the ether *in vacuo*, crude IV (101 g., 0.46 mole, 93% yield) was obtained. Fractionation through a 15-cm. Vigreux column gave pure IV, b.p. 88–89° (0.4 mm.), $[\alpha]^{25}D$ −99 ± 1° (*c* 2.04, acetone); ν_{max}^{neat} 1137 cm.$^{-1}$; n.m.r. (40% in $CHCl_3$), τ 7.30 and 7.32, peaks assigned to $CH_3S(O)O$– protons on basis of comparison to other alkyl methanesulfinates prepared in this laboratory.

Anal. Calcd. for $C_{11}H_{22}O_2S$: C, 60.51; H, 10.16. Found: C, 60.30; H, 10.10.

Methyl Phenyl Sulfoxide (V).—A Grignard reagent prepared from bromobenzene (31.4 g., 0.200 mole) and magnesium (5.5 g., 0.23 g.-atom) in anhydrous ether (100 ml.) was added at −10° over a 45-min. period with stirring to an ether solution (100 ml.) of (−)-menthyl (±)-methanesulfinate [39.2 g., 0.180 mole, $[\alpha]^{24}D$ −98 ± 1° (*c* 2.29, acetone)]. After stirring for 10 min. more without cooling, the mixture was hydrolyzed with saturated ammonium chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give an oil. Upon fractional distillation crude menthol (25.5 g., 0.163 mole, 91% yield) and crude methyl phenyl sulfoxide (V, 12.7 g., 0.0907 mole, 50% yield) were obtained. The crude sulfoxide was stirred overnight with dilute sodium hydroxide to hydrolyze traces of unchanged ester. Distillation then gave pure methyl phenyl sulfoxide, b.p. 85° (0.5 mm.), lit.[17] b.p. 139–140° (14 mm.), $[\alpha^{23}D$ +23 ± 1° (*c* 2.29, acetone). A vapor phase chromatogram indicated only an insignificant trace of (−)-menthol. The infrared spectrum was identical with that of an authentic sample. Oxidation of the sulfoxide with hydrogen peroxide in glacial acetic acid gave methyl phenyl sulfone, m.p. 86.5–87.5, lit.[17] m.p. 88°, which did not depress the melting point of an authentic sample.

Several repetitions of the above reaction on different samples of ester always gave (+)-methyl phenyl sulfoxide. Addition of the ester to the Grignard solution gave similar results, $[\alpha]^{23}D$ +19 ± 1° (*c* 2.07, acetone).

N-Methyl-N-[3-(methylsulfinyl)propyl]aniline (II).—A Grignard reagent prepared from N-methyl-N-(3-chloropropyl)aniline[18] (11.1 g., 0.0603 mole) and excess magnesium in an ether–benzene (50:50 ml.) mixture was added over a 30-min. period at 0° with stirring to an ether solution (50 ml.) of (−)-menthyl methanesulfinate (10.9 g., 0.0500 mole). A portion of the same preparation of ester as used in the synthesis of V was used. After standing for 4 hr., the mixture was hydrolyzed with dilute ammonium chloride. The ether layer was separated and extracted twice with 10% hydrochloric acid. The acid extracts were made basic with aqueous sodium hydroxide. The oil which separated was taken up in ether. After drying over magnesium sulfate and removal of the ether, a levorotatory oil (10.8 g.) which crystallized upon standing was obtained. The levorotation was not caused by (−)-menthol since blank experiments showed that a mixture of racemic sulfoxide and (−)-menthol was cleanly separated using the above procedure; the racemic sulfoxide did not show any levorotation due to contaminating (−)-menthol. The infrared spectrum of the crude sulfoxide did not include the

(16) I. B. Douglass and B. S. Farah, *Org. Syn.*, **40**, 62 (1960).
(17) H. Bohme, H. Fischer, and R. Frank, *Ann.*, **563**, 54 (1949).
(18) J. von Braun and G. Kirschbaum, *Ber.*, **52**, 1716 (1919).

very intense and characteristic sulfinate ester stretching band at about 1140 cm.$^{-1}$.

The sulfoxide was recrystallized several times from *n*-hexane to give pure II; m.p. 80.0–80.5°, $\nu_{max}^{CHCl_3}$ 1035 cm.$^{-1}$ (sulfoxide stretching). N.m.r. (25% in $CHCl_3$) is in τ-units: triplet, 6.57, J = 7 c.p.s. ($N-CH_2-$); singlet, 7.12 ($N-CH_3$); multiplet, 7.23–7.53 ($-CH_2-SO-$); singlet, 7.53 (CH_3-SO-); pentuplet, 8.03, J = 7 c.p.s. ($-CH_2-CH_2-CH_2-$). The n.m.r. assignments were made by comparison with the spectrum of N-methyl-N-propylaniline.

Anal. Calcd. for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11. Found: C, 62.51; H, 8.04.

The rotation went to zero as the recrystallization proceeded while the rotation of the oil from the mother liquors became more levorotatory. A racemic compound preferentially crystallized from the *n*-hexane. To circumvent this problem, the crude sulfoxide (5.5 g.) was distilled through a small Vigreux column. N-Methyl-N-propylaniline (0.9 g.) from the hydrolysis of the Grignard reagent was obtained as the first fraction, b.p. about 60° (0.5 mm.), lit.[19] b.p. 95–98° (10 mm.). The infrared and n.m.r. spectra were identical with those obtained from an authentic sample. The column was removed and the remainder of the material distilled to give II (2.2 g.); b.p. about 180° (0.6 mm); m.p. 75–78°; $[\alpha]^{28}D$ −12 ± 1° (c 2.54, acetone); O.R.D. (c 1.85, ethanol) gave a negative plain curve: $[\phi]_{600}$ −23°, $[\phi]_{500}$ −30°, $[\phi]_{400}$ −54°, $[\phi]_{350}$ −90°, $[\phi]_{340}$ −97°. Addition of gaseous hydrogen chloride to the ethanol solution to form the hydrochloride salt did not change the O.R.D. values indicating that the aniline group probably does not influence the sulfoxide chromophore very much.

The n.m.r. spectrum of the distilled sulfoxide was identical with that obtained from the recrystallized sulfoxide. Addition of 5% of (−)-menthol to the recrystallized sulfoxide gave a mixture whose n.m.r. spectrum clearly revealed the methyl groups of the menthol. In order to have $[\alpha]D$ −12°, the distilled sulfoxide would need to be contaminated with 20% (−)-menthol or 10% (−)-menthyl methanesulfinate. The n.m.r. spectrum ruled out such contamination.

Several repetitions of the reaction always gave levorotatory II. Addition of the ester to the Grignard reagent gave identical results: rotation of II, $[\alpha]^{25}D$ −11 ± 1° (c 2.07, acetone).

Instruments.—The infrared spectra were obtained on Perkin-Elmer Model 21 and Model 337 spectrophotometers, the n.m.r. spectra on a Varian Model A-60 spectrometer, and the O.R.D. curves on a Rudolph Model 260/655/850/810-614 recording spectropolarimeter.

(19) R. L. Bent, *et. al.*, *J. Am. Chem. Soc.*, **73**, 3100 (1951).

Acknowledgment.—The author is most grateful to Drs. W. Gaffield and G. G. Lyle for obtaining the O.R.D. curves, and to the National Science Foundation for a departmental grant, G-22718, enabling the purchase of an n.m.r. spectrometer.

The Chlorination of Active Hydrogen Compounds with Sulfuryl Chloride. I. Ketones

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A number of ketones possessing α-hydrogen atoms are readily chlorinated by sulfuryl chloride to yield α-chloro ketones according to $R-\overset{O}{\overset{\|}{C}}-CHR_2 + SO_2Cl_2 \rightarrow R-\overset{O}{\overset{\|}{C}}-CClR_2 + SO_2 + HCl$. In general, the order of preferred substitution is methine > methylene > methyl. In several cases, α,α-dichloro ketones were the major products. The chlorination is sensitive to steric factors as well as electronic ones; *e.g.*, 1,2,3-triphenylpropanone-1 did not react even when dissolved in an excess of sulfuryl chloride. An acid-catalyzed ionic mechanism is proposed to explain the experimental results.

A few isolated examples of the chlorination of active hydrogen compounds by sulfuryl chloride can be found.[1-7] The compounds studied (and the products obtained) included malonic esters[1,2] (chloromalonates), methyl ethyl ketone[3] (3-chlorobutanone-2), acetone[4] (1-chloropropanone-2 and 1,1-dichloropropanone-2), cyclopentyl phenyl ketone[5] (α-chlorocyclopentyl phenyl ketone), methyl and ethyl levulinate[6] (chlorination of the methylene group α to the keto carbonyl), and β-diketones[7] (2,2-dichloro-1,3-diketones). In all cases but one,[4] a single product was isolated and/or reported even though more than one α-methyl, methylene, or methine group was often present.

In order to gain a better understanding of the scope and limitations of the chlorination of active hydrogen compounds with sulfuryl chloride, a variety of ketones have been subjected to this reaction and the results are reported here.

Results

A total of nine different ketones was used in this investigation and the chlorinated products obtained from them are summarized in Table I. In every case chlorination occurred exclusively in the α-positions.

The "linear" ketones, acetone, methyl ethyl ketone, and diethyl ketone, each gave several products upon treatment with an equimolar amount of sulfuryl chloride. However, the major product[8] from each was the α,α-dichloro derivative [1,1-dichloropropanone-2 (60–70%), 3,3-dichlorobutanone-2 (48%), and 2,2-dichloropentanone-3 (58%), respectively]. The other products from the chlorination of methyl ethyl ketone and diethyl ketone consisted of nearly equal amounts of the α,α'-dichloro and monochloro derivatives. The methylene protons of methyl ethyl ketone were substituted much more readily than the methyl protons. On the other hand, very little 1,3-dichloropropanone-2 was formed

(1) A. K. Macbeth, *J. Chem. Soc.*, 1116 (1922).

(2) K. G. Naik and N. T. Talati, *J. Indian Chem. Soc.*, **8**, 203 (1931).

(3) E. R. Buchman, A. O. Reims, and H. Sargent, *J. Org. Chem.*, **6**, 764 (1941).

(4) E. R. Buchman and H. Sargent, *J. Am. Chem. Soc.*, **67**, 401 (1945).

(5) G. Cauquil and J. Rouzaud, *Compt. rend.*, **237**, 1720 (1953).

(6) H. Yasuda, *J. Sci. Res. Inst.* (Tokyo), **513**, 32 (1957).

(7) E. Gudriniece, G. Vanags, A. Kurzemnicks, and Z. Grants, *Izv. Vysshikh Uchebn. Zavedenii Khim. i Khim. Tekhnol.*, **3**, 119 (1960); *Chem. Abstr.*, **54**, 17,352.

(8) The per cent yields given, unless otherwise specified, are based upon the relative quantity of chlorinated products which were obtained. The actual yields in terms of conversion of sulfuryl chloride were generally high, *i.e.*, >80%.

TABLE I

PRODUCTS FROM THE CHLORINATION OF KETONES WITH SULFURYL CHLORIDE

Ketone	moles of SO_2Cl_2 / moles of $R_2C{=}O$	Products (% yield)[a]
Acetone	1	1,1-Dichloropropanone-2 (58), 1-chloropropanone-2 (41)
Acetone	1[b]	1,1-Dichloropropanone-2 (61), 1-chloropropanone-2 (38)
Acetone	2	1,1-Dichlorobutanone-2 (72), 1,1,3-trichloropropanone-2 (20), 1,3-dichloropropanone-1 (6)
Methyl ethyl ketone	1	3,3-Dichlorobutanone-2 (48), 1,3-dichlorobutone-2 (27), 3-chlorobutanone-2 (19)
Methyl ethyl ketone	2	3,3-Dichlorobutanone-2 (42), 1,1-dichlorobutanone-2 (7), 1,3-dichlorobutanone-2 (46)
Diethyl ketone	1	2,2-Dichloropentanone-3 (58), 2,4-dichloropentanone-3 (20, *meso* and *dl* isomers), 2-chloropentanone-3 (15)
Methyl isopropyl ketone	1	3-Chloro-3-methylbutanone-2 (77), 1-chloro-1-methylbutanone-2 (15)
Diisopropyl ketone	1	2-Chloro-2,4-dimethylpentanone-3 (95), 2,4-dichloro-2,4-dimethylpentanone-3 (~5)
Desoxybenzoin	1	Desyl chloride (~100)
Phenylacetone	1	1-Phenyl-1-chloropropanone-2 (95), 1-phenyl-3-chloropropanone-2 (trace), 1,3-dichloro-1-phenylpropanone-2 (trace)
1,1-Diphenylacetone	1[c]	1,1-Diphenyl-1-chloropropanone-2 (53)[d]
1,1-Diphenylacetone	1[c]	1,1-Diphenyl-1-chloropropanone-2 (77)[f]
Phenylacetone + acetone	0.5[g]	1-Phenyl-1-chloropropanone-2 (82), 1-chloropropanone-2 (14)
1,2,3-Triphenylpropanone-1	1[h]	No reaction
1,2,3-Triphenylpropanone-1	3[c]	No reaction

[a] Per cent yields are based on sulfuryl chloride. [b] Acetone added to sulfuryl chloride; the opposite order of addition was used in all other cases. [c] Carbon tetrachloride was used as solvent. [d] This yield was obtained after 6 hr. [e] No solvent was used. [f] This yield was obtained after 24 hr. [g] An equimolar quantity of each ketone was used. [h] Reactions were attempted in benzene and carbon tetrachloride solutions.

during the chlorination of acetone. When acetone was chlorinated by slowly adding it to sulfuryl chloride, rather than by the inverse procedure, no significant differences in the yields or product distribution were found.

Both acetone and methyl ethyl ketone reacted with an excess (twofold) of sulfuryl chloride. The major product in the case of acetone was again the α,α-dichloro derivative (72%), and the next major product was the trichlorinated compound (20%), 1,1,3-trichloropropanone-2. Under these conditions methyl ethyl ketone gave essentially equal amounts of 3,3-dichlorobutanone-2 (42%) and 1,3-dichlorobutanone-2 (46%).

The branched ketones, methyl isopropyl ketone and diisopropyl ketone, each gave a monochloro derivative as the major product (in total yields of 87% and 95%, respectively). The methine proton of methyl isopropyl ketone was replaced more readily than the methyl protons. Since there are three methyl protons and one methine proton and since the ratio of methine substitution to methyl substitution was 5.1:1 (77 *vs.* 15%), it is apparent that the methine proton is ~15 times as reactive as the methyl protons in this reaction.

Both desoxybenzoin and phenylacetone reacted rapidly and exothermally with an equimolar amount of sulfuryl chloride. The former gave desyl chloride in virtually quantitative yield. Practically no α,α-dichlorodesoxybenzoin was produced. Similarly, the major product (95%) from phenylacetone was 1-phenyl-1-chloropropanone-2, and very little (~3%) 1,1-dichloro-1-phenyl-propanone-2 and 1-chloro-3-phenylpropanone-2 (trace) were formed.

The reaction of 1,1-diphenylacetone with sulfuryl chloride either neat or in carbon tetrachloride was very slow and the sole product was 1,1-diphenyl-1-chloropropanone-2. No reaction occurred over 3–12-hr. periods when 1,2,3-triphenylpropanone-1 was dissolved in a threefold excess of sulfuryl chloride or when attempts were made to carry out the chlorination in benzene or carbon tetrachloride.

Finally, a competitive chlorination between acetone and phenylacetone showed the latter to be much more reactive. Considering only the acetone methyl groups (and not that from phenyl acetone) and the phenyl acetone methylene group, there is a statistical factor of 3 in favor of acetone. Since ~6 times as much 1-phenyl-1-chloropropanone-2 as 1-chloropropanone-2 was formed, the methylene protons of the former are ~18 times more susceptible to substitution in this reaction than the methyl protons of acetone.

Discussion

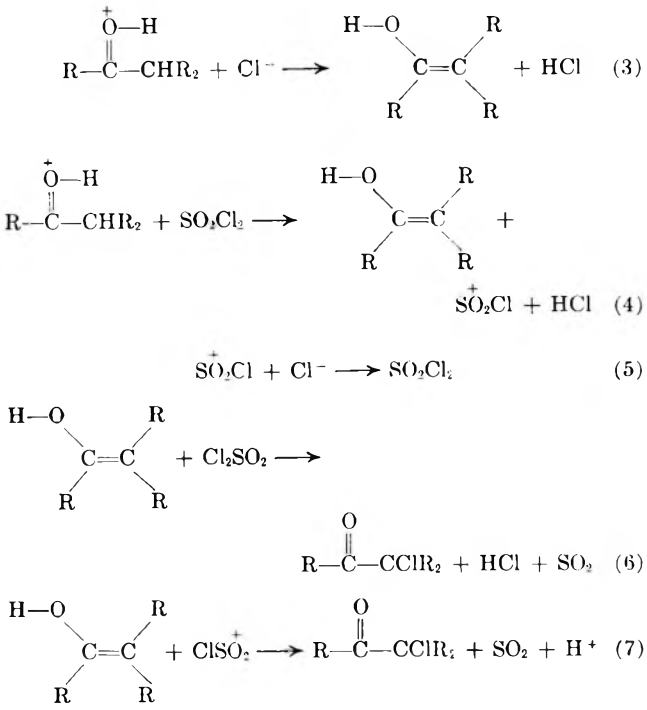
The experimental conditions (relatively low temperatures), the preponderance of α,α-dichloro ketones as products in many cases, exclusive α-chlorination, and sensitivity to steric factors clearly indicate that the chlorination of ketones by sulfuryl chloride proceeds *via* an ionic mechanism. Acid catalysis is most likely involved. One of the acids, hydrogen chloride, is generated during the reaction *via* eq. 1, following.

$$R{-}\overset{\overset{O}{\|}}{C}{-}CHR_2 + SO_2Cl_2 \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}CClR_2 + SO_2 + HCl \quad (1)$$

Accordingly, the following reaction sequence[9] (eq. 2–7) is plausible.

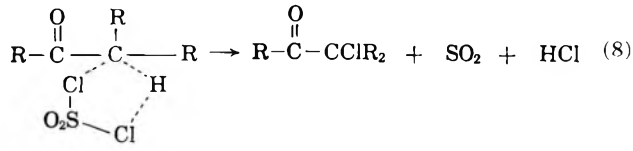
$$R{-}\overset{\overset{O}{\|}}{C}{-}CHR_3 + HCl \rightleftharpoons R{-}\overset{\overset{\overset{+}{O}{-}H}{\|}}{C}{-}CHR_2 + Cl^- \quad (2)$$

(9) The possibility that sulfuryl chloride can catalyze the enolization is not ruled out *per se;* however, it is felt that the over-all explanation would not differ significantly from the one shown in eq. 2–7, should this be a catalyst as well as hydrogen chloride.



The equilibrium shown in eq. 2 is well known.[10] The same enolic intermediate is formed in eq. 3 and 4, which differ only in the mode of abstraction of the proton. It has been shown[11-13] that halide ions, *e.g.*, chloride and bromide, can function as bases in the manner shown in eq. 3. On the other hand, sulfuryl chloride has been found to catalyze the condensation of aldehydes[14] and the Pechman reaction.[15] Whether either or both eq. 3 and 4 actually are involved can best be resolved by a detailed kinetic analysis of the system.

An alternate path for substitution conceivably could involve a concerted reaction (eq. 8) which proceeds



through a cyclic transition state. In the case of the chlorination of methyl isopropyl ketone, the major product was 2-chloro-2-methylbutanone-3 rather than the product from substitution on the methyl group, 1-chloro-3-methylbutanone-2. Since the two electron-releasing methyls of the isopropyl group make the methine carbon more nucleophilic while decreasing the acidity of the methine proton (relative to the carbon and protons of the methyl group), it would be concluded that, if eq. 8 applies, chloronium transfer (bond making) is more important than proton abstraction (bond breaking). On the other hand, chlorination of acetone gave 1,1-dichloropropanone-2 as the major product. Thus, in this case, the protons of the CH_2Cl group were much more susceptible to reaction than those of a corresponding methyl group. If this result is explained in terms of eq. 8, it is apparent that a conclusion directly opposite that which was obtained from the chlorination of methyl isopropyl ketone *will* be reached; *i.e.*, "bond breaking" is more important than "bond making." Therefore, eq. 8 does not offer a consistent explanation of the experimental observations.

While it has not been proved conclusively that chlorinations with sulfuryl chloride proceed *via* eq. 2–7, it should be pointed out that these are formally similar to the pathways proposed to explain other acid-catalyzed halogenations, *e.g.*, bromination with bromine.[11] On the other hand, the possibility that molecular chlorine from $SO_2Cl_2 \rightleftarrows SO_2 + Cl_2$ is actually an important component of this chlorination system can be ruled out because this does not appear to be important at much higher temperatures in free-radical chlorinations.[16]

Steric considerations are also of considerable importance in chlorination of ketones with sulfuryl chloride. For example, the electronic arguments which might explain the formation of large quantities of 1,1-dichloropropanone-2 during the chlorination of acetone would lead one to expect that large amounts of 1,1,1-trichloropropanone-2 would also be formed; however, only trace amounts arose even in the presence of an excess of sulfuryl chloride. Similarly, the major product from the chlorination of phenylacetone was 1-chloro-1-phenylpropanone-2 (95% yield) rather than a dichloro derivative. The same result was obtained with desoxybenzoin. The more hindered ketone, 1,1-diphenylacetone, gave 1,1-diphenyl-1-chloropropanone-2 as the sole product, but the reaction was notably slower than in the case of the other ketones even in an excess of sulfuryl chloride. While 1,2,3-triphenylpropanone-1 is nearly as hindered as 1,1-diphenylacetone, it lacks the driving force derived from the formation of an enolic intermediate conjugated with two benzene rings; consequently, it failed to react. Since it is unlikely that protonation of a carbonyl group is subject to steric inhibition, it is possible that this effect arises from hindrance to the approach of a halide ion or sulfuryl chloride molecule in the proton abstraction steps (eq. 3 and 4).

Finally, it is worth emphasizing that chlorinations of ketones with sulfuryl chloride are simple reactions to perform, the yields are generally very high, and, in many cases, the position of substitution is quite selective. Thus, sulfuryl chloride is a very useful reagent for the preparation of a variety of chlorinated ketones.

Experimental

General.—All of the ketones used in this investigation, except 1,2,3-triphenylpropanone-1 whose preparation is described below, were commercially available and were used as received. Melting points are corrected but boiling points are not. Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., or by the Galbraith Laboratories, Inc., Knoxville, Tenn. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 spectrometer (60 Mc., 37 ± 1°). The spectra were taken of the neat liquids or of carbon tetrachloride solutions, and tetramethylsilane (TMS) was

(10) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

(11) R. F. W. Cieciuch and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 2591 (1963).

(12) S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Letters*, **No. 9**, 24 (1960).

(13) D. N. Kevill and N. H. Cromwell, *J. Am. Chem. Soc.*, **83**, 3812 (1961).

(14) M. Backes, *Compt. rend.*, **196**, 1674 (1933).

(15) V. M. Dixit and L. N. Mulay, *Proc. Indian Acad. Sci.*, **27A**, 14 (1948).

(16) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957 pp. 380–381.

used as an internal reference.[17] Both preparative and analytical gas chromatography (v.p.c.) measurements were made with a column composed of 20% Ucon polar, 50-HB-2000 (60–80 mesh) on a Chromosorb-P support.

Chlorination of Acetone.—Acetone (58 g., 1 mole) was placed in a 300-ml. round-bottom flask equipped with a condenser (protected from the atmosphere with an anhydrous calcium chloride drying tube), dropping funnel, and magnetic stirrer. Sulfuryl chloride (135 g., 1 mole) was added dropwise over a period of 50 min. The reaction was very exothermic and the temperature was maintained between 30 and 40° by controlling the rate of addition. Both sulfur dioxide and hydrogen chloride were rapidly evolved during the reaction. After the addition was complete, the dark brown solution was distilled. The major portion of the product, after the removal of the unconverted acetone, boiled at 117–118° and weighed 95 g. Elemental analysis indicated that this was a mixture of a mono- and dichlorinated acetone.

Anal. Found: C, 49.8; H, 3.93; Cl, 49.8.

Vapor phase chromatography (v.p.c.) showed that the two major peaks with relative areas of 41 and 58% were present along with with a minor peak (~1%) due to a higher boiling substituent. From a comparison of retention times[18] it was found that the largest peak (58%) was due to 1,1-dichloropropanone-2, and the next largest peak (41%) was due to 1-chloropropanone-2. The identity of the trace (~1%) substituent was not definitely established, but it may have been 1,1,1-trichloropropanone-2.

The reaction conducted with the reverse mode of addition, *i.e.*, addition of acetone to sulfuryl chloride, exhibited the same characteristics as described above and was analyzed in the same way (Table I).

The reaction conducted with a sulfuryl chloride–acetone ratio of 2 was performed by the dropwise addition of sulfuryl chloride (0.5 mole) to the acetone (0.25 mole) as described above. After the addition was complete the reaction mixture was allowed to stir at room temperature overnight. Fractionation was performed through a 14-in. Vigreux column. The first fraction was 1,1-dichloropropane-2, b.p. 117–118°, n^{25}D 1.4463, which was obtained in 72% yield (22.8 g.)

Anal. Calcd. for $C_3H_4Cl_2O$: C, 28.38; H, 3.15; Cl, 55.95. Found: C, 27.94; H, 3.29; Cl, 55.82.

The n.m.r. (neat liquid) spectrum of this material consisted of two singlets, τ 7.54 and 3.85, with relative intensities of 3.1:1, respectively.

The next fraction, 6% (1.9 g.), was 1,3-dichloropropanone-2, b.p. 78–80° (30 mm.), n^{25}D 1.4795, lit.[19] n^{46}D 1.4711.

The n.m.r. spectrum of this compound consisted of a sharp singlet, τ 5.55. No methyl group absorptions (7.25 μ) were present in the infrared spectrum.

The final fraction was 1,1,3-trichloropropanone-2, b.p. 91–94° (30 mm.), n^{25}D 1.4695, lit.[20] n^{20}D 1.4711, obtained in 20% yield (8.1 g.). The n.m.r. spectrum (neat liquid) of this compound consisted of two singlets, τ 5.30 and 3.61, in the ratio of 2.01:1, respectively. No methyl group absorption (7.25 μ) appeared in the infrared spectrum.

Chlorination of Methyl Ethyl Ketone.—The experimental procedure was identical with that used in the case of acetone. The dropwise addition of sulfuryl chloride (1 mole) of the ketone (1 mole) resulted in an exothermic reaction which was kept below 40° by controlling the rate of addition (40 min.). The reaction mixture was distilled through a 14-in. Vigreux column and 35 g. of methyl ethyl ketone was recovered. The residue was separated by preparative v.p.c. The first component (19%) was 3-chlorobutanone-2, n^{25}D 1.4158, lit.[21] n^{26}D 1.4168. The n.m.r. spectrum of this material consisted of a quartet, τ 5.25; singlet, 7.85; and a doublet, 8.95; in the relative intensity ratios of 1:2.95:2.98 (1:3:3), respectively. The next component (48%) was 3,3-dichlorobutanone-2.

Anal. Calcd. for $C_4H_6Cl_2O$: C, 34.00; H, 4.26; Cl, 50.40. Found: C, 33.78; H, 4.11; Cl, 50.66.

The n.m.r. spectrum (carbon tetrachloride solution) of this compound consisted of 2 singlets, τ 7.48 and 7.88, with a relative intensity ratio of 1:1.05, respectively. The infrared spectrum showed a strong methyl absorption at 7.25 μ.

The highest boiling component (27%) was 1,3-dichlorobutanone-2, n^{25}D 1.4625, lit.[20] n^{20}D 1.4650. The n.m.r. spectrum of this compound (carbon tetrachloride solution) consisted of a quartet, τ 5.25; singlet, 5.60; and a doublet, 8.46; in the relative intensity ratios of 1:2.1:2.98 (1:2:3), respectively.

The experiment above was repeated with a sulfuryl chloride–methyl ethyl ketone ratio of 2. After stirring overnight the components were again separated *via* preparative v.p.c. The first component (42%) was 3,3-dichlorobutanone-2. The second component (7%) was considered to be 1,1-dichlorobutanone-2 on the basis of its n.m.r. spectrum (carbon tetrachloride solution): singlet, τ 3.70; quartet, 7.11; and triplet, 8.78; with relative intensity ratios of 1:2.1:3.05 (1:2:3), respectively. The final component (46%) was 1,3-dichlorobutanone-2.

Chlorination of Diethyl Ketone.—The dropwise addition of 1 mole of sulfuryl chloride to 1 mole of diethyl ketone was very exothermic and was performed over a period of 1.33 hr. At no time was the temperature of the reaction allowed to exceed 40°. The reaction mixture was light yellow at the end of the addition. The system was separated by preparative gas chromatography. Four major components were detected. The first of these was diethyl ketone. The second (15%) was considered to be 2-chloropentanone-3 on the basis of its n.m.r. spectrum (carbon tetrachloride solution): quartet, τ 5.69; multiplet,[21] 7.30; doublet, 8.42; and triplet, 8.93: in the relative intensity ratios of 1:2.05:3.1:3.09, respectively. The third component (58%) was 2,2-dichloropentanone-3.

Anal. Calcd. for $C_5H_8Cl_2O$: C, 38.70; H, 5.16; Cl, 45.75. Found: C, 38.41; H, 5.12; Cl, 45.98.

The n.m.r. spectrum (neat liquid) of this material consisted of a quartet, τ 7.02; singlet, 7.83; and a triplet, 8.81; in the relative intensity ratios of 2:2.90:3.00, respectively. The final component (20%) was 2,4-dichloropentanone-3.

Anal. Calcd. for $C_5H_8Cl_2O$: C, 38.7; H, 5.16; Cl, 45.75. Found: C, 38.48; H, 4.98; Cl, 46.05.

The n.m.r. spectrum (neat liquid) of this compound was unusual and consisted essentially of a complex multiplet (τ ~5.20) and another multiplet, consisting of four sharp lines of nearly equal intensity (τ ~8.38). The peaks were in a total intensity ratio of 1:3, respectively (actually 1:3.15). No triplets were present (ruling out methylene groups). Consequently, the compound appears to be 2,4-dichloropentanone-3. The complexity of the spectrum can be explained on the basis of the presence of equal amounts of *meso* and *dl* isomers.

Chlorination of Methyl Isopropyl Ketone.—Sulfuryl chloride (0.5 mole) was added dropwise over a period of 25 min. to 0.5 mole of methyl isopropyl ketone. Heat was evolved (the temperature rose to ~40°) and the reaction mixture became red. Stirring was continued for 1 hr. after the addition was complete. Analysis was done by means of v.p.c. which indicated three major components: methyl isopropyl ketone (8%), 3-chloro-3-methylbutanone-2 (77%), and 1-chloro-3-methylbutanone-2 (15%). The two chlorinated products were also separated by distillation through a 12-in., helice-packed distillation column. The major product, 3-chloro-3-methylbutanone-2, b.p. 143–145°, n^{25}D 1.4378 (lit.[20] b.p. 142–143°, n^{20}D 1.4390), was obtained in 60% yield (36.2 g.). The n.m.r. spectrum (neat liquid) of this compound consisted of two sharp singlets, τ 7.65 and 8.31, in the ratio of 1:2.11, respectively. The minor component, 1-chloro-3-methylbutanone-2, b.p. 74–76° at 40 mm., lit.[22] b.p. 58° at 30 mm., was obtained in 6% yield (3.6 g.). The n.m.r. spectrum of this compound (neat liquid) consisted of a singlet, τ 5.72; multiplet, 7.15; and doublet, 8.83; in the ratio of 1.95:1:6.31, respectively. A viscous, dark residue remained after the distillation.

Chlorination of Diisopropyl Ketone.—The experimental procedure was identical with that used in the chlorination of methyl

(17) Strictly speaking, the τ-scale for expressing chemical shifts in reference to TMS (τ 10.0) is usually applied to measurements made in an inert solvent, *e.g.*, carbon tetrachloride; *cf.* G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1150 (1958). Furthermore, the line positions of the protons in halogenated ketones are noticeably solvent dependent (private communication from Dr. B. L. Shapiro). Therefore, many of the τ-values given here are approximate.

(18) Monochloroacetone used as a standard for the v.p.c. measurements was synthesized through the reaction of sulfuryl chloride with a twentyfold excess of acetone.[4]

(19) W. Polaczkowa and Z. Bankowska, *Roczniki Chem.*, **30**, 119 (1956).

(20) G. B. Bachman and T. Hokama, *J. Org. Chem.*, **25**, 178 (1960).

(21) The multiplet peaks for the CH_2 group, rather than the simple first-order quartet, arise because the two protons are not magnetically equivalent; *cf.* E. I. Snyder, *J. Am. Chem. Soc.*, **85**, 2624 (1963).

(22) M. Thiel, F. Ansinger, and G. Peckling, *Ann. Chem.*, **611**, 131 (1958).

isopropyl ketone. From 0.5 mole of ketone and 0.5 mole of sulfuryl chloride there was obtained 57.3 g. (84%) of 2-chloro-2,4-dimethylpentanone-3, b.p. 143–145°, lit.[23] b.p. 142–143°. The n.m.r. spectrum (neat liquid) of this compound consisted of a multiplet, τ 6.55; singlet, 8.31; doublet, 8.34; in the ratio of 1:5.83:5.78, respectively. A higher boiling compound (approximately 5% yield), presumably 2,4-dichloro-2,4-dimethylpentanone-3, was detected *via* v.p.c. The yield of the main product, 2-chloro-2,4-dimethylpentanone-3 was 94% according to v.p.c.

Chlorination of Desoxybenzoin.—Sulfuryl chloride (0.5 mole) was added dropwise to 0.5 mole of desoxybenzoin over a period of 20 min. The rate of addition was such that the temperature of the reaction mixture did not exceed 40°. The viscous yellow liquid which formed was stirred at room temperature (~22°) for 2 hr. It slowly solidified to a white crystalline solid. The temperature rose to 55° during the course of the solidification (~20 min.). The yield of crude product was 117 g. A portion of this material was recrystallized from petroleum ether (b.p. 60–70°) to yield white needles, m.p. 65.0–65.5°. A mixture of this material with deoxybenzoin had m.p. 37–39°. An analytical sample (m.p. 66–66.25°) was obtained by recrystallizing the crude product three times from petroleum ether. A mixture with authentic desyl chloride melted at 66–67°.

Chlorination of Phenylacetone.—Phenylacetone (0.25 mole) was chlorinated by the dropwise addition to it of 0.25 mole of sulfuryl chloride. The reaction was exothermic and the addition was conducted over a period of 25 min. at such a rate that the temperature did not exceed 40°. Upon distillation there was obtained 40.2 g. (95%) of 1-chloro-1-phenylacetone, b.p. 123–124° at 30 mm., $n^{26}D$ 1.5339. The n.m.r. spectrum of this compound consisted of two singlets, τ 4.53 and 7.42, as well as the aromatic protons below τ 3 in the intensity ratio of 1:3.12:5.34, respectively. Analysis by v.p.c. indicated that ~3% of 1-phenylpropanone-2 and trace amounts of two higher boiling components, presumably 1-phenyl-3-chloropropanone-2 and 1,1-dichloro-1-phenylpropanone-2, were also present.

Chlorination of 1,1-Diphenylacetone.—Reactions were conducted with 0.05 mole of ketone and 0.05 mole of sulfuryl chloride in carbon tetrachloride solvent or without solvent. The reaction in carbon tetrachloride (50 ml.) was terminated after 6 hr. (at room temperature) by pouring the reaction solution onto 200 g. of a mixture of ice and water. The carbon tetrachloride layer was removed and then dried over anhydrous calcium chloride. Removal of the carbon tetrachloride *in vacuo* left a light yellow liquid residue which was separated by preparative gas chromatography into two components. The first of these was unconverted 1,1-diphenylacetone while the second was 1,1-diphenyl-1-chloropropanone-2. This structure was assigned on the basis of the infrared spectrum, which showed strong methyl absorption at 7.25 μ; the n.m.r. spectrum (carbon tetrachloride solution), which showed aromatic protons at τ ~2.8 and a sharp singlet at 7.75, in the ratio of 3.71:1, respectively; as well as the elemental analysis which showed that the compound contained only one chlorine atom.

Anal. Calcd. for $C_{15}H_{13}ClO$: C, 73.70; H, 5.32; Cl, 14.50. Found: C, 73.58; H, 5.19; Cl, 14.48.

The yield of 1,1-diphenyl-1-chloropropanone-2 under these conditions was 53%. In a similar reaction conducted without solvent the yield of the same product was 77% after 24-hr. reaction at room temperature. Only traces (<1%) of a slightly higher boiling product, presumably 1,1-diphenyl-3-chloropropanone-2, were detected.

Synthesis of 1,2,3-triphenylpropanone-1.—Desoxybenzoin (98 g., 0.5 mole) was dissolved in 300 ml. of refluxing, anhydrous ethanol which contained 28 g. (0.5 mole) of potassium hydroxide. Benzyl chloride (64 g., 0.505 mole) was added dropwise to the refluxing solution over a period of 4 hr. The mixture was stirred and refluxed an additional 4 hr. after the addition. The reaction mixture was allowed to cool to room temperature, and then it was diluted with 1 l. of cold water. Crude 1,2,3-triphenylpropanone-1 (115 g., 80%) separated in the form of a tan crystalline solid. It was recrystallized from petroleum ether in the form of fine white needles, m.p. 125°, lit.[24] m.p. 122.

Attempted Chlorination of 1,2,3-Triphenylpropanone-1.—Attempts were made to chlorinate the compound in benzene, in carbon tetrachloride, and without solvent in a threefold excess of sulfuryl chloride. No evidence of reaction was found (no hydrogen chloride or sulfur dioxide evolution). In each case the starting ketone could be recovered without change (infrared and mixture melting point) after 24 hr. at room temperature.

Chlorination of a Mixture of Acetone and Phenylacetone.—Sulfuryl chloride (34 g., 0.25 mole) was added dropwise over a period of 30 min. to a well-stirred mixture of acetone (0.25 mole) and phenylacetone (0.25 mole). The temperature of reaction was kept below 40° by adjusting the rate of addition. Stirring was continued for 1 hr. after addition and then the crude mixture (a light yellow liquid) was analyzed by v.p.c. It consisted of 82% of 1-phenyl-1-chloroacetone, 14% of 1-chloropropanone-2, and traces of other components (yields are based on sulfuryl chloride).

Acknowledgment.—We are indebted to Mr. Carl Lindemann and Mr. Frank Michalek for the gas chromatographic separations, and to Dr. B. L. Shapiro for helpful discussions concerning the n.m.r. spectra and other phases of this program.

(23) F. Asinger, M. Thiel, and V. Tesar, *Ann. Chem.*, **619**, (1958).

(24) A. McKenzie, R. Roger, and G. O. Wills, *J. Chem. Soc.*, 779 (1926).

Nitration and Acetylation of 9-Alkylfluorenes[1]

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The products from nitration and acetylation of some 9-alkylfluorenes have been investigated. Nitration gave either 2-nitro derivatives (12–38% yield) or 2,9-dinitro (tentative assignment) derivatives (33–60% yield). Monoacetylation occurred in 60–75% yield. Successive steps of oxime formation and Beckmann rearrangement converted the acetyl derivatives into acetylamino compounds. In one case (9-methylfluorene), the acetyl group was shown to occupy the 2-position. Air oxidation of the monoacetyl-9-ethylfluorene gave a crystalline product, assigned the structure of 2-acetyl-9-ethyl-9-fluorenyl hydroperoxide.

The high carcinogenic activities of 2-fluorenamine and related compounds have been recognized for some years.[4] In this respect, it seemed of interest to prepare similar derivatives of 9-alkylfluorenes for biological investigations. The present study is concerned with the syntheses and structural determinations of primary substitution products of 9-alkylfluorenes, obtained through processes of nitration and acetylation of the parent hydrocarbons Ia–d (Scheme I).

In an effort to prepare 2-nitro-9-alkylfluorenes, we followed the same general procedure (concentrated

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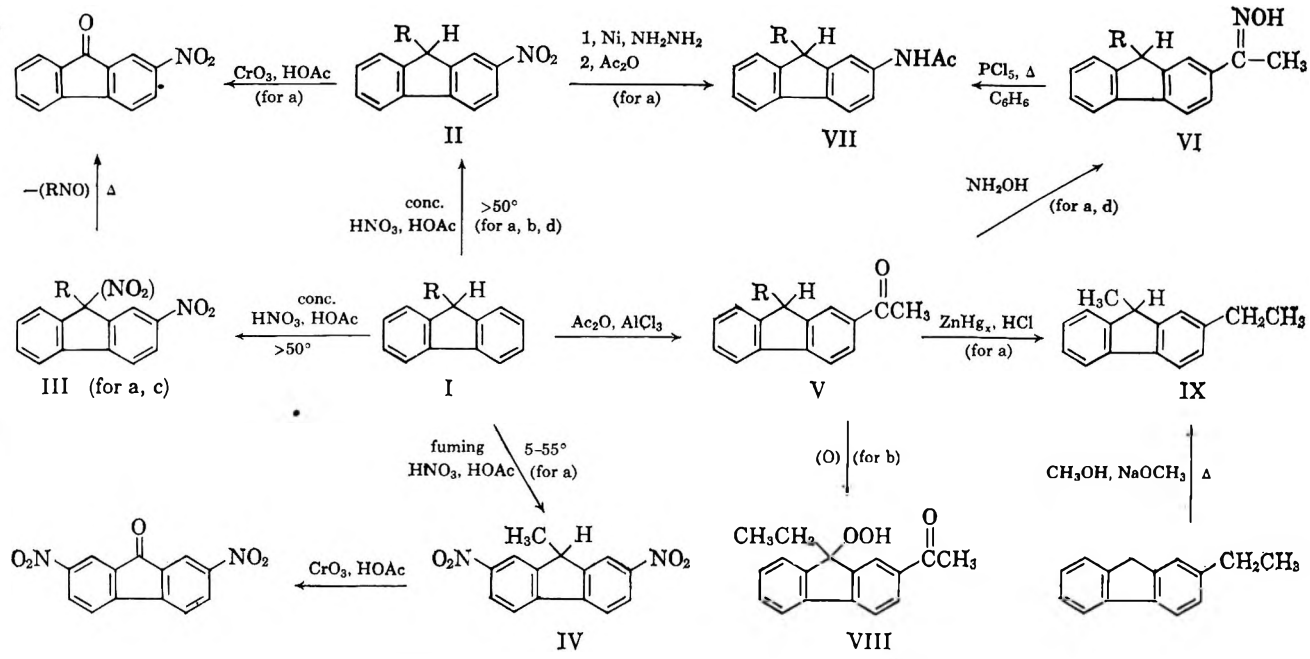
(4) E. K. Weisburger and J. H. Weisburger, "Advances in Cancer Research," Vol. 5, J. P. Greenstein and A. Haddow, Ed., Academic Press, Inc., New York, N. Y., 1958, pp. 331–431.

SCHEME I



a, R = Me; b, R = Et; c, R = *n*-Pr; d, R = *i*-Pr

nitric acid in glacial acetic acid at 50° and above) as was used to convert fluorene into 2-nitrofluorene in good yield.[5] For the isopropyl compound Id, the reaction proceeded similarly although the yield of mononitro derivative IId was considerably smaller (38%). However, with the 9-alkylfluorenes Ia and b, the reaction proved to be sufficiently exothermic that it was difficult to control the temperature in the same manner. Although the exact reasons for the differences are not yet clear, in two runs there resulted small yields (12–16%) of mononitro derivatives IIa and b, while in another run (with Ia), the product A, m.p. 185°, isolated in 60% yield, had an elemental composition consistent with the molecular formula $C_{14}H_{10}N_2O_4$. Analogously Ic formed B, $C_{16}H_{14}N_2O_4$, in 33% yield. Direct comparison of A with a synthetic sample of the dinitro-9-methylfluorene, prepared by means of fuming nitric acid in glacial acetic acid at 5–55° according to the directions of Wawzonek, Dufek, and Sial,[6] showed that the two compounds were different. Although Wawzonek, *et al.*, assigned a structure of 2,7-dinitro-9-methylfluorene (IV) to their product, they did not prove this structure.

For structural determinations on the preceding compounds, the following procedures were used. First of all, oxidation of the Wawzonek dinitro derivative served to confirm their suggested structure since it gave 2,7-dinitrofluorenone, identical (as based on several criteria) with an authentic sample prepared similarly from 2,7-dinitrofluorene. Likewise, oxidation of our mononitro-9-methylfluorene yielded 2-nitrofluorenone.[7] Pyrolysis of A or B produced a colorless gas (which turned reddish-brown on contact with air) and left a residue of 2-nitrofluorenone (corresponding to the loss of the elements of nitroso alkane). Oxidation of B (A was not investigated) likewise gave 2-nitrofluorenone. N.m.r. spectra of A and B showed no absorption band in the immediate vicinity of δ = 3.8 p.p.m., where absorption due to the lone hydrogen atom on the 9-position of 2-nitro-9-methylfluorene and of various other 2-substituted 9-alkylfluorenes occurs. Moreover, these spectra (*vide infra*) indicate that the alkyl groups are intact. It is thus apparent that the second nitro moiety must occupy the 9-position.

The action of nitric acid on alkylarenes has been reviewed by Topchiev.[8] As applied to the formation of A or B, it would appear that nitration in the 2-position (electrophilic substitution) should occur preferentially during the early stages of the reaction, but later in the process the effects of increasing dilution (by means of the water formed) of the nitric acid and of rising temperature should be to favor free-radical substitution of the tertiary hydrogen (which is also α to both aromatic rings) in the 9-position by an –OH, –NO, $-NO_2$, or –ONO group. Although an OH–NO combination would fit the analytical data, it is inconsistent with the aforementioned n.m.r. spectra and the absence of any OH band in the infrared spectra. The presence of interfering absorption by the 2-nitro group, moreover, prevented use of infrared or ultraviolet spectra for distinguishing between the 9-nitro and 9-nitrite possibilities in the manner applicable to monofunctional derivatives.[9]

A survey of the literature shows that 9-nitro-,[10] 9,9-dinitro-,[11] and 2,9-dinitrofluorenes[12] have been reported and found to undergo thermal decomposition

(5) W. E. Kuhn, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons' Inc., New York, N. Y., 1943, pp. 447, 448.

(6) S. Wawzonek, E. Dufek, and N. M. Sial, *J. Org. Chem.*, **21**, 276 (1956); see also G. B. Bachman and S. Polansky, *ibid.*, **16**, 1690 (1951).

(7) The structures of the other mononitro derivatives, IIb and d, are assigned by analogy with IIa.

(8) A. V. Topchiev, "Nitration of Hydrocarbons and Other Organic Compounds," Pergamon Press, Inc., New York, N. Y., 1959, pp. 155–179; see also A. I. Titov, *Tetrahedron*, **19**, 557 (1963).

(9) J. F. Brown, *J. Am. Chem. Soc.*, **77**, 6341 (1955); L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, Chapter 17; H. E. Ungnade and R. A. Smiley, *J. Org. Chem.*, **21**, 993 (1956).

(10) W. Wislicenus and M. Waldmüller, *Ber.*, **41**, 3334 (1908); C. D Nenitzescu and D. A. Isacescu, *ibid.*, **63**, 2484 (1930).

(11) H. Wieland and C. Reisenegger, *Ann.*, **401**, 244 (1913).

(12) W. Wislicenus and H. Weitemeyer, *ibid.*, **436**, 1 (1924).

near their melting points with the evolution of oxides of nitrogen and the formation of fluorenone (in the first two cases) or 2-nitrofluorenone (in the third case). The possibility that these "9-nitrofluorenes" were actually "9-fluorenyl nitrites" instead was not considered. The thermal instability (to form initially nitrosomethane and acetone) of *t*-butyl nitrite is well known.[13] However, both triphenylmethyl nitrite and triphenylnitromethane appear to be thermally unstable.[14] Pending a thorough investigation of the various "9-nitrofluorene" cases, we tentatively designate compounds A and B by the simpler terminology of 2,9-dinitro-9-alkylfluorenes.

Acetylation of three 9-alkylfluorenes (R = Me, Et, *i*-Pr) was conducted by means of the Friedel–Crafts method using acetic anhydride, aluminum chloride, and nitrobenzene. Yields of 60–75% of monoacetyl derivatives (V) were obtained. In the methyl and isopropyl cases, the ketones were first converted to oximes (80% yield of VI) by means of pyridine and hydroxylammonium chloride and then to their acetylamino derivatives (VII, 45% yield) through Beckmann rearrangement. That the acetylamino group in VIIa (and, hence, also the $CH_3C(=NOH)$– group in VIa and the acetyl group in Va) occupies the 2-position in the fluorene ring was established[15] by comparison of the amide from Beckmann rearrangement with that derived by catalytic reduction, and subsequent acetylation, of 2-nitro-9-methylfluorene (IIa). Although the two amides were obtained in somewhat different crystalline forms, they had identical melting points (undepressed on admixture) and infrared spectra (in chloroform solution). As a synthetic pathway to VIIa from the parent hydrocarbon 9-methylfluorene the route *via* the acetyl derivative (26% over-all yield) is clearly superior to that *via* the nitro derivative (16% yield on first step).

The structural assignment of 2-acetyl-9-methylfluorene (Va) was corroborated by a second series of transformations, wherein Va was reduced by the Clemmensen method to 2-ethyl-9-methylfluorene (IX), a liquid hydrocarbon likewise available from methylation of authentic 2-ethylfluorene by means of sodium methoxide in methanol at elevated temperatures (in the manner used for the synthesis of 9-methylfluorene from fluorene).[16] Proof of identity of the two samples of IX was hampered by the fact that autooxidation slowly occurs, presumably to form mixtures of IX and oxygenated derivatives, on standing in contact with air.[17] The pure hydrocarbons, however, were separable by means of vapor phase chromatography and showed identical, expected infrared spectra when fresh.

A minor product (m.p. 161°, 4% yield) was also obtained from acetylation of 9-ethylfluorene, where vacuum distillation (using an air bubbler) was employed in processing the product. In contrast, no minor products were isolated from acetylation of the homologous methyl and isopropyl compounds, where vacuum distillation was not used. This by-product had an elemental composition consistent with the formula $C_{17}H_{16}O_3$ and exhibited an OH– stretching band in its infrared spectrum. The n.m.r. spectrum showed no absorption in the region of 3.9 p.p.m., where a triplet (ascribed to the presence of a single hydrogen on C-9) occurs in the spectrum of 2-acetyl-9-ethylfluorene (Vb). Inasmuch as this compound gave a positive test with starch–iodide paper and could be synthesized by air oxidation of Vb, it is assigned the structure of 2-acetyl-9-ethyl-9-fluorenyl hydroperoxide (VIII).[18]

In Table I are presented pertinent data on the aliphatic proton absorption patterns in the n.m.r. spectra of fluorene and various derivatives of it. Examination of the table shows, as expected, the presence of a doublet for the 9-methyl group and a quartet for the 9-hydrogen for both 9-methylfluorene and 2-nitro-9-methylfluorene. The change to a singlet (at lower field) for the 9-methyl group and the loss of absorption for the 9-hydrogen are consistent with the structural assignment given to 2,9-dinitro-9-methylfluorene. A somewhat similar, but more complex, relationship can be noted between 9-*n*-propylfluorene and 2,9-dinitro-9-*n*-propylfluorene. Thus, in the nitro derivative the multiplet for the α-methylene hydrogens of the *n*-propyl group is shifted to lower field while absorption due to the 9-hydrogen (a triplet in the hydrocarbon) is missing. The superimposed absorption bands (consisting of two intense, but unequal, peaks plus a number of weak peaks) for the β-methylene plus methyl protons have closely similar shapes in both compounds. In 2-nitro-, 2-acetyl-, and 2-acetylamino-9-isopropylfluorene the expected doublet for the 9-hydrogen occurs at *ca.* 3.8 p.p.m. However, except for the third compound in one solvent (benzene), two doublets (centered at *ca.* 0.8 p.p.m.) appear for the methyl groups when only one might have been expected. Moreover, in the 2-nitro derivative the multiplet at *ca.* 2.5 p.p.m. shows at least ten peaks. It is proposed that the occurrence of the two doublets (and possibly of the decet or higher multiplet) may be ascribed to nonequivalence of the two methyl groups in the isopropyl substituent.[19] For the acetylamino derivative (which was investigated in three solvents) the magnitude of the primary splitting in these doublets (*ca.* 7 c.p.s.) did not vary significantly with change in solvent, while that of the secondary splitting (0 in benzene, 1.2 in pyridine, and 3 c.p.s. in deuteriochloroform) was solvent dependent. In contrast, for the parent hydrocarbon 9-isopropylfluorene no secondary splitting occurs even in deuteriochloroform.

Experimental[20]

2-Nitro-9-methylfluorene (IIa).—To a stirred solution of 18 g. (0.1 mole) of 9-methylfluorene[16] in 140 ml. of glacial acetic acid at 50–55° was added dropwise, over a period of 15 min., 22 ml. of concentrated nitric acid (69%). The temperature rose spontaneously to 65–70°. After 10 min. at this temperature, the mixture was gradually (over 2 hr.) cooled to room temperature and then poured into 2 l. of water. The pasty precipitate which formed on standing was dissolved in 50 ml. of

(13) J. B. Levy, *Ind. Eng. Chem.*, **48**, 762 (1956); P. Gray, *Chem. Ind.* (London), 120 (1960).

(14) W. Schlenk, L. Mair, and C. Bornhardt, *Ber.*, **44**, 1169 (1911); J. N. Ray, *J. Chem. Soc.*, **117**, 1335 (1920).

(15) By analogy with Va, the acetyl groups in Vb and d are also assumed to occupy the 2-position of the fluorene nucleus.

(16) K. L. Schoen and E. I. Becker, *Org. Syn.*, **39**, 43 (1959).

(17) Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 5449 (1958); see also ref. 27.

(18) For a review of the literature on alkyl hydroperoxides, see A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, Chapter 1.

(19) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 18–19.

(20) Microanalyses were performed by Micro-Tech Laboratory, Skokie, Ill. Ultraviolet absorption spectra were obtained by means of a Cary Model 11 spectrophotometer, infrared spectra, by means of a Beckman IR-7 instrument.

TABLE I

MAGNETIC RESONANCE CHARACTERISTICS AND ASSIGNMENTS FOR PROTONS ON ALIPHATIC CARBON ATOMS IN SOME SUBSTITUTED FLUORENES

Substituent(s) on fluorene			Characteristics and assignments,[b] δ, p.p.m.[c] (multiplicity),[d] J, c.p.s.		
9-Position	2-Position	Solvent[a]	9-H[e]	9-Alkyl substituent	2-Substituent
H, H	H	A	(s)		
H, H	Ac	A	(s)		2.44 (s)
H, Me	H	A	(q) 7.5	1.40 (d) 7.5	
H, Me	NO_2	A	(q) 7.5	1.38 (d) 7	
NO_2, Me	NO_2	B	*f*	2.26 (s)	
H, Me	Ac	A	(q) 7.5	1.49 (d) 7.5	2.51 (s)
H, Me	Et	A	(q) . . .[g]	1.5 (d) 7	2.7 (q) 7[h] 1.2 (t) 7[i]
H, Me	NHAc	C	(q?) . . .[g]	1.43 (d) 7	2.14 (s)
H, Et	Ac	A	(t) 6	2.07 (m) . . .[g, h]; 0.67 (t) 7.5[i]	2.52 (s)
H, Et	NO_2	A	(t) 6	2.04 (m) . . .[g, h]; 0.66 (t) 7.5[i]	
HOO, Et	Ac	B	*f*	*ca.* 2.4 (m) . . .[g, l]; 0.60 (t) 7.5[i]	2.49 (s)[l]
H, *n*-Pr	H	A	(t) 6	*ca.* 1.8 (m) . . .[g, j]; *ca.* 0.8 (m) . . .[g, k]	
NO_2, *n*-Pr	NO_2	A	*f*	*ca.* 2.5 (m) . . .[g, j]; *ca.* 0.8 (m) . . .[g, k]	
H, *i*-Pr	H	C	(d) 3.5	*ca.* 2.5 (m) . . .[g]; 0.82 (d) 7	
H, *i*-Pr	Ac	A	(d) 3.5	*ca.* 2.5 (m) . . .[l]; 0.82 (2d)[m]	2.5 (s)[l]
H, *i*-Pr	NO_2	A	(d) 4	*ca.* 2.5 (m) 4; 0.82 (2d)[n]	
H, *i*-Pr	NHAc	B	(d) 3.5	*ca.* 2.5 (m) . . .[g]; 0.81 (2d)[n]	2.23 (s)
H, *i*-Pr	NHAc	C	(d) 3.5	*ca.* 2.4 (m) . . .[g]; 0.77 (2d)[o]	2.14 (s)
H, *i*-Pr	NHAc	D	(d) 3.5	. . .[p]; 0.77 (d) 7	1.78 (s)

[a] A represents carbon tetrachloride; B, pyridine; C, deuteriochloroform; D, benzene. [b] Using tetramethylsilane as internal standard. [c] Given for 9-alkyl and 2-substituents only. [d] Singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m. [e] δ = 3.58 p.p.m. for the 9-hydrogen atoms in fluorene itself and 3.8 ± 0.1 for those in all of the other compounds listed. [f] No absorption near 3.8 p.p.m. [g] Resolution or concentration was inadequate to allow a suitable determination of *J*. [h] Methylene. [i] Methyl. [j] α-Methylene in the substituent. [k] Methyl plus β-methylene in the substituent. [l] Intense singlet (2-acetyl) superimposed on weak multiplet (methylene hydrogens on ethyl group or lone hydrogen on isopropyl group). [m] Two doublets: *J* = 7.5 c.p.s. for primary splitting and 2 c.p.s. for secondary splitting. [n] Two doublets: *J* = 7 c.p.s. for primary splitting and 1.2 c.p.s. for secondary splitting. [o] Two doublets: *J* = 7 c.p.s. for primary splitting and 3 c.p.s. for secondary splitting. [p] No absorption was detected above the noise level in the spectrum.

toluene. Addition of 150 ml. of cyclohexane to the toluene solution gave a precipitate which was recrystallized twice from methanol, yielding 3 g. of yellow crystals, m.p. 82–83°. Residues from evaporation of the organic layers were dissolved in the minimal quantity of chloroform and chromatographed on a 3.8 × 30 cm. column of Mallinckrodt silicic acid using 30–60° petroleum ether–benzene (4:1 v./v.) as eluent. The effluent furnished 0.7 g. more of product, m.p. 83–84° (total yield 16%). Recrystallization from absolute ethanol gave a sample for analysis, m.p. 84–85°, slightly yellow needles; $\lambda_{max}^{Et_2O}$ 237 mμ (log ε 4.25) and 327 (4.67).

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.61; H, 4.96; N, 6.38.

2-Nitro-9-ethylfluorene (IIb).—Nitration of 0.1 mole of 9-ethylfluorene[16] was conducted by the preceding method. The temperature rose more rapidly but was prevented from exceeding 83°. The toluene layer was washed with water, dried, and evaporated to leave a residue which was recrystallized from methanol, yielding 12%, m.p. 69–70°. Further recrystallizations gave yellow shiny leaves, m.p. 70–71°.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.09; H, 5.36; N, 6.20.

2-Nitro-9-isopropylfluorene (IId).—This was prepared from 9-isopropylfluorene[21] in the manner used for IIb, except that it was necessary to apply external heat in order to bring the reaction temperature up to 80°, yield 38%, m.p. 78–80°. Recrystallization from absolute ethanol gave faintly yellow prisms, m.p. 79.5–80.5°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.68; H, 5.99; N, 5.57.

2,9-Dinitro-9-methylfluorene (IIIa).—The nitration was conducted using 2.5 times the quantities of reagents employed for the preparation of IIa, but the same period of 15 min. for addition. Over *ca.* 40 min. the temperature of the reaction mixture was increased to 80°, where it was kept for 5 min. Then it was allowed to decrease to 20° over a period of 2.5 hr. The red-brown crystals which precipitated from the reaction mixture were separated, washed twice (using a solution of 0.5 g. of sodium acetate in 25 ml. of glacial acetic acid each time), and dried *in vacuo*. A second crop was obtained on pouring the mother liquor into water, to give a total yield of 40.3 g. (60%), m.p. 175–179°. Four recrystallizations from glacial acetic acid and one from toluene gave yellow needles, m.p. 184–185°; $\lambda_{max}^{Et_2O}$ 214 mμ (log ε 4.63), 241 (4.25), and 322 (4.57).

Anal. Calcd. for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.04; H, 4.01; N, 10.22.

2,9-Dinitro-9-*n*-propylfluorene (IIIc).—Following the preceding method, 52 ml. of concentrated nitric acid was added to a solution of 50 g. (0.24 mole) of 9-*n*-propylfluorene[16] in 330 ml. of glacial acetic acid. As the temperature was raised to 80°, however, an exothermic reaction suddenly occurred and the reaction temperature rose spontaneously to 110°. The mixture was cooled to 75° over a period of 2 min. and then subsequently to room temperature over a period of 2 hr. The pasty precipitate which formed on pouring the mixture into 1.5 l. of water was collected and recrystallized once from ethanol, yielding 23.6 g. (33%), m.p. 95–108°. Four recrystallizations from toluene and one from ethanol gave yellow prisms, m.p. 111–112°; $\lambda_{max}^{Et_2O}$ 216 mμ (log ε 4.71), 241 (4.35), and 324 (4.62).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.66; H, 4.87; N, 9.35.

Oxidation of Nitrofluorenes. A.—Synthetic 2-nitrofluorenone, m.p. 220–221°, was obtained by nitration of fluorene[6] and subsequent oxidation with chromium trioxide in glacial acetic acid.[22] 2,7-Dinitrofluorene (Aldrich Chemical Co., Milwaukee, Wis.) was converted to 2,7-dinitrofluorenone (m.p. 291–292°) in a similar manner.[23] When dissolved in concentrated sulfuric acid, 2-nitrofluorenone gave a red color[24] and 2,7-dinitrofluorenone gave a yellow-green color.

B.—A refluxing solution of 1 g. of 2,7-dinitro-9-methylfluorene (m.p. 246–247°, synthesized by the method of Wawzonek, Dufek, and Sial)[6] in 70 ml. of glacial acetic acid was treated with 7 g. of chromium trioxide, added in three portions over a period of 1.5 hr. After 1 hr. of additional refluxing, the mixture was

(21) D. N. Matthews and E. I. Becker, *J. Org. Chem.*, **21**, 1317 (1956).

(22) J. Strasburger, *Ber.*, **17**, 107 (1884).

(23) G. T. Morgan and R. W. Thomason, *J. Chem. Soc.*, 2691 (1926).

(24) I. Heilbron, "Dictionary of Organic Compounds," Vol. III, Oxford University Press, New York, N. Y., 1953, p. 688.

poured into water and the collected precipitate was recrystallized first from glacial acetic acid and then from toluene, m.p. 286–290°, undepressed on admixture with a sample of synthetic 2,7-dinitrofluorenone from A. The two samples were also identical in infrared spectra and color test with concentrated sulfuric acid.

Thermal Decomposition of 2,9-Dinitro-9-alkylfluorenes.—Heating 2,9-dinitro-9-methylfluorene at 210° in a small-diameter glass tube for 5 min. gave evolution of a colorless gas which turned reddish brown (probably to form nitrogen dioxide) on contact with air. When evolution of gas had ceased, the residue was recrystallized first from glacial acetic acid and then from absolute ethanol, m.p. 219–221°, identified as 2-nitrofluorenone by direct comparison (mixture melting point, infrared spectrum, color test) with the preceding synthetic sample.

Similar treatment of 2,9-dinitro-9-*n*-propylfluorene at 220–230° gave a residue which (after one recrystallization from pyridine) gave an infrared spectrum identical with that of 2-nitrofluorenone.

Acetylation of 9-Alkylfluorenes.—To a cold (−5°) stirred mixture of 14.6 ml. of acetic anhydride, 34.6 g. of anhydrous aluminum chloride, and 150 ml. of nitrobenzene was added 0.12 mole of 9-alkylfluorene in portions. The mixture was stirred for 3 hr. at 0° and then for 3 hr. at 20°. It was poured into a mixture of ice and 10% hydrochloric acid. For R = Me, the nitrobenzene was removed by steam distillation and the residual solid was recrystallized from acetone (using decolorizing charcoal), m.p. 116–118°, 20-g. (75%) yield. Further recrystallization from methanol gave leaves of 2-acetyl-9-methylfluorene (Va), m.p. 116.5–117.5°, which produced a greenish yellow color when dissolved in concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.24; H, 6.46.

For R = *i*-Pr, there resulted a 60% yield of crude product, obtained as needles of 2-acetyl-9-isopropylfluorene (Vd), m.p. 77–78° after four recrystallizations from methanol.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.71; H, 7.26.

For R = Et, the nitrobenzene layer was separated, washed successively with concentrated hydrochloric acid, dilute aqueous sodium carbonate solution, and water, dried, and distilled *in vacuo* (first at 18 mm.), yielding 67% of yellow viscous liquid, b.p. 165–168° (0.6 mm.). Recrystallization from absolute ethanol gave needles of 2-acetyl-9-ethylfluorene (Vb), m.p. 86–87°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.45; H, 6.74.

2-Acetyl-9-ethyl-9-fluorenyl Hydroperoxide (VIII).—Also isolated from the recrystallization solvent for Vb was a 4% yield of yellow by-product, m.p. 159–161°; on recrystallization from ethanol it was converted to yellow flakes of VIII, m.p. 160–161°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.39; H, 6.18.

To a cold (−20°) solution of 67 mg. of Vb in 3 ml. of anhydrous pyridine was added 1 drop of Triton B solution. Dry air was passed over the rapidly stirred, deep blue mixture for 1 hr. (After 15 min. the color had become pale green). The reaction mixture was warmed to room temperature, treated with excess dilute hydrochloric acid, and extracted with chloroform. Evaporation of the dried solvent gave 40 mg. of VIII (m.p. 155–156°), identical (after further recrystallization) with the previously described by-product as based on infrared spectra.

Methyl 9-Methyl-2-fluorenyl Ketoxime (VIa).—A mixture of 15 g. of 2-acetyl-9-methylfluorene, 15 g. of hydroxylammonium chloride, 75 ml. of absolute ethanol, and 75 ml. of pyridine was refluxed for 3 hr. Removal of solvents and stirring the residue with water yielded 13 g. (81%) of crystals. Four recrystallizations from methanol gave cubes, m.p. 167–168°.

Anal. Calcd. for $C_{16}H_{15}NO$: N, 5.90. Found: N, 5.89.

Methyl 9-Isopropyl-2-fluorenyl Ketoxime (VId).—In the preceding manner was obtained an 84% yield of crude oxime, m.p. 160–161°. Recrystallization gave long, cotton-like needles, m.p. 161–162°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.45; H, 7.11; N, 5.05.

2-Acetylamino-9-methylfluorene (VIIa). A. From the Nitro Derivative.—To a warm (50°), stirred solution of 4.3 g. of 2-nitro-9-methylfluorene in 75 ml. of toluene and 25 ml. of absolute ethanol was added 3.1 ml. of hydrazine (95%) and then (in four equal portions over a period of 1 hr.) 20 mg. of Raney nickel.[25] The colorless mixture was distilled until the distillate no longer gave an alkaline test. The filtered residual mixture was concentrated to *ca.* 13 ml., diluted with 9 ml. of absolute ethanol, and cooled to 0° to give hygroscopic crystals of amine (dried in a desiccator). A solution of 1 g. of this amine in 5 ml. of anhydrous pyridine and 10 ml. of acetic anhydride was left at room temperature for 24 hr. and then evaporated. The *residue* was triturated with water and recrystallized repeatedly from methanol to give faintly cream platelets, m.p. 173.5–174.5°.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.19; H, 6.53; N, 6.00.

B. From the Oxime Derivative.—To a cold (10°) solution of 12 g. of oxime VIa in benzene was added 13 g. of phosphorus pentachloride. The mixture was refluxed for 15 min. and then poured into ice and water. The residue remaining from evaporation of benzene extracts of the aqueous mixture was recrystallized twice from methanol (5.2-g yield, 43%) and then sublimed at 0.3 mm. and 150° to give a cotton-like product, m.p. 173–174°, undepressed on admixture with product from A. Infrared absorption spectra in chloroform solution of amides from A and B were identical.

2-Acetylamino-9-isopropylfluorene (VIId).—Following the preceding Beckmann rearrangement method B, there was obtained (from 6.1 g. of oxime VId) 2.6 g. (43%) of once-recrystallized product, m.p. 145–147°. Repeated recrystallizations from methanol gave faintly yellow prisms, m.p. 148–149°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.21; H, 7.29; N, 5.49.

2-Ethyl-9-methylfluorene (IX). A. From 2-Ethylfluorene.—2-Ethylfluorene was obtained by Clemmensen reduction of 2-acetylfluorene (Aldrich Chemical Co.)[26] according to the directions of Campbell and Wang.[27] A mixture of 11 g. of analytically pure 2-ethylfluorene, m.p. 99.5–100.5°,[28] and a solution made from 2 g. of sodium metal and 40 ml. of absolute methanol was heated at 170–180° for 16 hr. in a 500-ml. rocking autoclave. The mixture was then processed in the manner used for similar synthesis of 9-alkylfluorenes,[16] yielding 5.6 g. (48%) of liquid, b.p. 110–120° (0.2 mm.). Redistillation at 0.2 mm. gave a central fraction of slightly yellow liquid, b.p. 114°, for an analytical sample.

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.13; H, 7.85.

A **1,3,5-trinitrobenzene complex** was obtained as bright yellow needles from absolute methanol, m.p. *ca.* 78°.[29]

Anal. Calcd. for $C_{16}H_{16}{\cdot}C_6H_3N_3O_6$: N, 9.97. Found: N, 10.03.

B. From Va.—Clemmensen reduction, in the preceding manner, on 4.7 g. of Va gave 3 g. of crude product. Two fractional distillations gave an analytically pure sample of light yellow liquid, b.p. 112° (0.15 mm.), $n^{25}D$ 1.4968.

Anal. Found: C, 92.56; H, 7.75.

Infrared spectra on freshly prepared samples from A and B were identical, as were those on samples which had stood in stoppered containers for a few months. The older samples, however, showed strong OH bands and gave positive tests with starch–iodide paper. Gas chromatography of older samples using Apiezon L as stationary phase and 250° gave two major fractions. Infrared analysis indicated that the fraction of shorter retention time was nearly pure IX while the second fraction was a ketone, not further identified.

N.m.r. Spectra.—Proton magnetic resonance spectra were obtained by means of a Varian Associates A-60 spectrometer using tetramethylsilane as internal standard. Data relative to absorption by aliphatic protons for selected compounds are presented in Table I. All compounds also exhibited multiple absorptions at $\delta > 6$ p.p.m. for the aromatic protons present.

(25) Adapted from the procedure of T. L. Fletcher and M. J. Namkung [*J. Org. Chem.*, **23**, 680 (1958)] for reduction of 2-nitrofluorene to 2-aminofluorene. Note that our hydrazine was nearly anhydrous and not 64% as employed by Fletcher and Namkung.

(26) Melting point undepressed on admixture with product from direct acetylation of fluorene by the method of W. E. Bachmann and J. C. Sheehan [*J. Am. Chem. Soc.*, **62**, 2687 (1940)].

(27) N. Campbell and H. Wang, *J. Chem. Soc.*, 1513 (1949).

(28) E. Sawicki, *J. Am. Chem. Soc.*, **76**, 2269 (1954); see also J. D. Dickinson and C. Eaborn, *J. Chem. Soc.*, 2337 (1959).

(29) Near this temperature it was difficult to decide from visual observation if the sample were a solid, a liquid, or both.

Free-Radical Chemistry of Cyclic Ethers. VII. Ultraviolet Photolysis of Epoxides and Propylene Sulfide in the Liquid Phase[1]

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Ultraviolet light has been found to cause carbon–oxygen bond cleavage in epoxides and carbon–sulfur bond cleavage in a thioepoxide. Studies with unsymmetrical epoxides indicated that both carbon–oxygen bonds cleave and that the intermediate diradicals are converted, by subsequent radical reactions which involve no rearrangements, into alcohols and aldehydes or ketones. For example, the irradiation of propylene oxide gave acetone, isopropyl alcohol, propionaldehyde, and propyl alcohol, though not in equal amounts. A reaction sequence is suggested which is applicable to the irradiation of epoxides and the thioepoxide.

Results from the peroxide-initiated free-radical reactions of epoxides and thioepoxides[1] prompted a study of the effects of ultraviolet light on these classes of compounds in solution. It was thought that ultraviolet light would cleave the carbon–oxygen and carbon–sulfur bonds of the three-membered ring, thus stimulating interest in the type of bond scission reactions and the products arising from these scissions.

It is known from the pioneering work of Gomer and Noyes[3] that photolysis of ethylene oxide gives free radicals, but the products obtained indicate several different types of bond cleavage. Cvetanovic[4] has subsequently restudied the reaction and concurred as to the findings.

Further work by Cvetanovic and Doyle[5] on the gas phase photolysis of 2,3-butylene oxide led them to postulate a diradical intermediate for its breakdown. One interesting product which they identified was isobutyraldehyde which apparently formed by a free-radical rearrangement reaction. It was hoped that the rearrangement might also occur in the present study when the photolysis was done in solution. The carbon–oxygen bond scission as postulated by Cvetanovic[5] is well supported by the data of Gray and Williams[6] who reported that the bond energies for the carbon–oxygen bonds to be about 30 kcal./mole less than those for carbon–carbon bonds.

The ready availability of both symmetrical and unsymmetrical epoxides permitted a study which could determine the effect of substituents on bond cleavage. The paucity of sulfur compounds of this nature dictated the use of only one representative epoxide for comparison studies.

Results

The products identified from the ultraviolet light-initiated free-radical reactions of epoxides carried out to only a few per cent of reaction to eliminate secondary reactions have indicated that both carbon–oxygen bonds in an unsymmetrical epoxide undergo homolytic cleavage. The intermediate diradicals formed from the initial cleavages are converted, by subsequent radical reactions, into alcohols and ketones. Some of the intermediate radicals have been found to dimerize and have also been found to add to 1-octene. The modes of the initial epoxide cleavages are seen from the products identified from the photolysis of propylene oxide in the presence and absence of 1-octene, as contained in Table I.

TABLE I

PRODUCTS IDENTIFIED FROM THE ULTRAVIOLET LIGHT IRRADIATION OF PROPYLENE OXIDE

Propylene oxide, moles	1-Octene, moles	Products identified	Origin
Neat		Acetone	C-1–O cleavage
		Isopropyl alcohol	C-1–O cleavage
		Propionaldehyde	C-2–O cleavage
		Propyl alcohol	C-2–O cleavage
1.5	1.5	Acetone	C-1–O cleavage
		Isopropyl alcohol	C-1–O cleavage
		Propionaldehyde	C-2–O cleavage
		Propyl alcohol	C-2–O cleavage
		2-Hendecanone	C-1–O cleavage with addition to 1-octene
		2-Hendecanol	C-1–O cleavage with addition to 1-octene
		2,5-Hexanedione	C-1–O cleavage with dimerization
		2,5-Hexanediol	C-1–O cleavage with dimerization

Cyclohexene oxide and styrene oxide were photolyzed and found to undergo the same type of cleavage reactions as propylene oxide. Subsequent radical reactions to form alcohols and ketones also occurred. The quantitative data are presented in Table II.

TABLE II

QUANTITATIVE IRRADIATION OF EPOXIDES

Reactant	Product	Yield,[a] % conversion
Propylene oxide	Acetone	0.28
	Isopropyl alcohol	0.21
	Propionaldehyde	0.01
	Propyl alcohol	0.01
	2,5-Hexanedione	0.22
Cyclohexene oxide	Cyclohexanone	0.23
	Cyclohexanol	0.14
Styrene oxide	Acetophenone	0.03
	2-Phenylethanol	0.14
	1-Phenylethanol	0.13

[a] Based on the original charge of epoxide.

(1) Part VI: *Nature*, **198**, 284 (1963); previous paper to this study is V: *J. Org. Chem.*, **28**, 3437 (1963).

(2) To whom inquiries should be addressed at IBM.

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The ultraviolet photolysis of propylene sulfide resulted mainly in the formation of a high-boiling clear resinified material. No compound boiling lower than allyl disulfide was obtained, and the only product that could be identified was allyl disulfide. Table III summarizes the photolytic reactions of propylene sulfide.

TABLE III

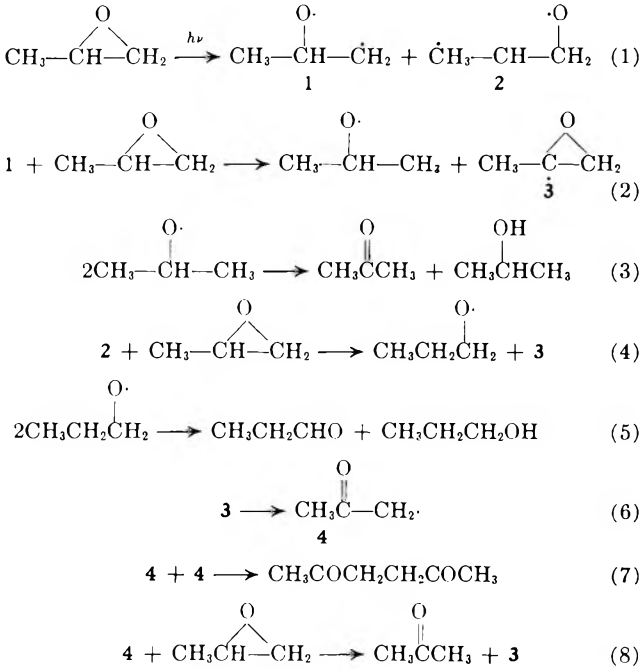
REACTIONS OF PROPYLENE SULFIDE

Reactants (moles, g.)	Reaction conditions	Products identified	Yield,[a] % conversion	Residue, g.
Propylene sulfide (0.10, 7.41)	Ultraviolet, 15°, 72 hr.	Allyl disulfide	0.05	5.95
Propylene sulfide (0.10, 7.41)	Ultraviolet, 15°, 24 hr.	Allyl disulfide	<0.01	6.00

[a] Based on the total amount of propylene sulfide used.

Discussion

The ultraviolet photolysis of the symmetrical epoxide, cyclohexene oxide, resulted in the homolytic cleavage of a carbon–oxygen bond with subsequent formation of cyclohexanol and cyclohexanone. In the unsymmetrical epoxides, propylene oxide and styrene oxide, both carbon–oxygen bonds were found to undergo scission. The following sequence would describe the photochemical decomposition of propylene oxide and is applicable to the breakdown of the other epoxides.



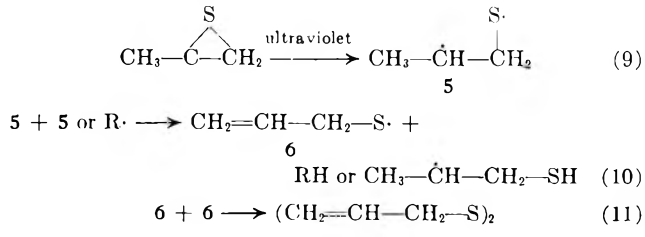
Although the reactions in the above sequence rationalize the formation and amounts of the observed products, they are not intended to constitute the only possible mechanism for these reactions, for one can also include other mixed dimerization reactions of the acetonyl radical.

An important reaction and one of major concern to this study is the initial homolytic cleavage of both carbon–oxygen bonds to form diradicals **1** and **2**. The subsequent rearrangements of **1** directly to acetone and **2** to acetaldehyde were neglected since hydrogen atom shifts are very rare.[7a] The hydrogen atom abstraction reactions 2 and 4 involved carbon–hydrogen bond formation and *not* oxygen–hydrogen bond formation; not only because it permits a reasonable mechanism to be written, but also because the polar effects in the two possible transition states predict carbon–hydrogen bond formation to be favored.[7b] The formation of the acetonyl radical, **3**, in the same reactions may require that a short-chain reaction be operating; the slight excess of acetone over isopropyl alcohol suggests that this is the case. Most of the acetonyl radicals apparently disappear by reaction 7, as evidenced. Finally, it can be noted that the products are similar to those obtained in vapor phase photolyses of epoxides and those formed from the diradical which results when an oxygen atom adds to an olefin.[8]

The proposed C–O bond scissions receive added support when other initial cleavages are considered. If C-1–H scission is considered with propylene oxide, the formation of propyl alcohol cannot be explained. If C-2–H scission (that found in the peroxide initiated reaction[1]) is occurring, the isopropyl alcohol found cannot be explained. An finally, if C–C bond cleavages are considered, the three carbons skeleton cannot arise from this path and many more products should be formed.[5]

The quantitative data indicate that the C-1–O to C-2–O cleavage ratio is about 25:1 with propylene oxide and about 1:1 with styrene oxide. The differences in the two ratios is not ready explained; more study is necessary to clarify these ratios. The cyclohexene oxide study only gives an indication of the importance of the various chain and termination steps.

The photolytic stability of propylene sulfide is very low, for almost complete resin formation resulted where most of the epoxides were recovered unchanged. Interestingly, no thioacetone trimer was found, only allyl disulfide. The nature of the initial cleavage is undoubtedly the cleavage of a S–C bond to give a biradical which readily polymerizes. The product probably forms by the following reaction sequence.



Experimental

Reagents.—Propylene oxide (Matheson Coleman and Bell, b.p. 34°, $n^{20}D$ 1.3622) and 1,2-butylene oxide (Dow Chemical Co., b.p. 60.5°, $n^{20}D$ 1.3831) were purified by distillation through an 80-plate concentric tube Podbielniak column (Model No. 2208). The styrene oxide, the 1-octene, the cyclohexene oxide prepared from 2-bromocyclohexanol, and the propylene sulfide prepared from propylene oxide and thiourea[9] were distilled through efficient columns equipped with a tantalum-wire spiral before use. All starting materials were shown to be pure (<0.001%) by gas chromatography and the *pure* materials did

(7) (a) C. Walling, "Molecular Rearrangements," Vol. 1, P. D. Mayo, Ed., New York, N. Y., 1963, p. 416; (b) G. A. Russell, *J. Org. Chem.*, **23**, 1407 (1958).

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not change on standing either in the bottle or the reaction vessels.

The authentic compounds used for comparative gas chromatographic and infrared identifications were either purified commercially available compounds or ones prepared in these laboratories by known methods.[1] The ultraviolet-initiated free-radical reactions were carried out with end absorption from a spiral internal light source which emitted 95% of light of 2537 Å. (Hg resonance lamp) to a limited extent to eliminate secondary reactions. For the quantitative determination of products the reactions were maintained at approximately 15°. The following illustrative reaction mixtures were photolyzed for 72 hr., except in the case of propylene sulfide. For gas chromatography, column A was 10 ft., Ucon polar; column B was 10 ft., 3% Carbowax; column C was 10 ft., di-*n*-decyl phthalate; and column D was 10 ft., silicone.

Irradiation of Propylene Oxide with 1-Octene.—Propylene oxide (1.5 moles, 87.12 g.) and 1.5 moles of 1-octene (168.32 g.) were photolyzed and the reaction mixture was distilled to remove the unchanged epoxide and 1-octene. Continued distillation through the 12-in. nichrome-wire-spiral column separated the distillable materials (1.91 g.) from the high boiling residue (0.40 g.). The infrared spectra of the distillate fractions possessed the following two important bands: 3475 (hydroxyl function) and 1710 cm.$^{-1}$ (carbonyl function). Identification of products was made by comparitive gas chromatography: acetone, column A, 46°, 5 lb. of He, 11.5 min., and column A, 70°, 5 lb., 5.7 min.; isopropyl alcohol, A, 70°, 5 lb., 11.2, and A, 85°, 5 lb, 7.5 min.; propionaldehyde, A, 45°, 10 lb., 6.0 min., and A, 55°, 10 lb. 4.6 min.; propyl alcohol, A, 70°, 5 lb., 22.2 min., and A, 85°, 5 lb., 14.5 min.; 2-hendecanone, column B, 157°, 10 lb., 6.0 min.; 2-hendecanol, column B, 157°, 10 lb., 8.8 min.; 2,5-hexanedione, B, 157°, 5.4 min.; and 2,5-hexanediol, 156°, 10 lb., 19.0 min.

Irradiation of Propylene Oxide.—Propylene oxide (3.1 moles, 180 g.) was photolyzed as described above. The reaction mixture was distilled through an 18-in. tantalum-wire-spiral column to give (1) a fraction containing mainly unchanged propylene oxide (approximately 160 g.), (2) a fraction whose infrared spectrum showed the presence of bands ascribable to the hydroxyl and carbonyl functions (*ca.* 5 g.), and (3) a polymeric residue (approximately 1 g.). Identification of products was made by gas chromatography on column A: acetone, 50°, 5 lb. of He, 8.9 min.; propionaldehyde, 50°, 5 lb., 7.4 min.; isopropyl alcohol, 89°, 10 lb., 7.8 min.; and propyl alcohol, 89°, 10 lb., 15.4 min.

Irradiation of Propylene Oxide. Quantitative Run.—Propylene oxide (0.20 mole, 11.62 g.) was photolyzed at 15° as described. A very slow distillation of the reaction mixture through an 18-in. tantalum-wire-spiral column removed only propylene oxide. The remaining material was quantitatively analyzed by gas chromatography and the following conversions were calculated: acetone, 0.28%; isopropyl alcohol, 0.21%; propionaldehyde, 0.01%; propyl alcohol, 0.01%; 2,5-hexanedione, 0.22%; all based on the original charge of epoxide.

Irradiation of Cyclohexene Oxide in the Presence of 1-Octene.—Cyclohexene oxide (0.20 mole, 19.63 g.) and 0.02 mole of 1-octene (2.24 g.) were photolyzed as described above. The infrared spectrum of the irradiated reaction mixture showed bands at 3475 and 1710 cm.$^{-1}$. These bands were not present in the spectrum of the nonirradiated cyclohexene oxide. Identification of products from the distilled reaction mixture was made by gas chromatography: cyclohexanone, column B, 106°, 10 lb., 6.5 min., and column A, 95°, 10 lb., 13.3 min.; and cyclohexanol, B, 106°, 10 lb., 10.5 min., and A, 95°, 10 lb., 16.7 min. Identification of the products arising from the intermediate radicals adding to 1-octene was not made.

Irradiation of Cyclohexene Oxide. Quantitative Run.—Cyclohexene oxide (0.10 mole, 9.81 g.) was photolyzed at 15° as described above. The infrared spectrum of the reaction mixture showed hydroxyl and carbonyl bands. The quantitative determinations were made by gas chromatography without distillation of the reaction mixture. The following conversions were obtained: cyclohexanone, 0.23%, and cyclohexanol, 0.14%.

Irradiation of Styrene Oxide. Quantitative Run.—Styrene oxide (0.10 mole, 12.01 g.) was photolyzed at 15° as described above. The infrared spectrum of the irradiated styrene oxide contained bands at 3475 and 1710 cm.$^{-1}$. These bands were not contained in the spectrum of the nonirradiated styrene oxide. Identification of products was made by gas chromatography: acetophenone, column C, 165°, 10 lb. of He, 23.2 min., 0.03%; 2-phenylethanol, B, 153°, 15 lb., 14.2 min., 0.14%; and 1-phenylethanol, 153°, 15 lb., 9.4 min., 0.13%.

Irradiation of Propylene Sulfide.—Propylene sulfide (0.10 mole, 7.41 g.) was photolyzed for 72 hr. as previously described. The viscous reaction mixture was distilled and only 0.15 g. of material was obtained (Kugelrohr tube distillation,[10] over 150°, 0.15 mm.) Identification of allyl disulfide was made by gas chromatography (column D, 104°, 5 lb. of He, 7.7 min., and 133°, 10 lb., 7.6 min.). Thioacetone or its trimer could not be identified in the reaction mixture (the gas chromatographic conditions caused the trimer to go to the monomer).

Irradiation of Propylene Sulfide.—Propylene sulfide (0.10 mole, 7.41 g.) was photolyzed for 24 hr. at 15° as previously described. The reaction mixture was again very polymeric and only 2.0 g. of material could be distilled by a Kugelrohr tube distillation[10] (over 150°, 0.01 mm.). Identification of allyl disulfide was made by gas chromatography (column A, 145°, 15 lb. of He, 3.6 min.). Thioacetone or its trimer could not be identified in the reaction mixture. Gas chromatography (column A, 15 lb. of He) showed that the propylene sulfide used did not contain allyl mercaptan.

Acknowledgment.—The authors wish to thank the U. S. Army Natick Laboratories for support of this research through Contracts DA-19-129-1051 and 1708, and Dr. Junji Kumamoto for his helpful comments.

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Synthesis of Carnosine, Anserine, and Isoanserine

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A new method for the synthesis of carnosine, anserine, and isoanserine is described. N-Phthalyl-β-alanine is condensed by the mixed anhydride method with histidine, 1-methylhistidine, and 3-methylhistidine, respectively, in aqueous solution. Hydrazinolysis of the phthalyl group yields the above dipeptides. An independent proof of structure for anserine is presented also.

Carnosine and anserine are dipeptides occurring in vertebrate skeletal muscle. Despite numerous publications relating to their physiological role, no valid biochemical function has as yet been assigned to them. Recent evidence[1] suggests that the two histidine peptides may provide a major portion of the buffering action necessary to maintain a physiological pH range in skeletal muscles during and immediately after strenuous exercise.

The constitution of carnosine has been established as β-alanyl-L-histidine by degradation and synthesis,[2-5] and that of anserine as β-alanyl-1-methyl-L-histidine.[6] Synthetic anserine was first obtained by Behrens and du Vigneaud[7] by condensation of 1-methyl-L-histidine methyl ester (prepared by hydrolysis of natural L-anserine and esterification of the 1-methyl-L-histidine thus obtained) with N-carbobenzoxy-β-alanyl azide followed by hydrolysis and hydrogenation of the reaction product.

In this paper we report a new more convenient method for the synthesis of carnosine, anserine, and "*iso*-anserine," together with independent proof of structure for anserine. The mixed anhydride obtained from N-phthalyl-β-alanine and ethyl chlorocarbonate was condensed with the lithium salt of L-histidine in aqueous solution to give a 60% yield of N-phthalyl-β-alanyl-L-histidine. Hydrazinolysis of the phthalyl group furnished L-carnosine in 96% yield. Similarly a 54% yield of N-phthalyl-β-alanyl-3-methyl-L-histidine was obtained from N-phthalyl-β-alanine and 3-methyl-L-histidine. After cleavage of the phthalyl group β-alanyl-3-methyl-L-histidine (isoanserine) was isolated as the nitrate in 54% yield. This peptide has not been encountered in nature and is described here for the first time.[8] The same procedure furnished N-phthalyl-β-alanyl-1-methyl-L-histidine in 65% yield and L-anserine nitrate in 98% yield. The free bases were obtained by removal of the nitrate ion with Dowex-3 resin. The optical rotation and melting point of L-anserine agreed with the values reported for the naturally occurring compound, but differed from those found for L-isoanserine.

1-Methyl-L-histidine, L-α-amino-β-(1-methyl-5-imidazolyl)propionic acid, and 3-methyl-L-histidine, L-α-amino-β-(1-methyl-4-imidazolyl)propionic acid, were prepared by treatment of L-histidine with sodium and methyl iodide in liquid ammonia[9] and separation of the isomers on a Dowex-50 column (α-picolinium form) essentially according to McManus.[10] 1-Methyl-L-histidine was racemized by heating with acetic anhydride in acetic acid according to Bergmann and Zervas.[11] The infrared spectrum of the racemic product was found to be identical with that of 1-methyl-DL-histidine of unequivocal constitution, synthesized according to Jones and McLaughlin,[12] thus proving the 1-position of the methyl group of 1-methyl-L-histidine obtained by methylation of L-histidine. These findings together with the synthesis described above provide independent confirmation of the structure of L-anserine as β-alanyl-1-methyl-L-histidine. The infrared spectrum of 3-methyl-DL-histidine obtained by racemization of 3-methyl-L-histidine with barium hydroxide was recorded for comparison.

It is interesting to note that racemization of 3-methyl-L-histidine with acetic anhydride in acetic acid[11] led to a mixture of three ninhydrin-positive substances from which 3-methyl-DL-histidine could be isolated only in poor yield and with great difficulty. Racemization with barium hydroxide[13] yielded 3-methyl-DL-histidine and a second more basic component, which were separated on an Amberlite CG-50 column. The nature of the second component has not yet been ascertained. 1-Methyl-L-histidine when racemized by barium hydroxide likewise gave two ninhydrin-positive materials, whereas L-histidine under the same conditions furnished DL-histidine only.

There are few references in the literature concerning the use of free amino acids in the synthesis of peptides. The simplicity of procedure and fair yields of peptides obtained in the present approach are therefore noteworthy.

Experimental[14]

N-Phthalyl-β-alanyl-L-histidine.—A solution of 5.26 g. of phthalyl-β-alanine[5] and 2.4 g. of freshly distilled triethylamine in 100 ml. of ethylene glycol dimethyl ether (dried over calcium hydride) was cooled to −5° in an ice–methanol bath. The solution was stirred mechanically and 2.6 g. of ethyl chlorocarbonate was added dropwise. The reaction mixture was stirred for an additional 10 min., filtered to remove triethylammonium chloride, and added all at once with vigorous stirring to an ice-cooled solution of 3.1 g. of L-histidine in 60 ml. of water contain-

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(13) F. Ehrlich, *Biochem. Z.*, **63**, 379 (1914).
(14) Melting points are uncorrected. Microanalyses were by A. Elek Microanalytical Laboratories, Los Angeles, Calif.

ing 1 mole equiv. of lithium hydroxide at pH 9.6. Vigorous evolution of carbon dioxide ensued, and the initially clear solution became turbid with formation of a gelatinous precipitate. After standing at 5° for 2 hr., the reaction mixture (pH 7.5) was adjusted to pH 5.0 with 1 *N* hydrochloric acid (approximately 20 ml.) and filtered. The filtrate was evaporated to dryness at low temperature and pressure and the resulting frothy glass-like residue was triturated with 200 ml. of methanol to give a white granular solid. Water (10 ml.) was added and the mixture was heated to boiling. The resulting solution was allowed to cool, whereupon it deposited crystalline N-phthalyl-β-alanyl-L-histidine in 3.5-g. yield. Evaporation of the mother liquors to dryness and recrystallization of the residue from a hot mixture of 50 ml. of methanol and 8 ml. of water furnished 0.8 g. of a second crop. The total yield was 4.3 g. (60%), m.p. 230–235° dec., $[\alpha]^{22}D$ +21.0°; lit.[5] m.p. 221–224° dec., $[\alpha]^{22}D$ +21.5°. In a large-scale experiment 1500 g. of phthalyl-β-alanine tri-*n*-butylammonium salt was condensed with 685 g. of L-histidine as outlined above. Filtration of the mixed anhydride solution was omitted since tri-*n*-butylammonium chloride is soluble in ethylene glycol dimethyl ether. The yield of recrystallized product was 57%.

L-Carnosine was obtained by hydrazinolysis of N-phthalyl-β-alanyl-L-histidine according to Turner,[5] m.p. 255–260° dec., $[\alpha]^{23}D$ +20.1° (*c* 2, water); lit.[5,15] m.p. 250–253° dec. and 260° dec., $[\alpha]^{22}D$ +21.7° and $[\alpha]^{25}D$ +20.5°.

N-Phthalyl-β-alanyl-1-methyl-L-histidine.—A solution of 8.8 g. of phthalyl-β-alanine and 8.1 g. of freshly distilled tri-*n*-butylamine in 180 ml. of ethylene glycol dimethyl ether (dried over calcium hydride) was stirred mechanically, cooled to −5°, and treated with 4.5 g. of ethyl chlorocarbonate as described above. After stirring for an additional 10 min., the mixed anhydride solution was added to 75 ml. of a cold aqueous solution of the lithium salt of 7.5 g. of 1-methyl-L-histidine (Calbiochem, Los Angeles, Calif.) with vigorous stirring. Stirring was continued for an additional 30 min. at 10°. The reaction mixture then was adjusted to pH 5.5 with 1 *N* hydrochloric acid and evaporated to dryness. The glossy white residue was distilled successively with 200 ml. of methanol and then with a mixture of 100 ml. of methanol and 100 ml. of 2-propanol. It then was boiled gently with 200 ml. of methanol while approximately 15 ml. of water was added cautiously until one phase was obtained. The solution was filtered and cooled to give 9.65 g. (65%) of crystalline product, m.p. 222–223°. After recrystallization from a mixture of 340 ml. of methanol and 34 ml. of water the product was dried *in vacuo* over phosphorus pentoxide, yielding 7.65 g., m.p. 228–230°.

Anal. Calcd. for $C_{18}H_{18}N_4O_5$: N, 15.13. Found: N, 15.13.

L-Anserine Nitrate.—N-Phthalyl-L-anserine (38.2 g.) was dissolved in 120 ml. of water and treated with a solution of 5.9 g. of hydrazine (95%) in 33 ml. of methanol. After standing at room temperature for 3 days, the reaction mixture was diluted with water and acidified with acetic acid. The precipitate of phthalyl hydrazide was removed by filtration and the filtrates were evaporated to dryness at low temperature and pressure. Traces of acetic acid were removed by two successive distillations with 25 ml. of water. The solid residue then was dissolved in 75 ml. of water containing 4.8 ml. (1 mole equiv.) of concentrated nitric acid. The solution was evaporated to dryness at low temperature and pressure, and the residue was redissolved in 25 ml. of methanol. 2-Propanol (150–200 ml.) then was added to the solution and the mixture was stored at 5° overnight. Anserine nitrate was obtained as shiny needles, 18 g., m.p. 220°. Concentration of the mother liquors and addition of 2-propanol yielded two further crops of material (8.4 and 4 g.) of similar quality. The total yield was 98%. The crude product was recrystallized by heating with 300 ml. of methanol and adding water (50–60 ml.) until one phase was obtained. The solution was refrigerated overnight and filtered. The precipitate of anserine nitrate was collected and dried at 60° over phosphorus pentoxide *in vacuo*, 20.5 g., m.p. 226–228°, lit.[7] m.p. 225°.

Anal. Calcd. for $C_{10}H_{17}N_5O_6$: C, 39.60; H, 5.65; N, 23.09. Found: C, 39.67; H, 5.72; N, 23.22.

L-Anserine.—A solution of 1 g. of anserine nitrate in 50 ml. of water was shaken with 5 g. of Dowex 3-X4 (free base) resin for 50 min. and filtered. The resin was washed twice with water and the pooled filtrates were evaporated to dryness. Traces of water were removed by three distillations with 10 ml. of 2-propanol. The residue was crystallized by heating with 10 ml. of methanol and adding water dropwise until one phase was obtained. Upon cooling, 0.45 g. of L-anserine was obtained, m.p. 240–242° dec. after drying at 60° over phosphorus pentoxide *in vacuo*, $[\alpha]^{23}D$ +11.4° (*c* 5, water); lit.[7,16] m.p. 238–239° dec., $[\alpha]^{30}D$ +12.25° and $[\alpha]^{16}D$ +11.26°.

Anal. Calcd. for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.72; N, 23.33. Found: C, 50.10; H, 6.47; N, 23.11.

N-Phthalyl-L-isoanserine.—The mixed anhydride prepared from 8.8 g. of N-phthalyl-β-alanine and 4.5 g. of ethyl chlorocarbonate in ethylene glycol dimethyl ether as described above, was condensed with 7.5 g. of 3-methyl-L-histidine (Calbiochem, Los Angeles, Calif.). The reaction mixture was adjusted to pH 5.5 and evaporated to dryness at low temperature and pressure. The sirupy residue was distilled successively with 200 ml. of methanol, a mixture of 100 ml. of methanol and 100 ml. of 2-propanol, and finally with 100 ml. of methanol to give a white, dry powder. The material was dissolved in 100 ml. of methanol, and 100 ml. of 2-propanol was added to the solution. The precipitate which formed on cooling was collected, washed with 2-propanol and ether, and dried over phosphorus pentoxide, yielding 10.1 g. A second crop (5.7 g.) was obtained from the mother liquors after further refrigeration. The material was recrystallized from a mixture of 150 ml. of methanol and 7 ml. of water in 8.5-g. (54%) yield. The product was a hydrate and melted at 152–155°. A sample was recrystallized and dried at 60° over phosphorus pentoxide *in vacuo*, m.p. 233–235° dec.

Anal. Calcd. for $C_{18}H_{18}N_4O_5$: C, 58.37; H, 5.16; N, 15.13. Found: C, 58.40; H, 5.00; N, 15.11.

L-Isoanserine Nitrate.—A solution of 1.8 g. of N-phthalyl-L-isoanserine in 6 ml. of water was treated with 0.3 g. of hydrazine (95%) in 2 ml. of methanol. After 3 days at room temperature, the reaction mixture was diluted with 10 ml. of water, acidified with acetic acid, and filtered. The filtrate was evaporated to dryness and the residue was distilled twice with 100 ml. of water to remove traces of acetic acid. The material then was dissolved in 50 ml. of water containing 0.4 ml. of concentrated nitric acid (20% excess) and the solution was evaporated to dryness. The residue was dissolved in a minimum volume of hot methanol. L-Isoanserine crystallized upon cooling, yielding 0.75 g. (54%), m.p. 178–180°. After a second crystallization from 15 ml. of methanol and 0.75 ml. of water and drying at 60° over phosphorus pentoxide *in vacuo*, the product melted at 183–185°.

Anal. Calcd. for $C_{10}H_{17}N_5O_6$: C, 39.60; H, 5.65; N, 23.10. Found: C, 39.36; H, 5.73; N, 23.03.

L-Isoanserine.—The free base was prepared by treatment of the nitrate with Dowex 3X-4 (free base) resin as described for L-anserine. The crude product was recrystallized from methanol containing 7% water and dried at 60° over phosphorus pentoxide *in vacuo*, m.p. 239–243° dec., $[\alpha]^{21}D$ +33.5° (*c* 1, water).

Anal. Calcd. for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.71; N, 23.33. Found: C, 49.79; H, 6.91; N, 23.05.

3-Methyl-DL-histidine.—A solution of 480 mg. of 3-methyl-L-histidine in 12 ml. of a saturated solution of barium hydroxide was heated to 150–160° in a sealed tube for 20 hr. After cooling to room temperature, carbon dioxide gas was passed through the reaction mixture and the precipitate of barium carbonate was removed by filtration. The filtrate was concentrated to a small volume, filtered once more, and evaporated to dryness. The residue was dissolved in 3 ml. of water. Paper chromatograms run on Whatman No. 1 paper (11.5 × 12.5 in.) in the solvent system 2-propanol–water (75:25) revealed the presence of two ninhydrin-positive components: 3-methyl-DL-histidine with R_f 0.22 and an unknown with R_f 0.38. The solution was then applied to a 12 × 0.9 cm. column of Amberlite CG-50 H-form resin. Elution with water (approximately 2500 ml.) yielded chromatographically pure 3-methyl-DL-histidine. The unknown remaining on the resin was eluted with 0.025 *M* acetic acid. The first eluate containing 3-methyl-DL-histidine was evaporated to dryness. The residue was dissolved in 7 ml. of methanol. The solution was filtered and evaporated to dryness. The residual solid was dissolved in 0.5 ml. of methanol, and 5 ml. of 2-propanol was added with stirring. Crystallization of 3-methyl-DL-histidine was induced by scratching with a glass rod. After cooling, filtering, and drying over phosphorus pentoxide

(15) R. H. Sifferd and V. du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935).

(16) D. Ackermann, O. Timpe, and K. Poller, *Z. Physiol. Chem.*, **183**, 1 (1929).

in vacuo, 370 mg. of product was obtained. It was further purified by recrystallization from a mixture of 3 ml. of methanol, 3 ml. of 2-propanol, and 5 drops of water, yielding 290 mg., m.p. 224–226° dec., $[\alpha]^{22}D$ 0.00 (*c* 3, water). The compound was chromatographically homogeneous in three different solvent systems: (1) 2-propanol–water (75:25), (2) pyridine–acetone–ammonia (6 *N*) (45:30:25), and (3) 2-propanol–formic acid–water (8:1:1).

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Synthesis and Reactions of Anhydrous Lithium Cyanide[1]

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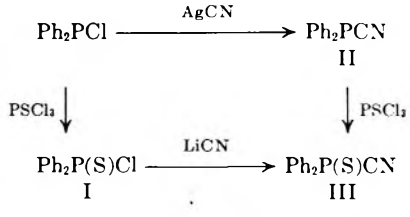
A new synthesis of anhydrous lithium cyanide is reported. Its reactivity is compared with that of silver cyanide. With organic halogen compounds it yields the normal cyano derivative. Its reactions with phenacyl bromide, diphenylchlorophosphine oxide and sulfide, and with diphenyldicyanosilane are described.

Anhydrous lithium cyanide has been found to be an effective reagent for replacing the chloro group by the cyano group in some compounds which do not react with silver cyanide. The latter reagent is usually employed for such replacements on halo phosphines.[2,3] However, it fails to react with diphenylchlorophosphine sulfide, diphenylchlorophosphine oxide, or diphenyldichlorosilane. Anhydrous lithium cyanide reacts readily with these compounds to give good yields of the cyano derivatives. This reactivity is not surprising in view of the good solubility of lithium cyanide in solvents of high dielectric constant, its low melting point, and the high charge density of the unhydrated lithium ion.

Anhydrous lithium cyanide is easily prepared in high purity and yield by the reaction of liquid hydrogen cyanide with *n*-butyllithium. Anhydrous lithium cyanide has been synthesized previously by the treatment of lithium foil with 50% hydrogen cyanide in benzene[4] and by the reaction of anhydrous hydrogen cyanide with an ether suspension of hydrated lithium hydroxide.[5]

The synthesis of diphenylcyanophosphine sulfide by the use of anhydrous lithium cyanide can serve to illustrate the greater reactivity of lithium cyanide than silver cyanide. The sulfide III was synthesized by the following two routes: (1) by the reaction of phosphorus thiochloride with diphenylcyanophosphine (II), and (2) by the reaction of anhydrous lithium cyanide with diphenylchlorophosphine sulfide (I).



The reaction of I with silver cyanide yielded only starting material. However, the reaction of anhydrous lithium cyanide with I at room temperature yielded III (70%). The recovered residue (26%) proved to be undistillable material of various degrees of polymerization. The synthesis of III can also be carried out, however, in high yield by the reaction of phosphorus thiochloride with II.

Neither potassium cyanide nor silver cyanide reacted with diphenylchlorophosphine oxide, only starting material being recovered. However, with lithium cyanide an undistillable solid product was obtained in 59% yield. This product gave the correct analysis for diphenylcyanophosphine oxide but is undoubtedly polymeric.

The greater reactivity of anhydrous lithium cyanide is illustrated again in its reaction with diphenyldichlorosilane. There was no reaction between silver cyanide and diphenyldichlorosilane in refluxing benzene overnight or at 160–185° for 6 hr. without solvent. Lithium cyanide and diphenyldichlorosilane in refluxing benzene gave diphenyldicyanosilane in 68% yield. Silver cyanide does react with diphenyldibromosilane to give diphenyldiisocyanosilane in 80% yield, as described by McBride.[6]

Lithium cyanide reacted readily with phenacyl bromide in dimethylformamide solution to form benzoylacetonitrile, indicating that it yields the cyano and not the isocyano derivative.

Experimental

Lithium Cyanide.—*n*-Butyllithium (64 g., 1.0 mole) in hexane (Foote Mineral Co.) was transferred by filter stick under nitrogen pressure into a 1-l. three-necked, round-bottomed flask fitted with a pressure-equalizing dropping funnel, a nitrogen inlet tube, and a cold finger trap cooled with trichloroethylene–Dry Ice to −14°. A solution of anhydrous hydrogen cyanide (26 g., 0.96 mole) in 32 ml. of dry benzene was added dropwise and with rapid stirring to the *n*-butyllithium at 0–5°. There was immediate precipitation of a white solid. After the addition was complete, the reaction mixture was stirred for an additional 15 min. The contents of the flask were rapidly transferred under nitrogen to a 500 ml. filter apparatus equipped with a large coarse fritted disk and a 40–50 ground glass joint to facilitate pouring from the reaction flask under dry nitrogen. The white solid was washed four times with dry benzene and four times with petroleum ether (b.p. 30–60°) and dried under vacuum at 100–110° to yield 33.1 g. (quantitative yield), m.p. 161–162° (lit.[4] m.p. 160°).

Benzylacetonitrile.—Lithium cyanide and phenacyl bromide in acetonitrile or in dimethylformamide yielded benzoylacetonitrile, m.p. 80.5–80.7°. By vapor phase chromatography the product

(1) Presented at the XIXth International Congress of Pure and Applied Chemistry, London, July 10–17, 1963.

(2) Michaelis, *Ann.*, **293**, 193 (1896); **294**, 1 (1896).

(3) Plets, dissertation, Kazan, 1938. As cited by G. M. Kosolapoff "Organophosphorus Compounds," John Wiley and Sons, Inc., N. Y., 1950, pp. 49, 55.

(4) A. Perret and R. Perrot, *Helv. Chim. Acta*, **15**, 1165 (1932).

(5) J. Meyer, *Z. anorg. Chem.*, **115**, 203 (1920).

(6) J. J. McBride, Jr., *J. Org. Chem.*, **24**, 2029 (1959).

was proved to be greater than 90% pure, showing that LiCN yielded the cyano and not the isocyano derivative.

Diphenylchlorophosphine Sulfide (I).—This compound was prepared in a manner analogous to those of Rattenbury[7] and Jansen.[8] Diphenylchlorophosphine (44 g., 0.2 mole, $n^{21}D$ 1.6325) and phosphorous thiochloride (34 g., 0.2 mole) were heated at 125° until evolution of the phosphorous trichloride ceased. Distillation of the residual solution *in vacuo* yielded 48 g. (95%) of I, a clear colorless liquid, b.p. 152–155° (0.55 mm.), $n^{20}D$ 1.6563 (lit.[9] b.p. 155–160° at 0.3 mm.).

Diphenylcyanophosphine Sulfide (III). **A. By II and Phosphorus Thiochloride.**—Diphenylcyanophosphine (II) was prepared by the reaction of silver cyanide with diphenylchlorophosphine according to the method of Plets.[3] The colorless liquid (94% yield, b.p. 187–188° at 13.5 mm., $n^{20}D$ 1.6205, d^{25}_4 1.1198) had elemental analyses in excellent agreement with the theoretical values. It did not solidify on standing (lit.[3] b.p. 170–175° at 15 mm., m.p. 39–40°).

Diphenylcyanophosphine (63 g., 0.3 mole) and phosphorus thiochloride (51 g., 0.3 mole, b.p. 125°) were heated at 102° until the by-product, phosphorus trichloride (b.p. 76°, 94%), ceased to distil. Distillation under reduced pressure yielded 56.8 g. (70%) of III as a colorless liquid, b.p. 149–151° (0.25 mm.), $n^{20}D$ 1.6414, d^{25}_4 1.2023. This liquid solidified upon standing to give a white solid, m.p. 50.0–50.2°.

Anal. Calcd. for $C_{13}H_{10}NPS$: C, 64.18; H, 4.14; N, 5.76; P, 12.73; S, 13.18. Found: C, 64.25; H, 4.31; N, 5.72; P, 12.97; S, 13.00.

In other runs, the distillation was carried out also at 214–216° (9 mm.) to give the pure product. The infrared spectrum of the compound is consistent with the structure. The CN peak is observed at 2180 cm.$^{-1}$.

B. By I and Lithium Cyanide.—Anhydrous lithium cyanide (6.6 g., 0.2 mole) was added in portions under nitrogen to a solution of diphenylchlorophosphine sulfide (50 g., 0.2 mole) in 50 ml. of dry benzene. There was no immediate heat effect. After standing overnight at room temperature, the deep brown reaction mixture was heated at reflux for 1 hr. and then filtered by coarse fritted disk under nitrogen pressure. The solid was washed with two small portions of benzene. The combined filtrate and benzene washings were concentrated to a small volume. Distillation under reduced pressure yielded 33.7 g. (70%) of a colorless liquid, b.p. 213–214° (8.6 mm.), $n^{20}D$ 1.6393. The liquid solidified on standing to a white solid. The values for melting point, boiling point, index of refraction, and the infrared spectrum are the same as those of the compound prepared by reaction of II with phosphorus thiochloride.

The pot residue consisted of a nondistillable brown solid with an average molecular weight of 1360 and believed to be low molecular weight polymers of diphenylcyanophosphine sulfide.

Diphenylcyanophosphine Oxide.—Diphenylchlorophosphine oxide (23.6 g., 0.1 mole, b.p. 168–169° at 1.2 mm., $n^{21}D$ 1.6112) and anhydrous lithium cyanide (3.3 g., 0.1 mole) in 30 ml. of dry benzene were heated at reflux overnight. The reaction mixture was processed in the same manner as above. Distillation under diminished pressure gave 5.6 g. of starting material and 13.9 (59%) of an undistillable brown residue, m.p. 60–70°. This is the compound in the polymeric form to which these nitriles are readily converted.

Anal. Calcd. for $C_{13}H_{10}NOP$: N, 6.17; P, 13.63. Found: N, 5.83; P, 13.52.

Diphenyldicyanosilane.—Diphenyldichlorosilane (25 g., 0.1 mole, b.p. 99–100° at 0.3 mm.) was added dropwise to a suspension of anhydrous lithium cyanide (6.8 g., 0.206 mole) in 100 ml. of dry benzene. There was no heat evolution. After being heated at reflux overnight, the reaction mixture was processed in the same manner as above. Distillation of the residual liquid yielded 15.8 g. (67.5%) of a clear, colorless liquid, b.p. 118–122° (0.28 mm.), $n^{20}D$ 1.5636, d^{24}_4 1.1146. The liquid was redistilled to give a main fraction, b.p. 122° (0.24 mm.), $n^{20}D$ 1.5626, d^{26}_4 1.1067 (lit.[6] b.p. 142° at 2 mm., m.p. 46–48°, $n^{30}D$ 1.559932, d^{30}_4 1.090432).

Anal. Calcd. for $C_{14}H_{10}N_2Si$: C, 71.75; H, 4.31; N, 11.35. Found: C, 71.36; H, 4.56; N, 10.56.

The infrared spectrum showed a major peak at 2180 cm.$^{-1}$ and a minor peak at 2260 cm.$^{-1}$. Separation by v.p.c. yielded two nearly equal components with the same absorption spectra except for the relative intensities of these two bands. It is possible, but as yet not proven, that the compound contains both cyano and isocyano groups.

(7) K. H. Rattenbury, U. S. Patent 2,993,929 (1961).
(8) W. L. Jansen, U. S. Patent 2,662,917 (1953).
(9) W. A. Higgins, P. W. Vogel, and W. G. Craig, *J. Am. Chem. Soc.*, **77**, 1864 (1955).

Preparation, Characterization, and Reactions of Lithium and Sodium Tetraalkylboron Compounds

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Lithium and sodium tetraalkylboron compounds have been prepared by the reaction of alkyllithium and alkylsodium reagents with trialkylboranes. These tetraalkylboron compounds show extreme reactivity toward air and were therefore identified by the formation of stable tetramethylammonium and tetrabutylphosphonium derivatives. Unusual infrared and n.m.r. absorption peaks at 2750–2800 cm.$^{-1}$ and 10–10.5 p.p.m., respectively, were present in the spectra of the tetravalent boron compounds. It was shown that these peaks arise from methylene groups adjacent to negative boron atoms. The stability of lithium tetraalkylboron compounds and tetramethylammonium tetrabutylboron in water, acetic acid, and sodium hydroxide solutions was studied. Hydrolysis with 20% acetic acid results in a rapid loss of 1 mole of alkane followed by a slow hydrolysis of the resultant trialkylborane. Air oxidation of lithium tetrabutylboron in tetrahydrofuran at 35° yielded 48% 1-butanol and 3% *n*-butyraldehyde of the theoretical amounts along with a 15% recovery of *n*-butane. The possible routes to these oxidation products are discussed.

Although the synthesis and chemistry of tetraaryl or mixed tetraarylalkylboron compounds have received considerable study,[1] relatively little is known about purely aliphatic tetravalent boron compounds. Over 30 years ago, Thompson and Stevens[2] reported an unsuccessful attempt to prepare these compounds. Soon after this report Johnson and his co-workers[3] observed a positive reaction when they combined tributylborane and *n*-butyllithium. In 1940 Schlesinger and Brown[4] obtained a white solid from the reaction of equimolar amounts of ethyllithium and trimethylborane, to which they assigned the formula $LiC_2H_5{\cdot}B(CH_3)_3$. In the ensuing years Hurd[5] prepared lithium tetramethylboron, and Parsons and co-workers[6] prepared lithium

(1) M. F. Lappert, *Chem. Rev.*, **56**, 1035 (1956).
(2) T. Thompson and T. S. Stevens, *J. Chem. Soc.*, 556 (1933).
(3) J. R. Johnson, H. R. Snyder, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **60**, 115 (1938).
(4) H. I. Schlesinger and H. C. Brown, *ibid.*, **62**, 3429 (1940).
(5) D. T. Hurd, *J. Org. Chem.*, **13**, 711 (1948).
(6) T. D. Parsons, M. B. Silverman, and D. M. Ritter, *J. Am. Chem. Soc.*, **79**, 5091 (1957).

TABLE I

TETRAMETHYLAMMONIUM AND TETRABUTYLPHOSPHONIUM DERIVATIVES OF TETRAALKYLBORON COMPOUNDS

Reaction: $MR'BR_3 + CBr \longrightarrow CR'BR_3 + MBr$

M = Li or Na
R′ = C_4H_9 or $C_{12}H_{25}$
R = C_2H_5 or C_4H_9
C = $(CH_3)_4N$ or $(C_4H_9)_4P$

$MR'BR_3$	% yield, $(CH_3)_4NR'BR_3$	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$Li(C_2H_5)_3BC_4H_9$	89	103–105 dec.	73.3	72.8	15.8	15.6	6.11	6.03
$Li(C_4H_9)_4B$	91	110–112 dec.	76.6	76.3	15.4	15.5	4.47	4.47
$Li(C_2H_5)_3BC_{12}H_{25}$	84	Oil	77.2	77.0	15.4	15.2	4.10	3.97
$Li(C_4H_9)_3BC_{12}H_{25}$	87	Oil	79.0	77.9	15.2	15.0	3.29	3.33
$Na(C_4H_9)_4B$	78	110–112 dec.	76.6	76.2	15.4	15.7	4.47	4.40
$Na(C_2H_5)_3BC_{12}H_{25}$	88	Oil	77.2	77.5	15.4	15.2	4.10	4.02

$MR'BR_3$	% yield, $(C_4H_9)_4PR'BR_3$	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
$Li(C_2H_5)_3BC_4H_9$	65	76–78 dec.	75.3	74.9	14.6	14.3	7.47	7.35
$Li(C_4H_9)_4B$	80	52–55 dec.	77.1	77.1	14.6	14.4	6.21	6.10
$Li(C_2H_5)_3BC_{12}H_{25}$	75	Oil	77.5	78.3	14.5	14.0	5.88	5.70
$Li(C_4H_9)_3BC_{12}H_{25}$	68	Oil	78.6	78.9	14.5	14.2	5.07	4.95

trimethylpropenylboron by this method. The structure of all these products was inferred from the stoichiometry of the reactions and some brief hydrolysis studies. More recently Honeycutt and Riddle[7] reported the preparation of several sodium tetraalkylboron compounds by the novel reaction of sodium triethylborohydride with an α-olefin. Assignment of structures was based on partial elemental analyses, hydrolysis data, and infrared spectra. Ethereal solvents, which give solvated products, were generally used in this reaction system.

Despite this past work, a detailed study of metal tetraalkylboron compounds had not been made. The purpose of this paper is to report the syntheses, characterization, and some of the chemical and physical properties of nonsolvated lithium and sodium tetraalkyl boron compounds.

Preparation.—Attempts to use the method of Honeycutt and Riddle to prepare sodium tetraalkylboron compounds resulted in impure materials which could not readily be purified. However, the direct reaction of an organometallic with trialkylborane in hydrocarbon diluent proceeds smoothly to give the desired MBR_4 compounds,[8] which are easily purified.

$$MR' + R_3B \xrightarrow{n\text{-alkane}} MR_3BR'$$

Compounds prepared

I, $Li(C_2H_5)_3BC_4H_9$
II, $Li(C_4H_9)_4B$
III, $Li(C_2H_5)_3BC_{12}H_{25}$
IV, $Li(C_4H_9)_3BC_{12}H_{25}$
V, $Na(C_4H_9)_4B$
VI, $Na(C_2H_5)_3BC_{12}H_{25}$

Sodium tetraalkylborons, prepared in this manner, are partially soluble in hexane and can be separated from the insoluble alkylsodium reagents by extraction. This resulted in low yields (20–30%) of the pure sodium products. The homogeneous reaction of organolithium and trialkylboron reagents in hexane or pentane provided an 80–95% recovery of insoluble $LiBR_4$ compounds by simple filtration and washing under an inert atmosphere.

Identification.—Since lithium and sodium tetraalkylboron compounds are quite reactive to air, direct analysis of these materials is difficult. It was found, however, that analyzable derivatives of these compounds could be easily prepared in high yields. Thus, water solutions of both lithium and sodium compounds afforded insoluble derivatives upon treatment with either tetramethylammonium or tetrabutylphosphonium bromides. The results from these reactions are summarized in Table I.

Since high yields[9] of pure derivatives are obtained in all cases, there can be little doubt that the original organoboron compounds are indeed pure. Both the ammonium and phosphonium derivatives could be transferred and recrystallized in air without appreciable decomposition. Apparently, the nature of the cation, besides changing the water solubility of the tetralkyl boron compounds, has a remarkable effect on the reactivity of these compounds with oxygen.

Additional evidence for the purity and structural assignments in this class of metal tetraalkylboron compounds was obtained from infrared and nuclear magnetic resonance (n.m.r.) spectra. Table II shows the pertinent infrared absorptions. Of particular interest is the strong absorption found in all these compounds at 2760–2780 cm.$^{-1}$. Peaks in this region immediately suggest a carbon–hydrogen stretching frequency that is shifted by 100–150 cm.$^{-1}$ from the normal region.[10] Absorptions quite similar to these reported here have been observed previously with methyl-, ethyl-, and phenyllithium.[11] To account for this low C–H stretching frequency, West and Glaze postulated association[12] of alkyllithiums to form electron-deficient lithium–carbon–lithium bonds. However, an explanation of this type is not applicable to the tetraalkylboron system for several reasons. First, the negative charge in these compounds represents an ionic charge, not a free

(7) J. B. Honeycutt, Jr. and J. M. Riddle, *J. Am. Chem. Soc.*, **83**, 369 (1961).

(8) All of the alkyl groups in our compounds are unbranched. The prefix *n* is generally omitted in the text for the sake of simplicity without misleading the reader.

(9) Slightly lower yields of the phosphonium–boron compounds, compared to yields of the ammonium–boron compounds, are probably due to the greater water solubility of the former.

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen and Company, London, 1958, p. 13.

(11) R. West and W. Glaze, *J. Am. Chem. Soc.*, **83**, 3580 (1961).

(12) Organolithium reagents have been found to be associated in solution and in vapor phase: *cf.* T. L. Brown, D. W. Dickerhoof, and D. A. Bafus, *ibid.*, **84**, 1371 (1962), and references therein, for a discussion of this phenomenon.

pair of electrons. Therefore, it is difficult to write reasonable structures to utilize the lithium orbitals in covalent bonding. Secondly, the tetramethylammonium and tetrabutylphosphonium tetraalkylboron compounds also have strong low frequency C–H absorptions and, since the ammonium and phosphonium cations could not possibly be involved in covalent bonding, another explanation is necessary to explain the observed infrared absorption.

TABLE II

MAJOR INFRARED ABSORPTIONS OF TETRAALKYLBORON COMPOUNDS,[a] CM.$^{-1}$

$Li(C_2H_5)_3B(C_4H_9)$	$Li(C_4H_9)_4B$	$Li(C_2H_5)_3BC_{12}H_{25}$
2940	2940	2940
2870	2870	2870
2770	2770	2760
1465	1465	1465
1375	1380	1380
1075	1095	1315
1060	1065	1080
1040	1040	1060
	740	890
		720

$Li(C_4H_9)_3BC_{12}H_{25}$	$Na(C_4H_9)_4B$[b]	$Na(C_2H_5)_3BC_{12}H_{25}$[b]
2940	2940	2940
2870	2870	2870
2760	2780	2770
1465	1465	1465
1380	1375	1380
1300	1095	1070
1095	1010	1040
1060	990	870
740	740	730
720		720

[a] Bands observed in Nujol and/or Kel-F mulls. All absorptions have a minimum absorbance value of 0.4 relative to the strong peak (A = 1.4) of $Li(C_4H_9)_4B$ at 2770 cm.$^{-1}$. [b] Samples were run as melts.

The most logical effect of the negative boron atom would be to donate charge inductively to the carbon skeleton, causing an infrared shift of the C–H stretching frequency. The literature reveals little information on the effect of negative atoms or groups on the C–H stretching mode.[13] We have, however, evidence that the absorption at 2770 cm.$^{-1}$ is due to the C–H stretching frequency of methylene groups adjacent to the negative boron atom. This information was gained by studying a series of tetrasubstituted boron compounds in which the number of methylene groups adjacent to the negative boron atom was varied. These compounds and their extinction coefficients are shown in Table III.

It is clear that the intensity of the absorption in the 2800-cm.$^{-1}$ region decreases progressively to zero as the number of α-methylene groups is varied from four in II to none in IX. This data provides strong evidence for the postulate that the α-methylene groups are responsible for the absorptions under discussion.[14,15]

(13) L. J. Bellamy [*J. Chem. Soc.*, 4221 (1955)] states that the $-CH_2-$ deformation frequencies of $CH_2{=}CRR'$ compounds decrease as the electronegativity of the R and R′ groups increase. In this study only groups with $-I$ effects were used. The effect of electron-donating and -withdrawing groups on the OH stretching frequency of carboxylic acids is well known [*cf.* J. D. S. Goulden, *Spectrochim. Acta*, **6**, 129 (1954)]. Whether these known effects would be applicable to a predicted change in C–H stretching frequency is open to debate.

TABLE III

EXTINCTION COEFFICIENTS OF TETRASUBSTITUTED BORON COMPOUNDS[a]

	No. of α-methylene groups	*Infrared* max., cm.$^{-1}$	Extinction coefficient, l./mole-cm.
$Li(C_4H_9)_4B$ (II)	4	2785	197 ± 10
$Li(C_4H_9)_3BC_6H_5$ (VII)	3	2800	157 ± 2
$Li(C_4H_9)B[C_6H_5]_3$ (VIII)	1	2800	28 ± 3
$Na(C_6H_5)_4B$ (IX)	0	None from 2750–2850	0

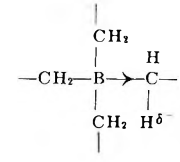
[a] Acetonitrile was used as a solvent for the infrared study. This solvent shifts the absorptions of tetrasubstituted boron compounds to slightly higher frequencies (10–20 cm.$^{-1}$) compared to the absorptions observed in Nujol mulls.

The transmission of negative charge from the boron atom to the α-methylenes is readily shown by the n.m.r. spectra of the tetraalkylboron complexes. Three bands were observed in the n.m.r. spectrum of lithium tetrabutylboron. Bands 1 and 2 were overlapping from 8.95 to 9.55 p.p.m.[16] and band 3 was separate and centered at 10.3 p.p.m. Integration shows a proton ratio of 7:2 for the ratio of the combined bands 1 and 2 compared to 3. From this information it is plausible that band 3 represents the α-methylene groups, and absorptions between 8.95 and 9.55 p.p.m. represent the propyl skeleton. Further evidence for this is shown in the n.m.r. spectrum of lithium tetraethylboron, where the methylene peak is centered at 10.5 p.p.m. and the methyl peak at 9.8 p.p.m. The absorptions at 10.3 and 10.5 p.p.m. are shifts of 1.6 and 1.8 p.p.m. from the methylene absorptions of normal hydrocarbons. A shift above 10 p.p.m. and at a higher field than methyl absorptions is typical of methylenes adjacent to negative charges and attached to metals.[17] All of the peaks are complex due to large J/δ values and to boron–hydrogen spin–spin coupling.[18]

The combined infrared and n.m.r. absorption spectra clearly show the pronounced influence of the negative boron atom on the α-methylene groups.

The band at 1100 cm.$^{-1}$ in Table II is most probably due to a B–C stretching frequency. Other B–C ab-

(14) The reason for low frequency infrared shifts is not clear. One possible explanation for the C–H shift of tetraalkylboron compounds involves contributing hydride structures of the type shown. Hydride character in the tetraalkylboron compounds was originally proposed and discussed by G. Wittig [*Angew. Chem.*, **70**, 65 1958)]. Evidence that these structures are possible is found in the fact that lithium tetrabutylboron is a good hydride donor [H. Jäger and G. Hesse, *Chem. Ber.*, **95**, 345 (1962)].



(15) (a) Because of the difference in inductive effect between phenyl and *n*-butyl there is no direct proportion between the extinction coefficients of compounds II through IX and the number of α-methylene groups. (b) Interestingly enough, Honeycutt and Riddle,[7] who reported the infrared spectrum of sodium tetraethylboron, did not observe the strong absorption at 2770 cm.$^{-1}$. This is due to masking of the absorption by complexed solvent. When our compounds were allowed to come in contact with diethyl ether, the band at 2770 cm.$^{-1}$ was obscured by ether bands.

(16) Measured relative to tetramethylsilane (10 p.p.m.) as an *external* reference.

(17) G. Frankel, D. G. Adams, and J. Williams, *Tetrahedron Letters*, **12**, 767 (1963), and references cited therein.

(18) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 298.

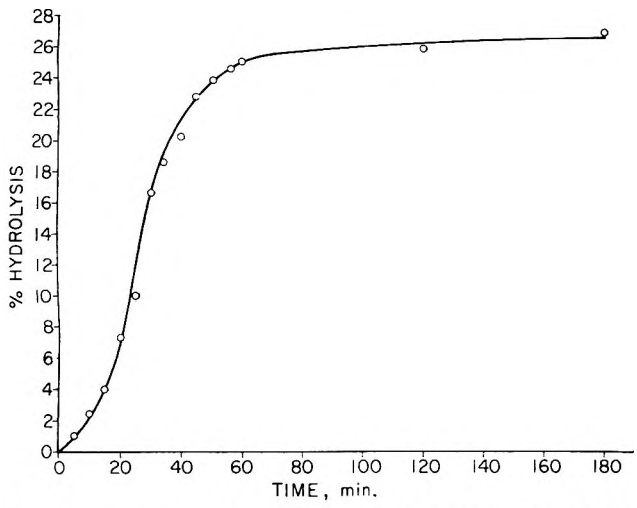


Fig. 1.—Hydrolysis of $Li(C_4H_9)_4B$ with 20% acetic acid at 60°.

sorptions in this general region have been observed in triethylborane and trimethylborane.[19]

Hydrolysis.—The stability of tetraalkylboron compounds in water, acids, and sodium hydroxide solutions was studied. There is ambiguity in the literature concerning the water stability of the tetravalent boron compounds. Honeycutt and Riddle[7] report that sodium tetraethylboron is hygroscopic and stable in water. Schlesinger and Brown[4] state that lithium triethylbutylboron dissolves in water and slowly evolves a gas; Hurd[5] claims that lithium tetramethylboron decomposes vigorously with a drop of water.

Our hydrolysis results are summarized in Table IV. The lithium tetraalkylboron compounds and tetramethylammonium tetrabutylboron were studied in detail because they represented extremes in reactivity toward water. All of the tetraalkylboron compounds were fairly stable in water, decomposing from 0.5 to 13% at 35° in 16 hr. Base did not have an appreciable effect on their stability, causing only a maximum of 3% change in the per cent hydrolysis. Acetic acid causes a rapid hydrolysis of the tetraalkylboron compounds at 60°. For example, the hydrolysis of lithium tetrabutylboron with 20% acetic acid evolved 25% of the theoretical volume of butane within 1 hr. An additional 2-hr. reaction time resulted in a total of 27% hydrolysis (see Fig. 1). From this information, and the similarity of this reaction to those of the other tetraalkylboron compounds, it is reasonable that the hydrolysis of these compounds involves a rapid protonation and loss of alkane, followed by a slow hydrolysis of the resulting trialkylboranes (reactions 1 and 2).

$$MBR_4 + AcOH \xrightarrow{\text{fast}} MOAc + R_3B + RH \quad (1)$$

$$R_3B + AcOH \xrightarrow{\text{slow}} 3RH + B(OAc)_3 \quad (2)$$

The exact nature of the initial proton transfer and loss of alkane cannot be defined from the available data; however, it is plausible that proton attack occurs at the electron dense α-carbon atom with accompanying loss of alkane.[20]

Correcting for statistical factors, the relative rate of bond cleavage of ethyl to butyl, ethyl to dodecyl, and butyl to dodecyl, is 1.75 ±0.20, 1.00 ± 0.10, and 0.95 ± 0.10, respectively.

Oxidation.—The lithium and sodium tetraalkylboron compounds are extremely reactive to both dry and moist air. Trialkylboranes react spontaneously with oxygen due to the ease of coordination between oxygen and the empty boron orbital.[21] This, of course, is impossible with tetravalent boron compounds and therefore some other pathway must be followed.

The oxidation of lithium tetrabutylboron (II) in tetrahydrofuran (THF) at 35° for 16 hr. followed by hydrolysis yielded 48 and 3%, respectively, of the theoretical amounts of 1-butanol and *n*-butyraldehyde. The other liquid products totaled only 1.4%. In addition, we obtained a 15% recovery of *n*-butane; and no other gaseous products were found. This relatively clean free-radical oxidation could be explained by assuming an equilibrium of II with butyllithium and tributylborane, followed by oxidation and basic hydrolysis.[22,23] However, there is strong evidence that this mechanism is not operative in our system. Lithium

$$\underset{\text{(II)}}{Li(n\text{-}C_4H_9)_4B} \xrightarrow{\text{THF}} n\text{-}C_4H_9Li + (n\text{-}C_4H_9)_3B \xrightarrow[\text{(2) NaOH–H}_2\text{O}]{\text{(1) O}_2} n\text{-}C_4H_9OH$$

TABLE IV

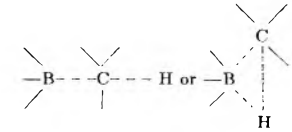
PER CENT HYDROLYSIS OF TETRAALKYLBORON COMPOUNDS[a]

Tetraalkylboron compound	NaOH solution, H_2O 35°, 16 hr.	NaOH solution, pH 10 35°, 16 hr.	20% HOAc 60°, 1 hr.
$Li(C_2H_5)_3B(C_4H_9)$			29.2
$Li(C_4H_9)_4B$	13	15.9	24.5
$Li(C_2H_5)_3BC_{12}H_{25}$	12[b]	12.5[b]	33.1[c]
$Li(C_4H_9)_3BC_{12}H_{25}$	12.8[b]	11.1[b]	36.5[c]
$(CH_3)_4NB(C_4H_9)_4$	0.45	3.0	55[d]

[a] Per cent hydrolysis is calculated on the basis of 4 moles of theoretical alkane for each mole of tetraalkylboron compound. [b] Based on per cent gas only. [c] Based on per cent gas and dodecane. [d] The extreme sensitivity of tetramethylammonium tetrabutylboron to acetic acid has not been studied.

(19) W. J. Lehmann, C. O. Wilson, Jr., and I. Shapiro, *J. Chem. Phys.*, **28**, 777, 781 (1958).

(20) Comparing hydrolysis reactions of tetraalkylboron compounds with those of sodium borohydride [R. E. Davis, E. Bromels, and C. L. Kibby, *J. Am. Chem. Soc.*, **84**, 885 (1962)] and sodium tetraphenylboron [J. N. Cooper and R. E. Powell, *ibid.*, **85**, 1590 (1963); V. A. Simon, *Dissertation Abstr.*, **13**, 1534 (1962)] provides some basis for these arguments. Cooper and Powell found no evidence for tetraphenylboric acid [$HB(C_6H_5)_4$] in their studies with tetraphenylboron. From this experiment it is highly unlikely that a five-coordinated boron species exists during the hydrolysis of tetraalkylboron compounds. The work of Simon as well as that of Cooper and Powell provides evidence that proton attack in the hydrolysis of tetraphenylboron occurs at the α-carbon atom. It is reasonable that the tetraalkylboron system should follow the same path. Finally, Davis, *et al.*, state that a DBH_4 species is not present during the reaction of sodium borohydride with deuterium oxide, but instead propose two activated complexes in which H–D bond formation is proceeding with B–H bond breaking in either a linear or triangular arrangement. A similar type complex, such as is presented, is a probable intermediate in the hydrolysis of tetraalkylboron compounds.



(21) S. B. Mirviss, *J. Am. Chem. Soc.*, **83**, 3051 (1961), and references cited therein.

(22) The major product (49%) in the oxidation of tributylboron by oxygen in THF is 1-butanol after hydrolysis (see ref. 21).

(23) It is well known that butyllithium reacts with air to produce 1-butanol upon hydrolysis: *cf.* E. Müller and T. Töpel, *Ber.*, **72**, 273 (1939).

tetrabutylboron does not react with benzyl chloride under the same solvent and temperature conditions used for the oxidation. We would certainly expect to obtain transmetalation or alkylation products at 35° in THF if butyllithium were in equilibrium with II.[24] Moreover, even at longer reaction times, II does not react with benzophenone. Some other path must then be operative. As *n*-butyl alcohol was obtained in high yields without the formation of iso- or *sec*-butyl alcohol, an initial reaction at the α-carbon atom, either by insertion of oxygen between boron and carbon, or by hydroperoxide formation, would give rise to likely precursors to our products. No attempt has been made at this time to differentiate between these two intermediates.[25]

$$Li^+(C_4H_9)_3B^-—\overset{\bullet}{O}—O—C_4H_9 \quad X$$

$$Li^+(C_4H_9)_3B^-—\underset{\displaystyle OOH}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}—C_3H_7 \quad XI$$

Experimental

Melting points of air-sensitive reagents were obtained in sealed tubes and are uncorrected. All compounds reactive to air and moisture were handled in an argon atmosphere. Hydrocarbon solvents were dried and distilled from sodium and stored over calcium hydride. Tri-*n*-butylborane and triethylborane (Callery Chemical Co.) were distilled before use.

***n*-Dodecyllithium** was prepared using a modification of a procedure of Meals.[26] In a typical preparation, lithium metal dispersion (Foote Chemical Co., 1.10 moles, 20% excess) was placed in a 1-l. three-necked flask equipped with an addition funnel, condenser, thermometer, argon inlet, and stirrer. The flask was modified to include a stopcock at the bottom. The lithium metal was washed with 100 ml. of benzene and two 50-ml. portions of hexane. Five milliliters of *n*-dodecyl chloride in 20 ml. of hexane was added and the mixture was heated to gentle reflux and stirred. The reaction usually started with a darkening of the lithium metal and a rise in temperature. The remaining *n*-dodecyl chloride (0.50 mole) was diluted with enough hexane to make a 1 *M* solution and added over 1 hr. to the mixture maintained at 65° by heating. After addition, the mixture was transferred to centrifuge bottles, covered with rubber serum caps, and centrifuged for 15–30 min. The supernatant liquid was removed with a syringe. The remaining solid in each bottle was extracted with two 50-ml. portions of hexane. Titration of the *n*-dodecyllithium by the Gilman procedure showed a 55–62% yield.

Preparation of Lithium Tetraalkylboron Compounds.—The lithium tetraalkylboron compounds were prepared by direct reaction of an organolithium reagent and a trialkylborane in hexane or pentane diluent. The following example illustrates the general procedure. Butyllithium (Foote Mineral Co., 0.10 mole) was placed in a 1-l. three-necked flask equipped with a stirrer, addition funnel, condenser, thermometer, and argon inlet. Tri-*n*-butylborane (0.10 mole, 18.2 g., 23.4 ml.) in an equal volume of hexane was added at room temperature with stirring. Formation of a white solid was immediately visible as the temperature rose to 30–40°. After addition, the heterogeneous mixture was heated to 45° and stirred for 1 hr. After cooling, the resultant solid was filtered, washed with five 50-ml. portions of hexane, and dried at 45° (0.1 mm.) for 2 hr.

The range of yields and melting points of the lithium tetraalkylboron compounds are shown in Table V.

TABLE V

	Compound	% yield	M.p., °C.
I,	$Li(C_2H_5)_3B(n\text{-}C_4H_9)$	92–93	122 dec.
II,	$Li(n\text{-}C_4H_9)_4B$	85–92	205 dec.
III	$Li(C_2H_5)_3B(n\text{-}C_{12}H_{25})$	77–85	93 dec.
IV,	$Li(n\text{-}C_4H_9)_3B(n\text{-}C_{12}H_{25})$	55–64[a] 86[b]	142 dec.

[a] Yield after washing the product with hexane. [b] Yield after washing the product with pentane. The higher yield of product using pentane as a wash solvent shows the lower solubility of IV in pentane.

Preparation of Lithium Triphenylbutylboron and Lithium Tributylphenylboron.—Triphenylborane (Aldrich Chemical Co.) was sublimed at 140° (0.09 mm.) to yield a white solid, m.p. 139–140°, lit.[27] m.p. 142–142.5°. To 2.5 g. (0.01 mole) of sublimed triphenylborane dissolved in 20 ml. of benzene, 6.4 ml. of 1.6 *M* butyllithium in 40 ml. of hexane was added. A white solid was formed which was filtered, washed with two 50-ml. portions of pentane, and dried at 30° (0.1 mm.) for 1 hr. A total of 1.8 g. (59%) of lithium triphenylbutylboron was recovered, m.p. 325° dec.

Anal. Calcd. for $C_{22}H_{24}BLi$: C, 86.3; H, 7.92. Found: C, 86.7; H, 7.72.

To 5.4 ml. (0.010 mole) of 1.84 *M* phenyllithium in 20 ml. of benzene, a solution of 2.0 g. (0.011 mole) of tributylboron in 40 ml. of benzene was added. No precipitate was formed, but the temperature rose to 32°, indicating a positive reaction. The solution was heated at 40° for 1 hr., cooled, and evaporated under nitrogen. The liquid product was further evaporated at 40° (0.1 mm.) for 24 hr. A total of 2.4 g. (91%) of lithium tributylphenylboron was recovered.

Anal. Calcd. for $C_{18}H_{32}BLi$: C, 81.6; H, 11.8. Found: C, 81.2; H, 11.5.

Preparation of Sodium Tetraalkylboron Compounds.—*n*-Butylsodium and *n*-dodecylsodium were prepared from *n*-alkyl chloride and sodium metal dispersion in *n*-octane by Morton's procedure.[28] Carbonation of the alkylsodium reagents indicated yields of 50–60%.

The general procedure for preparing sodium tetraalkylboron compounds is illustrated for sodium triethyldodecylboron. To 0.05 mole of *n*-dodecylsodium suspended in 150 ml. of *n*-octane was added 4.8 g. (0.05 mole) of triethylborane in 50 ml. of *n*-octane. A slight rise in temperature (5°) indicated the reaction had started. The mixture was stirred with a high speed stirrer for 1 hr. A thick, pasty material resulted and this was transferred to centrifuge bottles, capped, and centrifuged for 0.5 hr. The supernatant liquid was drawn off and discarded. The resultant solid was extracted with two 100-ml. portions of heptane. A total of 4.3 g. (32%) of white, solid material was recovered after drying at 40° (0.1 mm.) for 2 hr.

The results of these preparations follow.

	Compound	% yield	M.p. dec., °C.
V,	$Na(C_4H_9)_4B$	20	93 dec.
VI,	$Na(C_2H_5)_3B(n\text{-}C_{12}H_{25})$	32	45 dec.

Infrared and N.m.r. Spectra.—Infrared spectra were measured with a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics. Nujol mulls, Kel-F mulls, and solutions were prepared in an inert atmosphere. Ten to twenty per cent solutions of lithium tetrabutylboron, lithium triphenylbutylboron, lithium tributylphenylboron, and sodium tetraphenylboron (Matheson Coleman and Bell) in acetonitrile (spectroquality) were prepared. The lithium salts were found to follow Beer's law in the region of 2775 cm.$^{-1}$. Sodium tetraphenylboron did not absorb between 2750 and 2850 cm.$^{-1}$.

The n.m.r. absorption spectra of lithium tetrabutylboron (II) and lithium tetraethylboron (prepared from ethyllithium and triethylboron) were run as 10% solutions in acetone-d_6 (Merck, Canada) on a Varian A-60 spectrometer.

(24) This is the basis of the double titration method of H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 286 (1954).

(25) It should be noted that the boron peroxy compound X is quite similar to the compound $(C_4H_9)_2BOOC_4H_9$ postulated as an intermediate in the air oxidation of tributylboron in tetrahydrofuran.[21] The major products from this oxidation (1-butanol, butane, and *n*-butyraldehyde) essentially agree with those obtained in the present study. This would indicate that intermediate X is the most likely precursor to the products observed.

(26) R. N. Meals, *J. Org. Chem.*, **9**, 211 (1944).

(27) G. Wittig, G. Keicher, A. Rüchert, and P. Raff, *Ann.*, **563**, 110 (1949).

(28) A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little, and R. L. Letsinger, *J. Am. Chem. Soc.*, **72**, 3785 (1950).

Tetramethylammonium and Tetrabutylphosphonium Tetraalkylboron Compounds.—Relatively stable derivatives of sodium and lithium tetraalkylboron compounds were prepared in water solutions by reaction with tetramethylammonium or tetrabutylphosphonium bromide (the latter prepared by the method of Grayson and Keough[29] in 91% yield, m.p. 101–103°, lit.[29] m.p. 99–101°). The following derivative preparation is typical. To a solution of lithium tetrabutylboron (5.9 g., 0.024 mole) in 50 ml. of water was added a solution of 3.9 g. (0.032 mole, 33% excess) of tetramethylammonium bromide in 25 ml. of water. A white precipitate was immediately visible. The mixture was stirred for 0.5 hr., filtered, and washed until the washings showed no trace of bromide ion. The resulting solid was dried at 45° (0.1 mm.) for 1 hr. to yield 6.8 g. (91.4% yield) of tetramethylammonium tetrabutylboron, m.p. 106–112° dec. One recrystallization from ether–pentane raised the melting point to 110–112° dec. Table I summarizes our results from the preparation of stable derivatives.

Hydrolysis of Tetraalkylboron Compounds.—Hydrolysis reactions were performed in 100-ml. three-necked flask equipped with an addition funnel, magnetic stirrer, thermometer, and condenser. An outlet from the condenser led to a 100-ml. gas buret. Gases were collected at room temperature over mercury. The reaction flask was immersed in an oil bath maintained at 35 ± 1° or 60 ± 1°. Approximately 1 g. of tetraalkylboron compound was placed in a flask and allowed to equilibrate for 0.5 hr. Water, base, or acid, preheated to 35 or 60°, then was added in approximately 1 min. Zero time was taken immediately after the addition. During the reactions the volume of gas given off was recorded. After the recorded time interval (Table IV), the reaction mixture was neutralized and extracted with ether; the layers were separated. The ether layer was dried over magnesium sulfate and distilled through a 6-in. Vigreux column. After removal of the ether, tridecane was added and the distillation continued under vacuum until the head temperature reached 75° (1 mm.). The distillate was weighed and the amount of dodecane, from either III or IV, was calculated from the gas chromatographic analysis of the mixture.

The gases collected were examined by infrared and mass spectrometry and gas chromatography. Ethane and butane were separated by gas chromatography using either a silica gel column (10 ft., 60°) or an activated alumina column (Woelm, activity I, 10 ft., 70°).

No evidence for any gases except ethane or butane was obtained. Dodecane, triethylborane, and tributylborane were the only liquids isolated and identified.

Oxidation Procedure.—The following procedure for the oxidation of lithium tetrabutylboron with oxygen in tetrahydrofuran is typical.

A 500-ml. three-necked flask, equipped with a condenser, thermometer, gas inlet, and magnetic stirrer, was immersed in a constant temperature (35 ± 1°) oil bath. The outlet from the condenser led to two gas burets, one of 100-ml. capacity and the other of 500-ml. capacity. Dry tetrahydrofuran, 50 ml., was added to the flask and the apparatus, including the burets, was flushed with oxygen for 30 min. Tetrahydrofuran (25 ml.) was withdrawn and 1.0–1.5 g. of lithium tetrabutylboron dissolved in it. The solution was then introduced into the reaction flask and the system was closed to the atmosphere. Stirring was started and samples were withdrawn periodically by means of a syringe. The peroxide content was measured. No temperature rise was noted during the oxidation. A slight positive oxygen pressure (10–20 mm.) was maintained on the system and the amount of oxygen absorbed was measured by adjusting the burets. After 16 hr. argon was slowly introduced into the flask and the exit gases were passed through two Dry Ice–acetone cooled traps. Assuming all the gases except oxygen to be condensable by the traps, the amount of oxygen absorbed was calculated from the total volume decrease minus the volume of the gas in the traps. A total of 38% of the theoretical amount of oxygen was absorbed, assuming 4 moles of oxygen are required for each mole of lithium tetrabutylboron. The gas in the trap was shown to be butane by infrared and gas chromatography. A total of 15% was recovered.

The liquid layer was hydrolyzed with excess 20% sodium hydroxide solution at 60° for 2 hr. After acidification with HCl, extraction with ether, and separation of layers, the ether layer was dried with magnesium sulfate. The ether was removed by distillation and the resulting liquid was fractionated by distillation and analyzed by infrared and gas chromatography.

A 10-ft. Carbowax 20 M column at 80° was used to identify *n*-butyl alcohol (48%) and *n*-butyraldehyde (3%). The other volatile components totaled 1.4%. Only a trace amount of butyric acid remained in the distillation pot.

The oxidation of lithium tetrabutylboron was also studied in dimethylformamide and ethylene glycol dimethyl ether. Similar results were obtained.

Normal alcohols were also found to be the major products in the oxidation of lithium triethylbutylboron, lithium triethyldodecylboron, and lithium tributyldodecylboron.

Acknowledgment.—The author is indebted to Dr. C. D. Broaddus for his suggestions and stimulating discussions concerning this work. He also wishes to thank Drs. T. J. Flautt and W. L. Courchene for aid in interpreting the n.m.r. and infrared spectra and Mr. Warren Foster for patiently performing most of the work in the laboratory.

(29) M. Grayson and P. T. Keough, *J. Am. Chem. Soc.*, **82**, 3919 (1960).

Epoxidations with *m*-Chloroperbenzoic Acid

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m-Chloroperbenzoic acid is a convenient reagent for studying epoxidation reactions. When the effect of the solvent upon the rates of epoxidation of *trans*-stilbene and ethyl crotonate was examined, it was found that, with ethyl crotonate, changing the solvent had no effect on the rate of epoxidation so long as the intramolecular hydrogen bonding of the peracid was not disrupted. With one solvent, acetonitrile, an apparent zero-order reaction was observed. A scheme is proposed to account for these results.

While there have been several recent studies of epoxidations with peracids,[1-3] the only olefins examined were those that react rather readily with the peracid. Since *m*-chloroperbenzoic acid recently has become available,[4] and since solutions of this peracid are stable at moderate temperatures for prolonged periods, we were enabled to study the epoxidation of the unreactive α,β-unsaturated esters as well as *trans*-stilbene in a variety of solvents without complications due to side reactions. In all cases, blanks consisting of *m*-chloroperbenzoic acid and the solvent showed less than 2% decomposition after the epoxidation had proceeded to 50–60%. Ethyl β-methylglycidate and *trans*-stilbene epoxide were isolated in good yield from these reactions.

The second-order rate constants for the epoxidation of *trans*-stilbene with *m*-chloroperbenzoic acid at 30°

(1) R. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).
(2) G. Berti and F. Bottari, *J. Org. Chem.*, **25**, 1286 (1960).
(3) P. Renolen and J. Ugelstad, *J. Chim. Phys.*, **57**, 634 (1960).
(4) Anon., *Chem. Week.*, **92**[14], 55 (April 6, 1963).

TABLE I

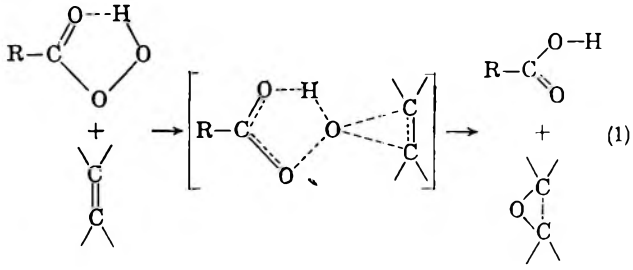
RATE CONSTANTS FOR THE EPOXIDATION OF *trans*-STILBENE WITH *m*-CHLOROPERBENZOIC ACID AT 30°
(Reactants at *ca.* 0.05 mole/l.)

Solvent	k_2, l./mole-sec. × 10^4	Dielectric constant (30°)
CCl_4	14.6	2.2
$CHCl_3$[a]	36.0	4.6
CH_2Cl_2	36.1	8.7
$ClCH_2CH_2Cl$[b]	32.7	10.1
$(CH_3)_3COH$	0.42	11.7
C_6H_6	18.9[c]	2.26
C_6H_5Cl	27.3	5.54
o-$C_6H_4Cl_2$	36.3	9.45

[a] 2 mole % CF_3CO_2H/mole of peracid. [b] Rate unaffected by 2 mole % CF_3COOH/mole of peracid. [c] Lynch and Pausacker (ref. 1) give 23.3.

in several solvents are given in Table I. The dielectric constants of the solvents also are tabulated. The only solvent in this series likely to disrupt the intramolecular hydrogen bonding of the peracid is *t*-butyl alcohol (in which, incidentally, the peracid is extremely stable). When the reaction was run in chloroform, a small amount of trifluoroacetic acid was added. The blank in chloroform remained constant in the presence of this strong acid, which did not seem to affect the rate of epoxidation (*cf.* reaction in 1,2-dichloroethane and reactions with ethyl crotonate).

These results indicate that, in agreement with Renolen and Ugelstad,[3] the rates of epoxidation, where intramolecular hydrogen bonding is intact, are roughly parallel to the dielectric constant of the solvent, as would be expected for reactions between unionized molecules if the transition state were more polar than the reactants.[5] The nonionic mechanism shown here has been proposed by several authors[1-3] to account for these observations.



(1)

The effect of solvents which can form intermolecular hydrogen bonds with the peracid, however, reduces the effective concentration of the cyclically bonded peracid and retards the epoxidation rate.

When the epoxidation rates of ethyl crotonate with *m*-chloroperbenzoic acid were determined in a variety of solvents, the solvent effects were somewhat different. In general the rates were much slower than with *trans*-stilbene, and slowest in those solvent systems in which the intramolecular hydrogen bonding of the peracid was disrupted, but, in nonhydrogen bonding solvents, the rate was identical in solvents of widely varying dielectric constant. The second-order rate constants are given in Table II. The reaction in diethyl ether was very slow, and meaningful results could not be obtained owing to decomposition of the peracid.

(5) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 140.

The recent report by Berti and Bottari[2] that trichloroacetic acid catalyzes the epoxidation of *trans*-stilbene was not confirmed for the epoxidation of ethyl crotonate. When equimolar amounts of *m*-chloroperbenzoic acid, trichloroacetic acid, and ethyl crotonate were allowed to react in 1,2-dichloroethane, the reaction was still second order, but somewhat slower than in the absence of trichloroacetic acid, probably owing to disruption of intramolecular hydrogen bonding of the peracid by trichloroacetic acid.

In the acetic acid–acetic anhydride system, an additional retardation may be due to the formation of peroxides from the peracid.

TABLE II

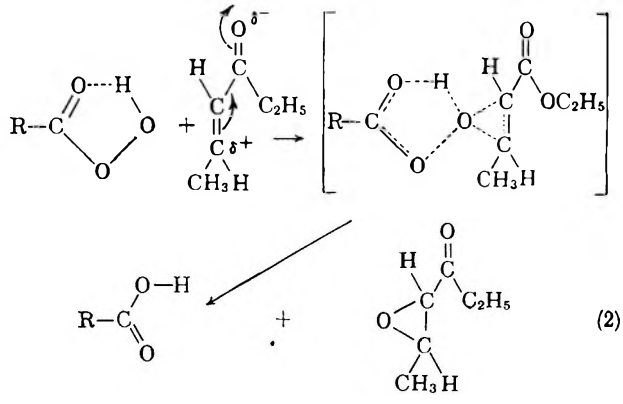
RATE CONSTANTS FOR EPOXIDATION OF ETHYL CROTONATE WITH *m*-CHLOROPERBENZOIC ACID

Solvent	Temp., °C.	k_2, l./mole-sec. × 10^5	Dielectric constant
CH_3COOH (95%) + $(CH_3CO)_2O$ (5%)	30	0.075	...
CH_3COOH (90%) + H_2O (10%)	30	0.53	...
$CH_3COOC_2H_5$	25	0.193	6.02
CCl_4	25	1.15	2.23
$CHCl_3$[c]	25	1.15	4.73
CH_2Cl_2	25	1.15	8.89
$ClCH_2CH_2Cl$[b]	25	1.15	10.36
$ClCH_2CH_2Cl$	30	1.73	10.1
C_6H_6	30	1.73	2.26
$ClCH_2CH_2Cl$[c]	25	0.77	10.36

[a] 2 mole % CF_3CO_2H/mole of peracid. [b] Rate unaffected by 2 mole % CF_3CO_2H/mole of peracid. [c] Equivalent amounts of Cl_3CCO_2H, peracid, and ethyl crotonate.

The constancy of the rates in nonhydrogen-bonding solvents of widely varying dielectric constants may be a result of the disruption of the ground state resonance in ethyl crotonate so that there is only a very slight over-all difference in polarity between the ground and transition states.

The constancy of the rate in media of dielectric constants varying from two to ten is evidence against the possibility that the rate-determining step is the formation of a hydrogen-bonded complex between the peracid and ethyl crotonate. In addition, if such a



(2)

complex were formed to any great extent, the addition of excess peracid should increase the rate, and may even change the order of the reaction, since excess free peracid would then be capable of epoxidizing the complex. This, however, does not occur. The results

TABLE III

EPOXIDATION OF ETHYL CROTONATE WITH *m*-CHLOROPERBENZOIC ACID IN 1,2-DICHLOROETHANE AT 30°

Peracid, mole	Ethyl crotonate, mole	k_2, l./mole-sec. × 10^3
0.505	0.250	1.75
0.500	0.500	1.73
0.258	0.501	1.75

of changing the ratios of the reactants are shown in Table III.

When ethyl crotonate was epoxidized with *m*-chloroperbenzoic acid in acetonitrile, it was found that, as expected, the initial rate was slower than in the halogenated hydrocarbons, but, to our surprise, the reaction was apparently zero order: the peracid titer decreased linearly with time. These rates are given in Table IV.

TABLE IV

EPOXIDATION OF ETHYL CROTONATE WITH *m*-CHLOROPERBENZOIC ACID IN ACETONITRILE

Peracid, mole l.	Ethyl crotonate, mole l.	Temp., °C.	k_0, mole-sec. × 10^6
0.5	0.5	25	0.625
0.5	0.5	50	6.95

The following scheme may account for the kinetics of this epoxidation in various solvents.

$$RCO_3H + \text{solvent} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{complex} \qquad (3)$$

$$RCO_3H + CH_3CH{=}CHCO_2C_2H_5 \xrightarrow{k_2} RCO_2H + CH_3\underset{\diagdown\,O\,\diagup}{CH{-}CH}CO_2C_2H_5 \qquad (4)$$

$$\text{Complex} + CH_3CH{=}CHCO_2C_2H_5 \xrightarrow{k_3} RCO_2H + CH_3\underset{\diagdown\,O\,\diagup}{CH{-}CH}CO_2C_2H_5 + \text{solvent} \qquad (5)$$

If $k_1 > k_{-1}$, $k_2 > k_{-1}$, and $k_2 \gg k_3$, the concentration of free peracid would reach a steady state and the reaction would be independent of initial peracid concentration. If solvation does occur, but k_3 is not negligible with respect to k_2, the reaction would be slower than in the absence of solvation, but still first order in peracid and ethyl crotonate.

There is some evidence for reversible interaction between *m*-chloroperbenzoic acid and acetonitrile. When the nitrile is added to a solution of the peracid in dichloromethane, an increase of 25 cm.$^{-1}$ is observed in the carbonyl frequency of the infrared spectrum. When the solvents are removed under reduced pressure, *m*-chloroperbenzoic acid is recovered quantitatively. The interaction of nitriles with methanolic solutions of aqueous hydrogen peroxide to form peroxycarboximidic acids as postulated by Payne,[6] is presumably different from the interaction observed here, since the formation of the peroxycarboximidic acid probably involves the peroxy anion and subsequent reaction with a hydroxylic solvent. In the present instance, however, hydroxylic compounds, except for the peracid, are absent, and the solution is not basic. The detailed nature of the present interaction is under investigation.

It is stated that monoperphthalic acid reacts more slowly in epoxidations than perbenzoic acid,[7] in contrast to the observation that electron-withdrawing substituents usually increase the rates of epoxidation.[1] The slow rates with monoperphthalic acid may be due to intramolecular hydrogen bonding between the carboxy and percarboxy groups. Kinetic studies with the recently prepared permaleic acid[8] have not been described, but it may be expected the epoxidations with permaleic acid would be slower than with the hypothetical peracrylic acid, if these compounds could be compared in the absence of other carboxylic or hydroxylic compounds. The presence of at least equivalent amounts of water and about 20 mole % maleic acid in the permaleic acid reagent as normally prepared also would tend to reduce epoxidation rates, and would have to be considered in any kinetic study. Trifluoroperacetic acid[9] as normally prepared also has water and trifluoroacetic acid present, and these contaminants may retard epoxidation rates to some extent. Comparisons of the normal trifluoroperacetic acid reagent and pure, anhydrous trifluoroperacetic acid have not been described. Retardation due to water and acetic acid is, however, well established for epoxidations with peracetic acid. It is well known that peracetic acid in aqueous acetic acid is ineffective in the epoxidation of α,β-unsaturated esters,[10] but it was found recently that anhydrous peracetic acid in ethyl acetate or acetone is capable of converting these unsaturated esters to the corresponding glycidates.[11]

Experimental

Materials.—*trans*-Stilbene, Scintillation grade, m.p. 124–125°, was obtained from Matheson Coleman and Bell, and ethyl crotonate was distilled before use, the fraction having $n^{25}D$ 1.4226 being retained. *m*-Chloroperbenzoic acid of 99+% assay was obtained by washing the commercial 85% material (FMC Corporation) with a phosphate buffer of pH 7.5, and drying the residue under reduced pressure. The peracid was assayed iodometrically before use. 1,2-Dichloroethane was fractionated and a center cut retained, and diethyl ether and benzene were distilled from sodium. *t*-Butyl alcohol was treated with potassium and the distillate used. Reagent grade carbon tetrachloride, chloroform, methylene chloride, ethyl acetate, trichloro- and trifluoroacetic acids, acetic anhydride, acetic acid, chlorobenzene, and *o*-dichlorobenzene were used without further purification.

Methods.—In a typical run with ethyl crotonate a sample of 99+% *m*-chloroperbenzoic acid, corresponding to 8.629 g. (0.05 mole) of 100% material was placed in a 125-ml. iodine flask and about 70 ml. of solvent was added. After the peracid dissolved (endothermic reaction), the solution was raised to the desired temperature, transferred to a 100-ml. volumetric flask, and the iodine flask rinsed with three small portions of fresh solvent which were then added to the volumetric flask. Ethyl crotonate, 5.707 g. (0.05 mole), was then added to the volumetric flask with sufficient solvent to fill the flask to the mark. After thor-

(6) G. B. Payne, P. H. Deming, and P. H. Williams, *J. Org. Chem.*, **26**, 659 (1961).

(7) H. Bohme and G. Steinke, *Ber.*, **70B**, 1709 (1937).

(8) R. W. White and W. D. Emmons, *Tetrahedron*, **17**, 31 (1962).

(9) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287, (1955).

(10) D. Swern, *Chem. Rev.*, **45**, 1 (1949).

(11) D. L. MacPeek, P. L. Starcher, and R. Phillips, *J. Am. Chem. Soc.*, **81**, 680 (1959).

ough mixing, the flask and a blank prepared as above but without ethyl crotonate were placed in a water bath at the desired temperature.

Periodically, 5-ml. aliquots were withdrawn, added to solutions of 3 ml. of acetic acid in 10 ml. of 20% potassium iodide, and the liberated iodine titrated with *ca.* 0.11 *N* sodium thiosulfate.

Results of a typical run (benzene at 30°) are shown.

Time (hr.)	0	2.5	5.5	21.5	29
[Peracid] (moles/l.)	0.500	0.465	0.425	0.290	0.255

After 30 hr., the blank still had 0.492 mole/l. of peracid.

Experiments with *trans*-stilbene were run in the same way, except that initial concentrations were usually about 0.05 *M* because of the lower solubility of the *trans*-stilbene.

A Re-examination of the Polymerization of Sterculic Acid. I. Reaction of Sterculene with Acetic Acid

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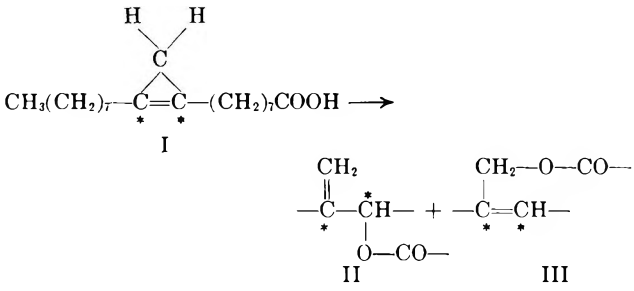
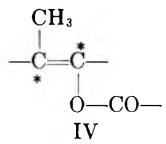
The reaction of sterculene (1,2-di-*n*-octylcyclopropene, V) with acetic acid gave 9-acetoxy-10-methyleneoctadecane (VI), 9-acetoxymethyl-9-octadecene (VII), and 9-acetoxy-10-methyl-9-octadecene (VIII).

Sterculic acid (I) polymerizes with destruction of the cyclopropene ring and formation of a polyester.[1-3] A similar reaction occurs with acetic acid, and from permanganate–periodate oxidations of the reaction products, the structures II and III were inferred to be



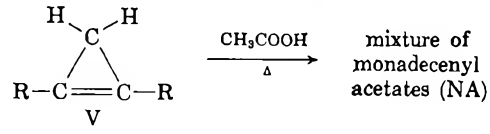
present in the mixture as well as in the polymer.[3] The olefinic carbon atoms in I and its reaction products are starred.

Although Faure and Smith[2] noted an increase in the infrared absorption at 7.72 μ, which they attributed to methyl groups, Rinehart, *et al.*,[3] found no chemical or spectroscopic evidence for the enol ester group IV.



Earlier work in this laboratory on gas chromatography (g.l.c.) of the methyl esters of the acids produced by saponification of the sterculic acid polymer suggested that structure IV is present in the polymer.[4] The availability of sterculene[5] (V) prompted us to reinvestigate the problem because the products expected from V and acetic acid would be more amenable to chromatography and yield simpler compounds on degradation than those derived from I.

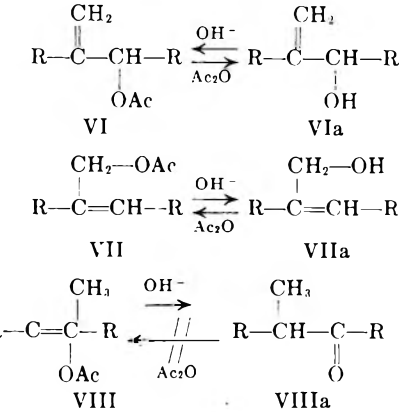
When sterculene was heated with acetic acid, a mixture was obtained from which the reaction product was separated by distillation. The product was a mixture of nonadecenyl acetates (NA) that gave two



R (in this and succeeding diagrams) = n-C_8H_{17}–

peaks on g.l.c. and two spots on thin layer chromatography (t.l.c.). Saponification (calcd. for $C_{19}H_{37}$-OAc, 324; found, 321 and 322) gave a mixture (NA, OH^-) that showed two different peaks on g.l.c. and three different spots on t.l.c. Acetylation of NA,OH^- gave a product (NA,OH^-,Ac) that showed the original two peaks on g.l.c. plus the smaller one in the NA,OH^- diagram (Fig. 1), and the original two spots on t.l.c. plus the smaller one of highest R_f given by the NA,OH^- mixture (Fig. 1). The saponification equivalent of NA,OH^-,Ac (345) indicated that a portion of the saponified nonadecenyl acetate mixture could not be reacetylated to an ester.

These results suggested that at least three components were present in NA: the methyleneacetoxy derivative VI and the acetoxymethyl derivative VII, on the basis of previous results,[3] as well as the enol acetate derivative VIII.



The infrared spectrum of NA,OH^- corroborated this supposition. A small band at 5.83 μ indicated the presence of a ketone such as VIIIa in the mixture of alcohols VIa and VIIa.

NA was ozonized in methylene chloride and the resulting solution decomposed with zinc in aqueous acetic acid. The aqueous fraction from the ozonolysis

(1) J. R. Nunn, *J. Chem. Soc.*, 313 (1952).
(2) P. K. Faure and J. C. Smith, *ibid.*, 1818 (1956).
(3) K. L. Rinehart, Jr., S. I. Goldberg, C. L. Tarimu, and T. P. Culbertson, *J. Am. Chem. Soc.*, **83**, 225 (1961).
(4) J. C. Masson, Ph.D. thesis, University of Arizona, 1959.
(5) H. W. Kircher, *J. Am. Oil Chemists' Soc.*, **41**, 4 (1964).

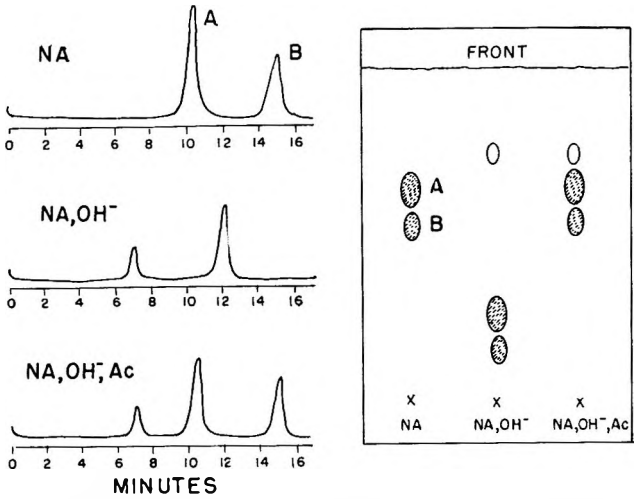


Fig. 1.—G.l.c. (left) of the nonadecenyl acetate mixture (NA) and its hydrolytic (Na,OH⁻) and reacetylated (NA,OH⁻,Ac) products (Aerograph Hy-Fi, 190°, 1 atm. He, 10-ft. ethylene glycol succinate column); t.l.c. (right): filled circles, 1% potassium permanganate spray; empty circles, 2,4-dinitrophenylhydrazine hydrochloride or 50% sulfuric acid sprays.

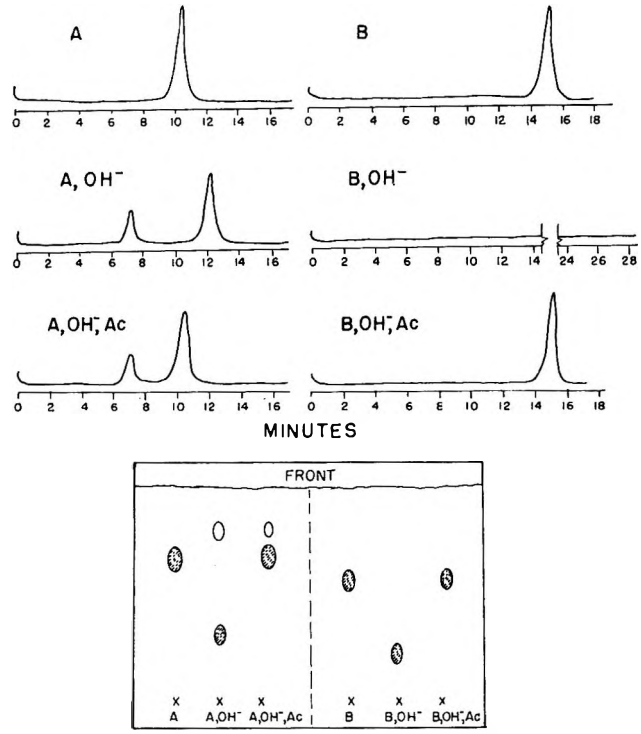


Fig. 2.—G.l.c. (upper left) of A and its hydrolytic and reacetylated products; g.l.c. (upper right) of B and its hydrolytic and reacetylated products; t.l.c. (lower) of the compounds (same g.l.c. and t.l.c. conditions as used in Fig. 1).

contained formaldehyde (from VI); the acid fraction contained only pelargonic acid (from VIII and from over oxidation of VII). The neutral fraction, after acetylation, showed four spots on t.l.c. corresponding in R_f to pelargonaldehyde (from VII), 2-decanone (from VIII), nonyloin acetate (from VI), and 2-ketodecyl acetate (from VII). The neutral fraction was distilled; the first fraction contained pelargonaldehyde and 2-decanone, which were separated with a preparatory g.l.c. column and identified as their 2,4-dinitrophenylhydrazones. The second fraction was mainly 2-ketodecyl acetate and the third, nonyloin acetate, which was identified by hydrolysis to nonyloin. Thus, all of the products expected from the ozonolysis of VI, VII, and VIII were obtained and *identified*.

NA was separated into the components A and B (Fig. 1) by several distillations through a spinning band column. Hydrolysis and reacetylation of A indicated that it was a mixture of VI and VIII (Fig. 2). Early fractions obtained from a redistillation of A were rich in VIII. The spectra of one such fraction (A-1), its hydrolytic product, and the mixture obtained on reacetylation are shown in Fig. 3. The enol acetate C–O stretching band at 8.25 μ[6] is readily distinguishable from the acetate C–O stretching band at 8.08 μ[7] in A-1; the ketone band at 5.83 μ is seen in the hydrolytic product and the presence of this band as a shoulder on the ester carbonyl band is visible in the spectrum of the reacetylated material.

Permanganate–periodate oxidation[8] of A-1 gave unchanged starting material and nonyloin acetate. Ozonolysis of A-1 yielded 2-decanone, pelargonic acid, and nonyloin acetate. The components of A are therefore VI and VIII.

Hydrolysis of B (Fig. 1) and reacetylation gave the results shown in Fig. 2. G.l.c. of B,OH⁻ produced no peak; the primary alcohol VIIa did not emerge from the column. The infrared spectrum of B,OH⁻,Ac was superimposable on that of B; the spectrum of B,OH⁻ showed no band in the carbonyl region. Permanganate–periodate oxidation of B went to completion to yield pelargonic acid and 2-ketodecyl acetate. B is therefore the acetoxymethyl derivative VII.

It was of interest to determine the ratios of VI, VII, and VIII in the sterculene–acetic acid reaction mixtures at various temperatures and times to see if VIII was produced by rearrangement of a previously formed product. It has been reported[3] that structure II is in 65% of the sterculic acid residues in the polymer and that structure III is in 35% of the residues. Since the three peaks in the chromatogram of NA,OH⁻,Ac correspond to VIIIa, VI, and VII, respectively (Fig. 1), measurement of the area under these peaks will give an estimation of the relative proportions of VIII, VI, and VII in the nonadecenyl acetate mixture.

Mixtures of sterculene and acetic acid were heated at 60, 80, 100, and 120° for various lengths of time and sampled periodically. The samples were hydrolyzed to VIa, VIIa, and VIIIa, reacetylated to VI, VII, and VIIIa, and analyzed by g.l.c. The extent of the reaction and the ratios of the three components were

TABLE I

EXTENT OF THE STERCULENE–ACETIC ACID REACTION AND PRODUCT RATIOS AT VARIOUS TEMPERATURES

Temp., °C.	Time, hr.	Sterculene reacted, %	Products, %[a] VI	VII	VIII
60	117	88	54 (54–57)	41 (39–41)	5 (3.6–5)
80	96	84	52 (51–55)	36 (35–38)	12 (10–12)
100	44	83	54 (52–55)	36 (35–37)	10 (10–13)
120	22	82	51 (48–55)	33 (33–37)	16 (13–17)

[a] The figures in parenthesis represent the range of values observed during the entire reaction, from 10 to 88% completion.

(6) R. N. Jones and F. Herling, *J. Am. Chem. Soc.*, **78**, 1159 (1956).

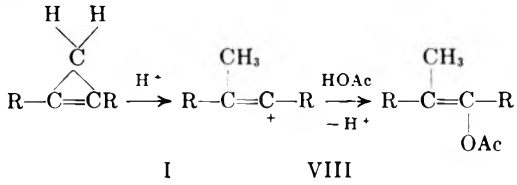
(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958.

(8) R. V. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955).

calculated from the areas under each peak and are given in Fig. 4 and Table I.

The amount of VIII in the reaction mixture increased with a rise in temperature at the expense of VI and VII. The ratios of the three components did not vary appreciably during a run at a particular temperature; the product ratio at the beginning of the reaction was about the same as that at the end of the reaction. A concomitant, but slower reaction, was the rearrangement of sterculene,[9] which decreased the extent of the sterculene–acetic acid reaction from 88% at 60° to 82% at 120°.

The mechanism proposed by Rinehart, *et al.*,[3] protonation of one of the olefinic carbon atoms of the cyclopropene ring followed by ring opening and addition of acetate, explains the formation of VI and VII. The formation of VIII cannot proceed by this pathway; it can be rationalized by the less likely protonation of the methylene group in the cyclopropene ring with ring opening and addition of acetate. The



I VIII

constancies of the product ratios at various temperatures and times indicate that VIII is formed from sterculene and acetic acid by an independent route and does not arise by rearrangement of VI or VII.

Experimental

Materials and Methods.—Pelargonaldehyde and 2-decanone were purchased from Calbiochem, Los Angeles, Calif., and pelargonic acid from Distillation Products Industries. Nonyloin was prepared[10] from methyl pelargonate and sterculene, as described previously.[5] G.l.c. was done with a 10-ft. 20% ethylene glycol succinate analytical column and a 5-ft. 20% diethylene glycol succinate preparatory column in the Aerograph Hy-Fi and A-90-C instruments. T.l.c. of the nonadecenyl acetates and alcohols on Silica Gel G (Research Specialties Co.) was done with a solvent composed of petroleum ether (b.p. 60–90°), diethyl ether, and acetic acid in the ratio 180:20:1 (v./v./v.). T.l.c. of the nonadecenyl acetate oxidation products used the same adsorbent and solvents in the ratio 80:20:1. Infrared spectra were obtained in carbon tetrachloride with the Perkin-Elmer 137-C Infracord.

Nonadecenyl Acetates.—A mixture of V (35.3 g.) and glacial acetic acid (150 ml.) was stirred for 18.5 hr. under nitrogen at 120°. Excess acetic acid was removed with a rotary evaporator and the residue distilled (72–120° at 0.035 mm.) to yield 41.8 g. of a mixture of rearranged sterculene[9] and product. The former was removed with a spinning band column (75–100° at 0.05 mm.) and the latter distilled (110–120° at 0.04 mm.) to yield 31.7 g. of nonadecenyl acetates (NA, Fig. 1). The infrared spectrum of NA showed strong bands at 5.75 and 8.08 (acetate ester[7]) and weaker bands at 6.05 and 11.03 μ (*unsym*-disubstituted olefin[7]).

Saponification.—Two samples of NA (4.445 and 3.600 g.) were hydrolyzed at 60–70° for 3 hr. with 1 *N* potassium hydroxide in ethanol (30 ml.). Titration of the samples and a blank with 0.510 *N* hydrochloric acid gave saponification equivalents of 321 and 322 (calcd. for $C_{19}H_{37}OAc$, 324). The isolated hydrolytic products (7.10 g.; NA,OH$^-$, Fig. 1) had infrared absorption bands at 2.72 and 9.5 (alcohol[7]), 6.05 and 11.03 (*unsym*-disubstituted olefin[7]), and at 5.83 μ (ketone[7]).

Reacetylation.—The hydrolyzed nonadecenyl acetates (6 g.) were acetylated with pyridine and acetic anhydride (15 ml. each) at room temperature for 18 hr. Water was added to the reaction mixture and the products (NA,OH$^-$,Ac, Fig. 1) were extracted with petroleum ether (b.p. 30–60°) and distilled (115–120° at 0.05 mm.). Two samples were saponified as above to give saponification equivalents of 345 and 345. On the basis of this value, 94% of NA,OH$^-$,Ac was the acetates VI and VII and 6% was the ketone VIIIa. The infrared spectrum of NA,OH$^-$,Ac was

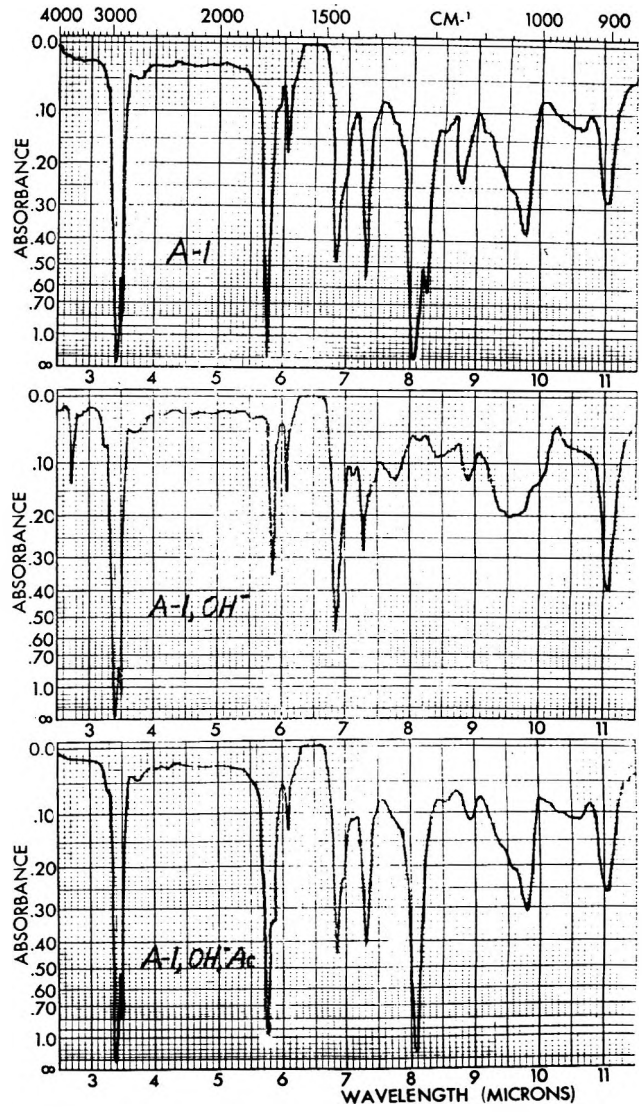


Fig. 3.—Infrared spectrum (top) of A-1, a mixture of VI and VIII; spectrum (middle) of A-1,OH$^-$, a mixture of VIa and VIIIa; spectrum (bottom) of A-1,OH$^-$,Ac, a mixture of VI and VIIIa.

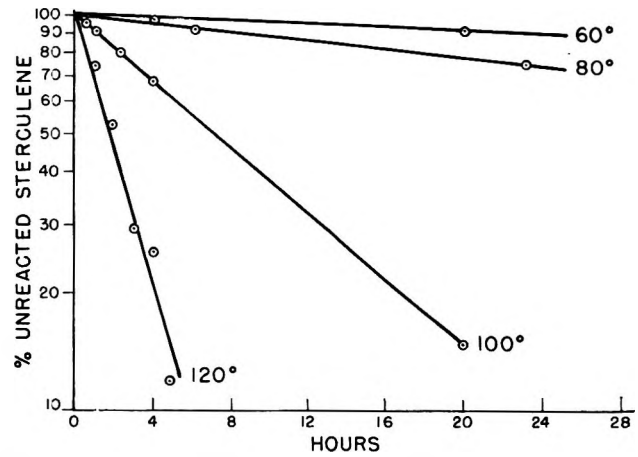


Fig. 4.--Reaction of sterculene and acetic acid at various temperatures.

(9) T. Shimadate, H. W. Kircher, J. W. Berry, and A. J. Deutschman, Jr., *J. Org. Chem.*, **29**, 485 (1964).

(10) V. L. Hansley, *J. Am. Chem. Soc.*, **57**, 2303 (1935).

almost superimposable on that of NA, a small shoulder on the ester carbonyl band (ketone) was discernible in NA,OH⁻,Ac, and a small band at 8.8 μ (enol acetate*) in NA was missing in NA,OH⁻,Ac.

Ozonolysis.—NA (20.35 g., 0.063 mole) in methylene chloride (250 ml.) was cooled to −45°. Ozone (0.15 mole) was passed through the solution over 2.5 hr. after which the temperature had risen to −32°. The solution was purged with nitrogen, warmed to room temperature, and added to a suspension of zinc dust (20 g.) in 50% aqueous acetic acid (200 ml.). The mixture was heated on a boiling water bath 1 hr. and the residue in the flask extracted with petroleum ether. The aqueous phase from the extraction was combined with that which had steam distilled with the methylene chloride and was treated with methone (20 g.) in ethanol (150 ml.). The next day the methone derivative of formaldehyde was obtained (5.94 g., 0.0202 mole) m.p. and m.m.p. 189.5–190°, lit.[11] m.p. 189°.

The petroleum ether phase was extracted with aqueous alkali. The alkaline solution was acidified and extracted with ether to yield an acid (1.40 g.), a portion of which was converted to the methyl ester with 7% boron trifluoride in methanol. G.l.c. of the ester showed only methyl pelargonate. The *p*-toluidide of the acid was prepared,[12] m.p. 81–81.5°, m.m.p. (with the *p*-toluidide of pelargonic acid) 82–84°, lit.[12] m.p. 84°.

The remaining petroleum ether phase was evaporated to leave a residue (18.4 g.) which showed six spots on t.l.c., some of which were suspected to be deacetylated oxidation products. The mixture was acetylated with pyridine and acetic anhydride (20 ml. each) to yield a product that showed only four spots on t.l.c. It was distilled; the first fraction (b.p. 91–114° at 26 mm., 2.25 g.) was composed of 70% pelargonaldehyde and 30% 2-decanone (by g.l.c.). These were separated on a preparatory column and the 2,4-dinitrophenylhydrazones of each were prepared: 2-decanone 2,4-DNP, m.p. and m.m.p. 73.5–74.5°, lit.[13] m.p. 73–74°; pelargonaldehyde 2,4-DNP, m.p. and m.m.p. 105–106°, lit.[14] m.p. 105–106°.

The second fraction from the distillation (b.p. up to 90° at 0.05 mm., 4.73 g.) crystallized in the receiver. It was recrystallized from methanol and identified as 2-ketodecyl acetate, m.p. 55.5–56.5°, lit.[3] m.p. 55.5–55.8°; infrared bands at 5.68 and 8.13 (acetate ester) and 5.75 μ (ketone).

The third fraction (b.p. 145–155° at 0.015 mm., 8.95 g.) had the same retention time on g.l.c. and R_f on t.l.c. as synthetic nonyloin acetate. A portion (5.2 g.) was hydrolyzed with alcoholic potassium hydroxide and the product crystallized from ethanol to yield 3.74 g. of nonyloin, m.p. 45–46.5°, m.m.p. 47–48°, lit.[10] m.p. 44°.

Separation of NA into A and B (Fig. 1).—The products from two sterculene–acetic acid reactions were combined (57.5 g.) and fractionated through a 20-in. spinning band column at 0.05 mm. Nine fractions were obtained (0.5 ml./hr.), the first (6.7 ml.) was largely forerun, fractions 2–5 (43.5 ml.) were 70–90% A, and fractions 6–9 (14.1 ml.) were 85–90% B. Fractions 2–5 were combined and redistilled to yield a fraction (A-1, 15.1 ml.) consisting only of A and enriched in the enol acetate derivative VIII. Fractions 6–9 were redistilled to yield a fraction (5.6 ml.) consisting only of B.

Identification of A.—Alkaline hydrolysis (A,OH⁻) and reacetylation (A,OH⁻,Ac) of 1 ml. of A-1 gave the chromatographic and spectroscopic data shown in Fig. 2 and 3. A solution of sodium periodate (6.85 g.), potassium permanganate (0.085 g.), and sodium bicarbonate (1.27 g.) in water (800 ml.)[8] was added to A-1 (1.30 g.). *t*-Butyl alcohol (250 ml.) was added to enhance the solubility of A-1 in the aqueous solution. The mixture was stirred for 44 hr., acidified, and extracted with petroleum ether. The extract was dried and evaporated to yield the oxidation products (1.62 g.). G.l.c. of the products showed no 2-decanone; t.l.c. showed unchanged starting material and nonyloin acetate.

A solution of A-1 (8.40 g.) in glacial acetic acid (175 ml.) was ozonized and worked up as described above to yield a product (7.76 g.). From this, pelargonic acid (1.61 g.) was obtained by alkaline extraction; it was identified by g.l.c. of its methyl ester and as its *p*-toluidide, m.p. 81–82°. 2-Decanone (0.45 g.) was distilled from the mixture (b.p. 90–91° at 10 mm.) and characterized as its 2,4-dinitrophenylhydrazone, m.p. and m.m.p. 74–74.8°. The remaining material had the chromatographic behavior of nonyloin acetate on g.l.c. and t.l.c. Component A was therefore a mixture of VI and VIII. Both of these were oxidizable with ozone, but only VI could be degraded by the permanganate–periodate procedure.

Identification of B.—Alkaline hydrolysis of 1 ml. of B gave an alcohol (B,OH⁻, Fig. 2) that did not pass through the g.l.c. column, which explains why only two peaks were observed on g.l.c. on the NA,OH⁻ mixture. It showed a single spot on t.l.c.; reacetylation of the alcohol gave an ester (B,OH⁻,Ac) that had the same chromatographic behavior and whose infrared spectrum was superimposable on that of B. A portion (1.36 g.) of B was oxidized by the permanganate–periodate procedure given above to yield a product (1.80 g.) that contained no starting material. It was separated into an acid fraction (0.55 g.) and a neutral fraction (1.01 g.). The former contained only pelargonic acid by g.l.c. of its methyl ester, *p*-toluidide m.p. and m.m.p. 82–84°. The latter was crystallized from methanol to yield 2-ketodecyl acetate, m.p. 55.8–56°, lit.[3] m.p. 55.5–55.8°. Component B is therefore VII.

Reactions of Sterculene and Acetic Acid at Various Temperatures.—The two reagents (1 ml. each) were placed in 4-ml. screw cap vials under nitrogen and placed in oil baths held at 60–65°, 80–85°, 100–105°, and 120–127° by hot plates. The reaction mixtures at the higher two temperatures became homogeneous within 1 hr.; those at 60 and 80° remained as two phases for almost 2 days. Six samples of 10 drops each were removed from the vials periodically and added to alcoholic potassium hydroxide; the hydrolyzed materials were reacetylated with pyridine and acetic anhydride and isolated from the water-diluted reaction mixtures. When two phases were present, the vials were vigorously shaken before the samples were removed to get a representative quantity of both phases. Ten microliters of the products from the esterifications was analyzed with the Aerograph A-90-C instrument.

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(12) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956.

(13) C. Jutz, *Ber.*, **91**, 1867 (1958).

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The Phenoxaphosphinic Acid and Phenothiaphosphinic Acid Ring Systems[1]

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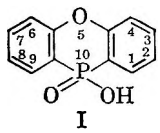
The phenoxaphosphinic acid ring system (I) was found to be remarkably stable. 2,8-Dimethylphenoxaphosphinic acid was oxidized to the corresponding dicarboxy compound, and dinitro derivatives of both the dimethyl and the dicarboxy compounds were prepared. 2,8-Dimethylphenothiaphosphinic acid was prepared by a variant of the Friedel–Crafts reaction in which *p*-tolyl sulfide and phosphorus trichloride were heated together in the presence of aluminum chloride and the reaction mixture was then hydrolyzed. The ultraviolet absorption spectra of the heterocyclic phosphorus compounds are described and discussed.

There are relatively few procedures available for the preparation of phosphinic acids in which the phosphorus atom is a member of a ring system.[2] The first such compound was prepared by a variant of the Friedel–Crafts reaction in which diphenylamine and phosphorus trichloride were heated together for several hours. When the product was extracted with water and then oxidized, phenazaphosphinic acid[3,4] was obtained. An attempt to extend this method to the preparation of phenoxaphosphinic acid (I) failed, because the phosphorus trichloride attacked a 4-



I

position of phenyl ether rather than a 2-position.[5] Several years ago we reported the preparation of 2,8-dimethylphenoxaphosphinic acid by refluxing a mixture of *p*-tolyl ether and phosphorus trichloride in the presence of aluminum chloride, and then hydrolyzing the reaction mixture.[6] The present paper is concerned with the preparation and properties of several derivatives of phenoxaphosphinic acid and of its sulfur analog, phenothiaphosphinic acid.

We have found that the phenoxaphosphinic acid ring system is remarkably stable. Thus, the 2,8-dimethyl derivative can be oxidized with potassium permanganate to the corresponding dicarboxy compound in satisfactory yield. As indicated in Table I, the ultraviolet absorption spectrum of 2,8-dicarboxyphenoxaphosphinic acid is characterized by intense absorption in the 270–285-mμ region. This feature is probably associated with resonance interaction between the ring oxygen atom and the carboxy groups in *para* position to it.[7] Attempts to decarboxylate the compound by the usual methods[8] have led only to recovery of the starting material. Fusion with sodium hydroxide yielded a reaction mixture from which no phosphinic acid could be isolated.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA[a]

Compound	λ_{max}, mμ	ϵ_{max}
2,8-Dimethylphenoxaphosphinic acid[b]	218	39,900
	243	20,500
	281[c]	2,800
	296[c]	5,100
	301	5,430
2,8-Dicarboxyphenoxaphosphinic acid	218	37,800
	271	21,400
	282[c]	21,400
	285	22,100
2,8-Dimethyl-4,6-dinitrophenoxaphosphinic acid	235[c]	17,300
	330	3,980
2,8-Dicarboxy-4,6-dinitrophenoxaphosphinic acid	255	16,200
	271	16,000
	305[c]	4,890
2,8-Dimethylphenothiaphosphinic acid	221	26,800
	267	14,500
	287	5,700
	310[c]	3,450
p-Tolyl sulfide	252	14,100
	275	6,540
2,8-Dimethyl-5,5-dioxophenothiaphosphinic acid	222	43,000
	275	2,570
	284	2,670

[a] The spectra of all compounds were determined in 95% ethanol with a Perkin-Elmer Model 350 spectrophotometer. [b] The spectrum of this compound was previously determined with a Beckman DU spectrophotometer; *cf.* ref. 6. [c] Shoulder.

Nitration of 2,8-dimethylphenoxaphosphinic acid with fuming nitric acid near room temperature gave a dinitro derivative. The structure of this compound was not established unequivocally, but it almost certainly is 2,8-dimethyl-4,6-dinitrophenoxaphosphinic acid for the following reasons. (1) Among the available positions the 4,6-positions are most activated by the ring oxygen atom and least deactivated by the phosphinico (PO_2H) group. (2) The nitration of *p*-tolyl ether leads only to compounds in which the nitro groups are *ortho* to the oxygen atom.[9] (3) The ultraviolet absorption spectrum (*cf.* Table I) of the dinitro compound is *less* intense than that of the starting material, even though nitro groups usually cause increased absorption. This decreased intensity can be explained by assuming steric inhibition of resonance between the ring oxygen atom and the benzene rings and between the nitro groups and the benzene rings. It is of interest that the spectrum of *o*-nitrophenyl phenyl ether[10]

(1) Supported in part by Research Grant GM-09479 from the National Institutes of Health, U. S. Public Health Service.

(2) See, for example, E. R. Lynch, *J. Chem. Soc.*, 3729 (1962).

(3) P. G. Sergeev and D. G. Kudryashov, *Zh. Obshch. Khim.*, **8**, 266 (1938); see also M. Häring, *Helv. Chim. Acta*, **43**, 1826 (1960).

(4) The nomenclature used in the present paper is based, in general, on the usage of F. G. Mann, "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, Bismuth, and Silicon," Interscience Publishers, Inc., New York, N. Y., 1950. At the suggestion of Dr. Leonard T. Capell, slight changes have been made in order to conform to current nomenclature practices.

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(7) *Cf.* L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).

(8) J. March, *J. Chem. Educ.*, **40**, 212 (1963).

(9) J. Reilly, P. J. Drumm, and H. S. B. Barrett, *J. Chem. Soc.*, 67 (1927).

(10) H. E. Ungnade and I. Ortega, *J. Org. Chem.*, **17**, 1475 (1952).

is characterized by a shoulder at 260 mμ (log ε 3.62) and a maximum at 315 mμ (log ε 3.33) and is thus somewhat similar to the spectrum of the dinitro derivative of 2,8-dimethylphenoxaphosphinic acid.

Nitration of 2,8-dicarboxyphenoxaphosphinic acid with fuming nitric acid gave a satisfactory yield of a dinitro compound. The structure of this material was not proven, but it undoubtedly is 2,8-dicarboxy-4,6-dinitrophenoxaphosphinic acid since both the carboxy and phosphinico groups are *meta* directing and the phenoxy group is *ortho, para* directing. The spectrum of this compound given in Table I is consistent with this formulation if we assume (as we did in the above paragraph) that the nitro groups are in the sterically hindered 4,6-positions.

We have extended the Friedel–Crafts reaction to the preparation of 2,8-dimethylphenothiaphosphinic acid by heating *p*-tolyl sulfide with phosphorus trichloride in the presence of aluminum chloride[11] and then hydrolyzing the reaction mixture. The success of this synthesis was somewhat surprising since it had been reported[12] that the reaction of phenyl sulfide, arsenic trichloride, and aluminum chloride at 175° yields hydrogen chloride and diphenylene disulfide but no organoarsenic compounds; when phenyl sulfide and aluminum chloride were heated together in the absence of arsenic trichloride, benzene and diphenylene disulfide were obtained.[13] The aluminum chloride catalyzed reaction between phosphorus trichloride and *p*-tolyl sulfide does seem to be considerably more complex than the corresponding reaction with *p*-tolyl ether. Thus, in spite of numerous attempts, we were unable to obtain more than a 25% yield of 2,8-dimethylphenothiaphosphinic acid (compared to a 73% yield of 2,8-dimethylphenoxaphosphinic acid). Traces of *p*-tolylphosphonic acid[14] and *p*-tolyl disulfide[15] were also isolated from the reaction mixture; it is clear, therefore, that the aryl sulfide system must be cleaved to some extent under the conditions of the reaction. No information was obtained concerning the mechanism of this cleavage.

It has been pointed out[16a] that the ultraviolet absorption spectra of aryl sulfides exhibit larger bathochromic shifts than do the spectra of the corresponding aryl ethers. This effect is apparently seen in the spectrum of 2,8-dimethylphenothiaphosphinic acid. The maximum at 267 mμ is probably the "first primary band" in the sense used by Doub and Vandenbelt[7] and corresponds to the 252-mμ band in *p*-tolyl sulfide and the 243-mμ band in 2,8-dimethylphenoxaphosphinic acid.

2,8-Dimethylphenothiaphosphinic acid was readily oxidized with hydrogen peroxide to the corresponding sulfone. The ultraviolet absorption of the sulfone in the 270–285-mμ region is less intense than that of the parent sulfide and undoubtedly reflects the lower conjugative ability of the sulfonyl group.[17] It is of interest that the "first primary band" of the heterocyclic sulfone occurs at 222 mμ which is a lower wave length than the corresponding band of *p*-tolyl sulfone.[18] This result is difficult to explain unless we assume, as Price and Oae[16b] have suggested, that the conjugation of two benzene rings through a sulfone group does not operate when the two rings are held in coplanar position. A scale model[19] indicates that 2,8-dimethyl-5,5-dioxophenothiaphosphinic acid has a nearly planar structure.

Experimental[20]

2,8-Dicarboxyphenoxaphosphinic Acid.—2,8-Dimethylphenoxaphosphinic acid (2.6 g.), dissolved in a mixture of 15 ml. of pyridine and 15 ml. of water, was oxidized with 25 g. of potassium permanganate by the method of Morgan and Herr.[21] After the excess pyridine was removed by steam distillation, the reaction mixture was filtered, decolorized with charcoal, and then added slowly with good stirring to 100 ml. of 10% hydrochloric acid. The analytically pure dicarboxy compound precipitated; the yield was 1.8 g. (56%), m.p. >300°.

Anal. Calcd. for $C_{14}H_9O_7P$: P, 9.67; neut. equiv., 106.7. Found: P, 9.45; neut. equiv., 106.9.

2,8-Dimethyl-4,6-dinitrophenoxaphosphinic Acid.—2,8-Dimethylphenoxaphosphinic acid (2.6 g.) was nitrated at 30–35° with 25 ml. of fuming nitric acid (*d* 1.5). The reaction mixture was poured onto 30 g. of ice, whereupon 1.4 g. (40%) of crude dinitrocompound crystallized from solution. Recrystallization from aqueous acetone yielded 0.52 g. of yellow needles, m.p. >300°. The analysis and spectrum of this material was not affected by further recrystallization.

Anal. Calcd. for $C_{14}H_{11}N_2O_7P$: N, 8.00; P, 8.84. Found: N, 7.87; P, 8.96.

2,8-Dicarboxy-4,6-dinitrophenoxaphosphinic Acid.—A solution of 3.2 g. of 2,8-dicarboxyphenoxaphosphinic acid in 25 ml. of freshly prepared 100% nitric acid[22] was gently heated for about 3 hr. until approximately two-thirds of the nitric acid was distilled. On cooling the reaction mixture to −25°, crystals were obtained which were removed by filtration and washed with a few milliliters of cold water. The yield was 3.0 g. (78%), m.p. >300°. The sample used for analysis and for the determination of the ultraviolet absorption spectrum was recrystallized from a mixture of acetone and ether and then dried *in vacuo* at 100°.

Anal. Calcd. for $C_{14}H_7N_2O_{11}P$: C, 40.99; H, 1.72; N, 6.83; P, 7.55; neut. equiv., 136.7. Found: C, 40.72; H, 1.85; N, 6.85; P, 7.33; neut. equiv., 138.6.

2,8-Dimethylphenothiaphosphinic Acid.—*p*-Tolyl sulfide[23] (21.4 g.), 35 ml. of phosphorus trichloride, and 17 g. of anhydrous aluminum chloride were placed in a 500-ml. two-necked flask equipped with a sealed stirrer and a reflux condenser protected with a drying tube. The mixture was stirred and refluxed gently for about 7 hr. and then allowed to stand overnight at room temperature. On pouring the reaction mixture over 800 g. of cracked ice, a heavy oil was obtained. The aqueous supernatant solution was poured off, and the oil was dissolved in 400 ml. of boiling 5% sodium hydroxide solution. The resulting solution was treated with decolorizing charcoal and then made very acid (pH <0) by the addition of concentrated hydrochloric acid. A white solid separated which was removed by filtration

(11) In the absence of aluminum chloride there was no reaction upon refluxing a mixture of *p*-tolyl sulfide and phosphorus trichloride for 24 hr.

(12) E. E. Turner and A. B. Sheppard, *J. Chem. Soc.*, **127**, 514 (1925).

(13) However, W. Dilthey, L. Neuhaus, E. Reis, and W. Schommer [*J. prakt. Chem.*, **124**, 81 (1930)] found that phenyl sulfide is not cleaved under Friedel–Crafts conditions and can be acylated normally by acetyl chloride and aluminum chloride.

(14) Identified by analysis, melting point, and mixture melting point with an authentic sample.

(15) Identified by analysis, melting point, and ultraviolet absorption, which was virtually identical with that reported by L. Bauer and J. Cymerman [*J. Chem. Soc.*, 109 (1950)].

(16) C. C. Price and S. Oae, "Sulfur Bonding," The Ronald Press Co., New York, N. Y., 1962: (a) p. 30; (b) p. 100.

(17) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 231 (1949).

(18) The "first primary band" of *p*-tolyl sulfone occurs at 245 mμ (log ε 4.32); *cf.* H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 485.

(19) Constructed with an atom model set manufactured by Waltham Enterprises, Ltd., England.

(20) Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer Model 421 spectrophotometer.

(21) P. W. Morgan and B. C. Herr, *J. Am. Chem. Soc.*, **74**, 5264 (1952).

(22) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1957, p. 468.

(23) J. Reilly, P. J. Drumm, and B. Daly, *Proc. Roy. Irish Acad.*, **39B**, 515 (1930).

and dried *in vacuo*. It was then extracted for 24 hr. with 500 ml. of anhydrous ether in a Soxhlet apparatus.[24] The ether-insoluble material in the thimble was then extracted for 48 hr. with 500 ml. of 95% ethanol. Pure 2,8-dimethylphenothiaphosphinic acid crystallized from the alcoholic solution, and a second crop could be obtained by evaporating the mother liquor to incipient crystallization. The yield was 6.90 g. (25%), m.p. >300°.

Anal. Calcd. for $C_{14}H_{13}O_2PS$: P, 11.21; S, 11.60; neut. equiv., 276.3. Found: P, 11.13; S, 11.80; neut. equiv. 279.1.

2,8-Dimethyl-5,5-dioxophenothiaphosphinic Acid.—When a suspension of 1.05 g. of 2,8-dimethylphenothiaphosphinic acid in 20 ml. of boiling glacial acetic acid was treated with 3.0 ml. of 30% hydrogen peroxide, virtually all the solid went into solution and soon a voluminous precipitate separated. The reaction mixture was then allowed to sit on a steam bath for 2 hr. and finally cooled. The precipitate was removed by filtration and washed with copious quantities of water. The yield was 1.02 g. (87%), m.p. >300°. The infrared absorption spectrum in potassium bromide exhibited strong maxima at 1158 and 1315 cm.$^{-1}$, which were assigned to the symmetric and asymmetric stretching modes of the SO_2 group.[25] These bands were absent in the parent sulfide.

Anal. Calcd. for $C_{14}H_{13}O_4PS$: C, 54.54; H, 4.25. Found: C, 54.39; H, 4.29.

(24) This step served to remove an oily material which was not identified.

Acknowledgment.—The authors wish to acknowledge the invaluable technical assistance given by Mrs. Joyce Edmisten Carevic.

(25) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 360–363.

Kinetics of the Reaction of Aromatic Aldehydes with Ammonia

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The kinetics of the reaction of aromatic aldehydes with ammonia to form hydrobenzamides have been studied spectrophotometrically in methanol at 30°. The reaction is first order with respect to aldehyde and first order with ammonia. The effect of water, potassium hydroxide, and temperature on the rate has been studied. The application of Hammett's law to the rates gives a positive ρ-value for the reaction of aldehydes with electron-releasing substituents and a negative ρ-value with electron-withdrawing substituents. Induction periods were observed in the formation of hydrobenzamides with electron-withdrawing substituents. These results suggest a probable mechanism involving α-aminobenzyl alcohol and benzylidenimine, etc.

The reaction of benzaldehydes with ammonia gives hydrobenzamides, ArCH=NCH(Ar)N=CHAr. Dobler has observed the rate of the reaction by means of acidimetry to be second order.[1] He observed no systematic substituent effect. The analogous condensation of aromatic aldehydes with *n*-butylamine,[2] semicarbazide,[3,4] or anilines[5] has been studied, Hammett's rule not being applicable for the benzylidenimine or semicarbazone formation. Some investigators have reported that the reaction of benzaldehyde with ammonia also produces benzylidenimine,[6,7] NH=CHPh; α,α'-dioxydibenzylamine,[8] $NH(CH(OH)Ph)_2$; and 2,4,6-triphenyl-1,3,5-hexahydrotriazine,[9] (—NH—CHPh—)$_3$. The present paper summarizes our data on the kinetic investigation of the reaction involving the effect of basicity of the solution, the effect of substituents, and a probable mechanism derived from the results. Since acidimetry gave no accurate rates of reaction, we employed spectrophotometry.

Experimental

Materials.—Commercial benzaldehyde, b.p. 78.8° (26 mm.), and *p*-anisaldehyde, b.p. 159.0° (44 mm.), were purified by vacuum distillation under nitrogen. *p*-Chlorobenzaldehyde, m.p. 46.5–47.5°, and *p*-cyanobenzaldehyde, m.p. 101–102°, were prepared by the chromic acid oxidation of *p*-chlorotoluene and *p*-tolunitrile,[10] respectively. Commercial methanol was purified by distillations and used as the solvent. Aqueous ammonia was of guaranteed reagent grade. Methanolic ammonia free of water was prepared by passing ammonia gas, dried with sodium hydroxide, into methanol dried by boiling with magnesium.

Products.—Hydrobenzamides were prepared by the reaction of concentrated aqueous ammonia and aldehydes in methanol, the resulting precipitates being recrystallized from methanolic ammonia: hydrobenzamide, m.p. 100–101° (lit.[11] m.p. 102°); hydroanisamide, m.p. 128.5–130.5 (lit.[12] m.p. 130°); 4,4′,4″-trichlorohydrobenzamide, m.p. 87–90°; 4,4′,4″-tricyanohydrobenzamide, m.p. 130–132°. Infrared spectra[13] of these products showed the C=N band at 1632–1636 cm.$^{-1}$, but no absorption corresponding to the C=O, =NH, or —OH band was observed. 4,4′,4″-Trichlorohydrobenzamide and 4,4′,4″-tricyanohydrobenzamide are new compounds.

Anal. Calcd. for $C_{21}H_{15}Cl_3N_2$: C, 62.78; H, 3.76; N, 6.97. Found: C, 62.73; H, 3.87; N, 6.87.

Anal. Calcd. for $C_{24}H_{15}N_5$: C, 77.20; H, 4.05; N, 18.76. Found: C, 77.62; H, 4.10; N, 18.18.

Rate Measurements.—For the determination of the concentrations of benzaldehyde [B] and hydrobenzamide [H], two wave lengths of benzaldehyde at 245 (absorption max.) and 270 mμ (absorption min.) were selected. Their concentrations were determined by ultraviolet spectrophotometry for binary mixtures.[14] The values of the molar extinction coefficient were determined experimentally: for benzaldehyde, ϵ_{max} 1.319×10^4 (lit.[15] $\epsilon_{210\ m\mu}$ 1.32×10^4), ϵ_{min} 1.098×10^3; for hydrobenzamide, ϵ_{max} 2.800×10^4, ϵ_{min} 1.016×10^4. The absorption of the product, hydrobenzamide, could be determined by converting the remaining benzaldehyde into acetal with a drop of sulfuric acid in methanol. The spectrum of hydrobenzamide (λ_{max} 251 mμ) showed a bathochromic shift (λ_{max} 281 mμ) by addition of sulfuric acid. A methanolic solution of hydrobenzamide was stable at room temperature. Since the decomposition of hydrobenzamide

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(8) F. Francis, *Ber.*, **42**, 2216 (1909).

(9) S. V. Svetozarskii, E. N. Zil'berman, and A. I. Finkel'shtein, *Zh. Obshch. Khim.*, **31**, 1717 (1961).

(10) S. V. Lieberman and R. Connor, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 441.

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(13) L. J. Bellamy "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958.

(14) C. N. R. Rao, "Ultraviolet and Visible Spectroscopy," Butterworth and Co. (Publishers) Lmt., London, 1961, p. 73.

(15) J. VanAllan and J. F. Tinker, *J. Org. Chem.*, **19**, 1243 (1954).

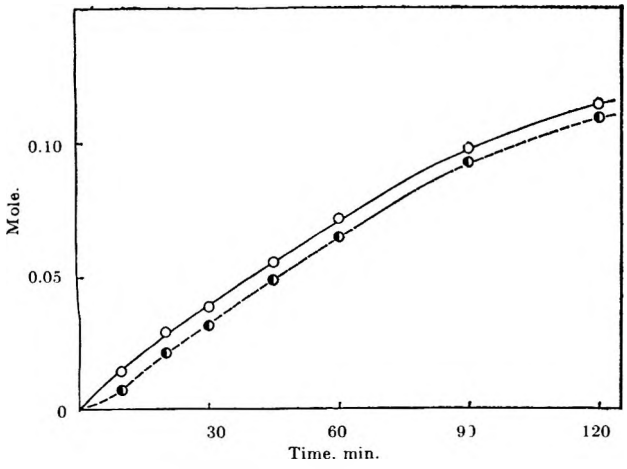


Fig. 1.—The comparison of the consumption of benzaldehyde and the formation of hydrobenzamide, $[NH_3]_0$ = 0.488 *M*, $[PhCHO]_0$ = 0.255 *M*, at 30°: ○, benzaldehyde consumed; ◐, benzaldehyde converted to hydrobenzamide.

was negligible within a minute after the addition of sulfuric acid, the absorbances were measured at just 1 min. after the addition. Then the rate of the formation of hydrobenzamide was measurable. The rate constants by both methods were identical within experimental error with unsubstituted benzaldehyde. The rates with other substituted benzaldehydes were estimated by the latter method. Absorption maxima of substituted hydrobenzamides were as follows: *p*-MeO, 320; *p*-Cl, 295; and *p*-CN, 270 mμ. The rate constants, k_2, with *p*-chloro- and *p*-cyanobenzaldehyde were calculated by eliminating their induction periods, which were obtained by the extrapolation of plots of the concentration of formed hydrobenzamides *vs.* time to zero concentration.

The typical experiment for the rate measurements was as follows: 0.450 *M* benzaldehyde (25 ml.) in methanol and 0.976 *M* methanolic ammonia (25 ml.) which had previously attained thermal equilibrium were mixed in a 100-ml. thermostated flask kept at 30.0 ± 0.1°. Aliquots were periodically withdrawn and diluted with methanol by a factor of 1.6 × 10^3. Then their absorbances at 245 and 270 mμ were determined by Shimadzu automatic spectrophotometer SV 50 A at room temperature. Infrared spectra were measured by Shimadzu spectrophotometer IR-27 B.

Results and Discussion

Rate Law.—The reaction was found to be second order and satisfied the rate equation that follows.

$$v = \frac{dx}{dt} = k_2(a - \frac{2}{3}x)(b - x) \qquad (1)$$

or

$$k_2 = \frac{1}{t}\frac{2.303}{\left(a - \frac{2}{3}b\right)}\left(\log\frac{a - \frac{2}{3}x}{b - x} - \log\frac{a}{b}\right) \qquad (2)$$

Here, *a* and *b* are the initial concentrations of ammonia and benzaldehyde, respectively, *x* the concentration of consumed benzaldehyde at time *t*, and k_2 the apparent second-order rate constant. Typical rate data are shown in Table I. The rate constant tended to decrease very slightly with increasing initial molar ratio of ammonia *vs.* benzaldehyde (Table II). As the reaction proceeds, the molar ratio with an excess of ammonia increases and hence the rate constants decrease very slightly at the end of the reaction. If the reactants are converted completely to the product, *x* moles of consumed benzaldehyde should yield *x*/3 moles of hydrobenzamide according to the following stoichiometric equation.

Table I

Typical Rate Data for the Reaction of Benzaldehyde and Ammonia at 30°[a]

Time, sec.	[PhCHO] *M*	Conversion, %	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$
0	0.225	0	
610	0.211	6.2	2.16
1225	0.196	12.8	2.34
1810	0.187	17.0	2.15
2710	0.170	24.4	2.19
3610	0.154	31.6	2.29
5400	0.128	43.1	2.31
7200	0.112	50.3	2.19
			Av. 2.23 ± 0.02

[a] Initial concentration: ammonia, 0.488 *M*; benzaldehyde, 0.225 *M*.

Table II

The Effect of the Initial Molar Ratio of Ammonia *vs.* Benzaldehyde on the Second-Order Rate Constant at 30°

Initial concn. of benzaldehyde, $[PhCHO]_0$, *M*	Initial concn. of ammonia, $[NH_3]_0$, *M*	$\frac{[NH_3]_0}{[PhCHO]_0}$	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$
0.0480	0.489	10.2	1.42
0.0968	0.744	7.7	1.68
0.0956	0.489	5.1	1.65
0.0927	0.360	3.9	1.89
0.143	0.489	3.4	1.86
0.0913	0.247	2.7	2.06
0.0887	0.196	2.2	2.06
0.225	0.488	2.2	2.23
0.142	0.251	1.8	2.46
0.105	0.148	1.4	2.54
0.179	0.239	1.3	2.24
0.252	0.251	1.0	2.37
0.292	0.201	0.7	2.84

$$3PhCHO + 2NH_3 \overset{K}{\rightleftarrows} (PhCH{=}N)_2CHPh + 3H_2O \qquad (3)$$

However, consumed benzaldehyde was not quantitatively converted to hydrobenzamide, as shown in Fig. 1, which suggested that a very small but constant amount of benzaldehyde existed as some intermediates during the reaction. The difference in the curves of Fig. 1 is more than the experimental error on the basis of several experiments. The difference is more obvious at a very early stage of the reaction. This effect was so small with benzaldehyde that the rate constant obtained by the estimation of the product (1.91 × 10^{-4} l. mole^{-1} sec.$^{-1}$) and that of the reactant (1.83 × 10^{-4} l. mole^{-1} sec.$^{-1}$) agreed. However, an induction period was observed with benzaldehydes having electron-withdrawing substituents, as will be stated later.

The Effect of Addition of Water or Alkali.—The addition of water retarded the apparent rate and the rate equation deviates from eq. 1. Conversions at 120 min. were as follows (added water in vol. % and conversion in %): 5, 47.5; 10, 43.6; 15, 37.8; 20, 35.2. These facts may be due to the predomination of the decomposition of the product or the reverse reaction of eq. 3. Observed equilibrium constants *K* in the presence of various amounts of water held constancy (Table III).

$$K = \frac{[(PhCH{=}N)_2CHPh][H_2O]^3}{[PhCHO]^3[NH_3]^2} \qquad (4)$$

In the presence of 20 vol. % of water, hydrobenzamide corresponding to 54% of consumed benzaldehyde was precipitated, hence the observed equilibrium constant

TABLE III

EFFECTS OF WATER ADDED AT 30°

Initial concn. $[NH_3]_0$, M	Initial concn. $[PhCHO]_0$, M	$[H_2O]$, vol. %	Rate constants, $k_2 \times 10^4$ l. mole^{-1} sec.$^{-1}$	Equilibrium constants, $K \times 10^{-5}$ l. mole^{-1}
0.494	0.215	5	2.11	1.37
0.494	0.219	10		1.37
0.490	0.224	15		1.24
0.490	0.227	20		2.62[a]
				(1.21)[b]
				Av. 1.30

[a] Hydrobenzamide was precipitated. [b] The value of the calculated equilibrium constant by eliminating the amount of precipitate.

became higher, while the equilibrium constant calculated by eliminating the amount of precipitate of hydrobenzamide agreed with other values.

It is well known that Schiff's base formation is subject to acid catalysis. The data in Table IV show that

TABLE IV

EFFECT OF POTASSIUM HYDROXIDE AT 30°

Initial concn. $[NH_3]_0$, M	Initial concn. $[PhCHO]_0$, M	Initial concn. $[KOH]_0$, M	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$	Time, min.	Conversion, %
0.251	0.142	0	2.46	240	60
0.250	0.149	0.152	1.52	240	33
0.252	0.139	0.247	0.94	240	26.7
0.232	0.123	0.280		240	23.2

an increase of concentration of alkali results in retardation of the formation of hydrobenzamide, hence increase in the concentration of intermediates (amino alcohols) and deviation from the above kinetic equation; *i.e.*, the order of the reaction became more than 2. These results may be caused by the suppression of acid catalysis for the dehydration of amino alcohols with added alkali.

Energy and Entropy of Activation.—The apparent energy and entropy of activation were calculated to be 9.73 kcal. mole^{-1} and −40.3 e.u., respectively, by means of the Arrhenius equation from the rate data: $k_2 \times 10^4$ l. mole^{-1} sec.$^{-1}$, 0.690 at 10°, 2.23 at 30°, 5.13 at 50°. These values can be expected in the analogous reaction, *i.e.*, the reaction of *p*-dimethylaminobenzaldehyde with ammonia (10.9 kcal. mole^{-1} −43.7 e.u.)[6], *p*-chlorobenzaldehyde with *n*-butylamine (7.0 kcal. mole^{-1}, −41.3 e.u.),[2] or *p*-nitrobenzaldehyde with *n*-butylamine (8.0 kcal. mole^{-1}, −33.7 e.u.).[2] These resemblances in energies and entropies of activation suggest that the analogous imine formation and transition state are involved. If the rate-determining step is the addition of ammonia to aldehyde, such a large negative value for entropy of activation is conceivable, since reactions in which the total number of molecules decreases[16] or the reactions involving a strongly polar transition state[17] produced from neutral molecules may be remarkably negative.

Effect of Substituents in Aldehydes on the Rate.—A simple Hammett's rule was not applicable to the reaction as shown in Fig. 2. The Hammett's plot reaction of benzaldehydes with ammonia in methanol

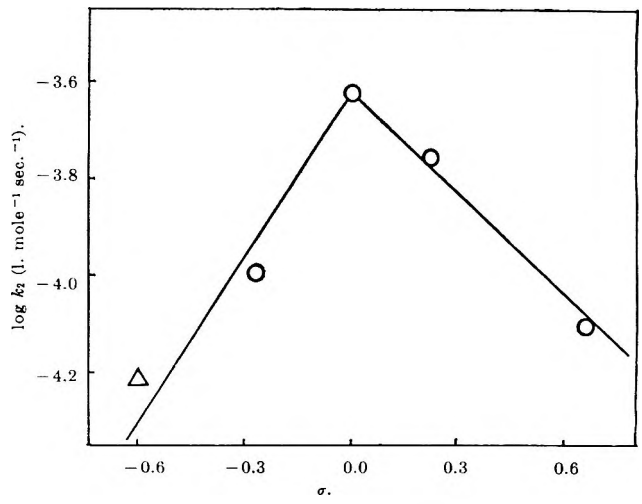


Fig. 2.—Hammett's plot for the reaction of aromatic aldehydes with ammonia: △, the value was calculated from the data of McLeod and Crowell.[6]

gave a positive ρ-value (+1.1) for the reaction of aldehydes with electron-releasing groups and a negative ρ-value (−0.65) with electron-withdrawing groups. Analogous relationships have been observed previously for the reaction of aromatic aldehydes with semicarbazide in 75% ethanol[3] and with *n*-butylamine in methanol.[2] The reaction was followed by the estimation of the rate of the formation of the products. No induction period was observed with an electron-releasing group (OCH_3), whereas an induction period was observed with electron-withdrawing groups (CN, Cl) as has been reported in the formation of oximes and semicarbazones[18] of aromatic aldehydes.

A 0.8 *M* *p*-chlorobenzaldehyde solution and a 0.8 *M* methanolic ammonia solution were mixed at 30°, and the absorption corresponding to carbonyl group (250–260 mμ) was measured. The absorption of the aldehyde at 255 mμ decreased at the start of reaction, and after an interval the absorption of hydrobenzamide at 259 mμ increased, until it became stronger than that at the start. The same phenomenon was also confirmed by means of infrared spectrum. The carbonyl absorption of *p*-cyanobenzaldehyde at 1702 cm.$^{-1}$ decreased at room temperature to 91% of the initial absorbance after 5 min., 86% after 14 min., 80% after 20 min., and 61% after 94 min. The absorption at 1635 cm.$^{-1}$ corresponding to C=N did not appear within 20 min., whereas the absorption was appreciable after 94 min. On the contrary, the absorption of unsubstituted hydrobenzamide at 1634 cm.$^{-1}$ increased with decreasing absorption at 1697 cm.$^{-1}$ in the reaction of benzaldehyde which had no induction period. The second-order rate constant (1.90×10^{-4} l. mole^{-1} sec.$^{-1}$) of the consumption of *p*-cyanobenzaldehyde calculated from the absorption at 1702 cm.$^{-1}$ was *ca.* twice as large as that of benzaldehyde (0.83×10^{-4} l. mole^{-1} sec.$^{-1}$) from 1697 cm.$^{-1}$ within 20% conversion under the same conditions. As shown in Fig. 2, the rate constant for the formation of hydrobenzamide was higher than that of 4,4′,4″-tricyanohydrobenzamide. These facts show that electron-withdrawing groups accelerate the rate of the consumption of aldehyde but retard the rate of the formation of

(16) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, Inc., New York, N. Y., 1960, p. 181.

(17) F. P. Price, Jr. and L. P. Hammett, *J. Am. Chem. Soc.*, **63**, 2387 (1941).

(18) W. P. Jencks, *ibid.*, **81**, 475 (1959).

the hydrobenzamide, and suggest that the rate-determining step shifts from addition to dehydration as suggested by Jencks in the formation of oximes and semicarbazones.[19]

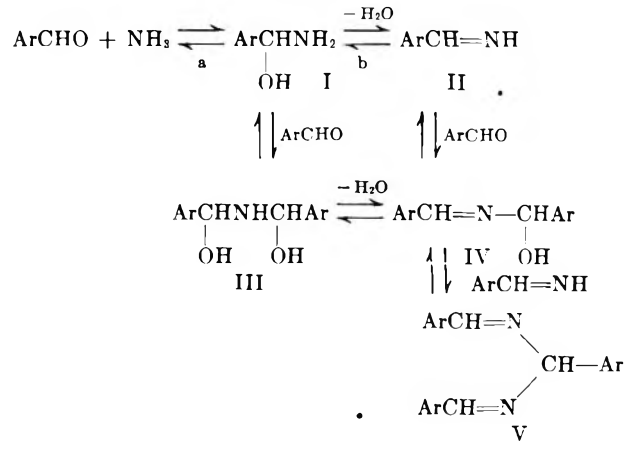
The Reaction Mechanisms.—The results in the reaction of benzaldehydes with ammonia in methanol are summarized (1–7) and suggest Scheme I.

(1) The over-all reaction is reversible, and the addition of water makes the reverse reaction appreciable.
(2) Since the reaction is second order, the rate-determining step may be the addition of ammonia with aldehyde or the dehydration of the resulting α-aminobenzyl alcohol.
(3) The rate of the formation of hydrobenzamide decreases slightly with increasing molar ratio of the initial concentration of ammonia *vs.* that of benzaldehyde.
(4) The addition of potassium hydroxide retards the rate of the reaction and the amount of intermediate may increase with increasing time.
(5) A positive Hammett's ρ-value was obtained with electron-releasing p-substituents in benzaldehyde and a negative ρ-value with the electron-withdrawing substituents.
(6) An induction period was observed in the formation of hydrobenzamides with electron-withdrawing substituents.
(7) The rate of the consumption is faster with p-cyanobenzaldehyde than with benzaldehyde, while the rate of the formation of hydrobenzamides from p-cyanobenzaldehyde is slower than that from benzaldehyde.

The steps leading to benzylidenimine (II) have been reported in very dilute solution.[5] As stated above, the rate-determining step may be the formation of α-aminobenzyl alcohol I (step a) or the dehydration to II (step b). The formation of hydrobenzamide V from II should be fast, since the rate is second order. The dehydration (b) may be rate determining in weakly basic media as reported by Jencks and others.[18,20]

(19) B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).

SCHEME I



The mechanism explains the facts that a constant amount of intermediates exists (Fig. 1), that the rate of the formation of hydrobenzamide decreases on addition of alkali by retarding acid-catalyzed dehydration, and that electron-withdrawing substituents increase the rate of the consumption of the reactants and reduce the rate of the formation of the products because of the elongation of induction period. However, in the reaction of benzaldehydes with electron-releasing groups the rate-determining step may be the addition (a) because of its positive ρ-value and the absence of induction period. When the initial concentration of benzaldehyde was higher than that of ammonia, the reaction of I with benzaldehyde yielding α,α'-dioxydibenzylamine (III) isolated by Francis[6] became appreciable and caused a little increase in the rate constant (Table II). There was no evidence for the formation of 2,4,6-triphenyl-1,3,5-hexahydrotriazine[8] under these conditions. Although the formation of hydrobenzamide from II or III seems to be fast, these steps are still obscure with the present data.

Acknowledgment.—This work was supported in part by Asahi Glass Company research fund.

(20) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 830 (1962).

Proton Magnetic Resonance Studies of Purines and Pyrimidines. XII. An Experimental Assignment of Peaks in Purine Derivatives[1a]

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Received November 1, 1963

A facile hydrogen for deuterium exchange in the purine nucleus and an unambiguous synthesis of 6- and 8-deuteriopurine have enabled us to determine the assignments for the proton magnetic resonance spectra of several purines and their nucleosides. An inversion of the order of peaks in passing from alkaline to acidic solutions occurs for several 6-substituted purines. A qualitative explanation for this effect is presented.

In a previous paper of this series[2a] assignments of the aromatic protons in the p.m.r. spectra of several purine derivatives have been proposed. These assignments were based solely on a comparison of different spectra and are therefore unsatisfactory for any detailed study. In the present investigation they were tested by the examination of p.m.r. spectra of several deuterated derivatives. 6-Deuterio- and 8-deuteriopurine were prepared by direct, unambiguous synthesis. A convenient method for the preparation of other 8-deu-

(1) (a) Supported in part by U. S. Public Health Service Grants GM-0951 and GM-K3 and by National Science Foundation Grant G-19296; (b) postdoctoral fellow of the U. S. Public Health Service.

(2) (a) C. D. Jardetzky and O. Jardetzky, *J. Am. Chem. Soc.*, **82**, 222 (1960). (b) NOTE ADDED IN PROOF.—A study of purine assignments similar to ours was recently reported by M. P. Schweizer, S. I. Chan, G. K. Helmkamp, and P. O. Ts'o [*J. Am. Chem. Soc.*, **86**, 696 (1964)].

terated derivatives arose from the observation made in this laboratory that the proton at position 8 of the purine nucleus is readily exchanged for deuterium by heating the material in D_2O at 90 to 100° for 10 to 20 min. The exchange is reversible in H_2O under similar conditions. The site of exchange was confirmed on the directly synthesized 8-deuterated purine. It is reasonable to assume that the proton exchangeable under these conditions is at position 8 in all the purine derivatives studied. Using this method for preparing 8-deuterated compounds we have been able to confirm and extend several previously proposed assignments.[2b]

Results

The spectra for purine and the 6- and 8-deuteriopurine, together with the assignments, are presented in Fig. 1. It was found that in this case the correct assignments are different from those made previously.[2a,3,4] The assignments and chemical shifts for other compounds studied are indicated in Table I

TABLE I

CHEMICAL SHIFTS[a]

Compd.	Concn.	Position C-8	Position C-2	Position C-6
Purine	0.1 *M* in 3 *M* NaOD	522	542	554
	0.1 *M* in D_2O	527	545	555
	0.1 *M* in 0.6 *M* D_2SO_4	563	579	589
Adenine[b]	0.1 *M* in 3 *M* NaOD	503*	512	
	0.05 *M* in D_2O, *ca.* 70°	(508)	(510)	
	0.1 *M* in 0.6 *M* D_2SO_4	532*	527	
Adenosine[c]	0.1 *M* in D_2O	509*	498	
	0.1 *M* in 0.6 *M* D_2SO_4	533*	527	
Hypoxanthine[d]	0.1 *M* in 3 *M* NaOD	495*	507	
	0.1 *M* in D_2O, *ca.* 70°	(509)	(511)	
	0.1 *M* in 0.6 *M* D_2SO_4	569	522	
Inosine[e]	0.1 *M* in D_2O	514	507	
	0.1 *M* in 0.6 *M* D_2SO_4	578	522	
Guanosine[f]	0.05 *M* in D_2O, *ca.* 80°	510		
	0.1 *M* in 0.6 *M* D_2SO_4	566		
6-Chloropurine	0.1 *M* in D_2O, 40% CH_3OH	525	531	
	0.1 *M* in 0.6 *M* D_2SO_4	568	549	

[a] All chemical shifts are in c.p.s. from hexamethyldisiloxane as external standard; * indicates confirmation of previous assignments (ref. 2a). Bulk diamagnetic susceptibility corrections are small (ref. 2a) and have been neglected. The correction for the methanol solution is +1.5 c.p.s. and has not been made. [b] 6-Aminopurine. [c] 6-Amino-9-β-D-ribofuranosyl-9H-purine. [d] Purin-6(1H)-one. [e] 9-β-D-Ribofuranosyl-9H-purin-6(1H)-one. [f] 2-Amino-9-β-D-ribofuranosyl-9H-purin-6(1H)-one.

together with the conditions of pD. Only the assignments for adenine and hypoxanthine in D_2O at neutral pD must still be considered tentative. Even in warm D_2O it was not possible to dissolve enough partially deuterated material to enable the peak of the C-8 proton to be clearly seen. Consequently it was necessary to compare in a separate experiment the shift of the single observed peak to a control. Since the peaks are separated by only 2 c.p.s. and the experimental error is possibly ±0.5 c.p.s., the conclusions are somewhat uncertain. On the other hand, the

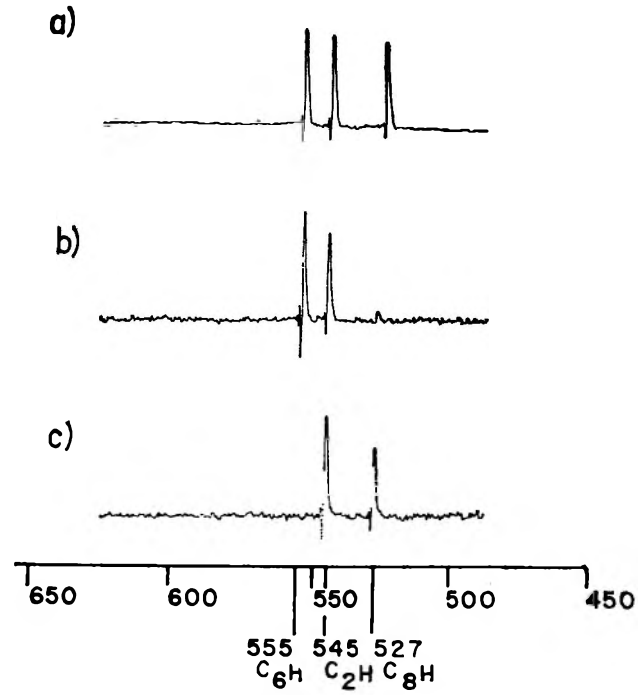


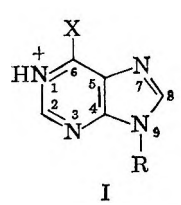
Fig. 1.—The spectra are for 0.1 *M* solutions and were determined at 60 Mc./sec.: (a) purine, (b) 8-deuteriopurine, (c) 6-deuteriopurine. (It is apparent that a small amount of exchange occurred at position 8 during the preparation of this compound.)

assignments for the acidic and basic solutions are not subject to this uncertainty. For reasons of solubility, the spectra of 6-chloropurine were run in aqueous methanol (3:2).

Of particular interest is the contrasting behavior of purine and the 6-substituted purines in alkaline and acidic solutions. In the 6-substituted purines there is a crossover of peaks, the peak due to the C-8 proton appearing at high field in basic solutions, but at low field in acidic solutions. This behavior is illustrated for adenine in Fig. 2. For purine, the C-8 proton is at high field under all conditions of acidity. In the nucleosides, the deshielding effect of the ribose causes the C-8 proton to appear at low field even in neutral solution.[2a] Consequently, the crossover phenomenon is not observed.

Discussion

Several studies indicate that many purines are protonated in the pyrimidine ring most probably at N-1.[2a,5,6] Yet even for purines known to be protonated at N-1, shifts of the C-8 protons comparable with, or greater than, those of the protons at C-2 or C-6 suggest that in acid solution there is some delocalization of



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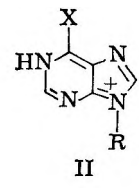


II

X = H, NH_2, Cl

(3) G. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.*, 1414 (1963).

(4) After this work was completed, the communication of S. Matsura and T. Goto, [*Tetrahedron Letters*, **No. 22**, 1499 (1963)] appeared. These workers have synthesized 2- and 6-deuteriopurine and independently reached the same conclusion.

(5) F. Bordwell and G. Cooper, *J. Am. Chem. Soc.*, **74**, 1058 (1952).

(6) (a) M. Tsuboi, Y. Kyogoky, and T. Shimanouchi, *Biochim. Biophys. Acta*, **55**, 1 (1962); (b) H. C. Borresen, *Acta Chem. Scand.*, **17**, 921 (1963); (c) W. Corchran, *Acta Cryst.*, **4**, 81 (1951).

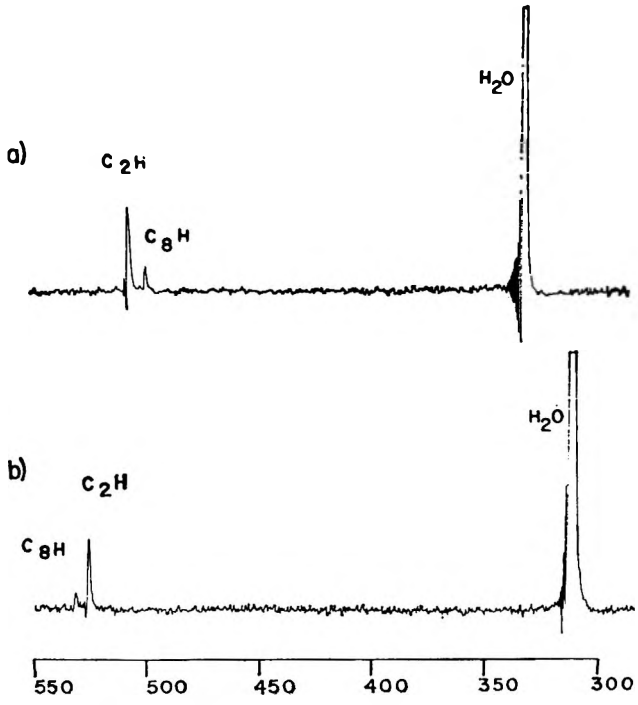
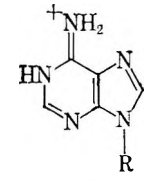


Fig. 2.—Adenine partially deuterated at position 8: (a) in 3 *M* NaOD, (b) in 0.6 *M* D_2SO_4.

charge into the imidazole ring. This may be accounted for by considering the cation as a linear combination of resonance structures I and II.

It is apparent from Table I that the C-2 protons of the 6-substituted purines undergo smaller shifts in passing from neutral to acidic solutions than is the case for purine itself. It is generally recognized that chemical shifts in aromatic molecules are a function of intra- and intermolecular ring current effects, magnetic anisotropy effects, and solvent effects. In several instances,[7-9] a relationship has been observed between the chemical shift and the charge density at the carbon to which the proton is bonded. In related isoelectronic aromatic species, such as a base and its cation or an acid and its anion, linear correlations have been made between changes in chemical shifts and charge densities.[10-12] It is our feeling that the chemical shift *differences* which we have observed between a purine base and its cation may be attributed in great part to changes in π-electron density at the carbon to which the observed proton is bound. These changes are caused by the inductive effect of a positively charged nitrogen in the ring and should be large at positions *ortho* to this nitrogen. The crossover of peaks observed in the 6-substituted purines might then be explained in either of two ways: (1) a larger contribution of structure II in the cation, or (2) contributions from structures such as III,[13] where the charge is further delocalized from C-2. This could lead to a smaller downfield shift of the C-2 proton as compared with that of the C-8 proton. The first possibility seems ruled out for adenine by the fact that the shift of the C-8 proton on cation formation is actually somewhat less than that of purine.[14]



III

Experimental

The n.m.r. spectra were recorded at 60 Mc./sec., using a Varian V-4310 instrument and calibrated by the standard side-band method.[15] The chemical shifts are accurate to ± 0.5 c.p.s. In preparing the deuterated purines by direct exchange, the base (100 mg.) was heated in 5 ml. of D_2O (or just sufficient D_2O to dissolve it at 100° if it were only partially soluble in this amount of D_2O) for 1 to 1.5 hr.; then the deuterated material was isolated by cooling the solution or evaporating the solvent *in vacuo*. 6-Chloropurine was exchanged in D_2O containing 40% methanol by refluxing for 2.5 hr. The material was about 30% deuterated by this procedure. Melting points were determined in unsealed capillary tubes using a Mel-Temp apparatus.

8-Deuteriopurine.—This material was prepared by a modification of the classical method of Traube[16] as has been described for purine.[17] 4,5-Diaminopyrimidine obtained from the Sigma Chemical Co. (0.5 g.) was dissolved in 7.0 ml. of D_2O and warmed for 10 min. The solvent was removed by lyophilization and the process was repeated. A sample of this material (200 mg.) was dissolved in 1.5 ml. of DCO_2D (Volk), and heated at 105° for 30 min. The bath temperature was raised to 205° during 50 min. and maintained at this temperature for 15 min. After cooling to 120°, the formic acid was evaporated in a stream of CO_2. Sublimation of the residue at 140° (1.5 mm.) yielded 98 mg. of material, m.p. 200–203°. Resublimation raised the melting point to 215–216°.[18] It did not depress the melting point of purine.

6-Deuteriopurine.—This method is a modification of a method previously used to prepare purine from 6-chloropurine.[17] The reduction was carried out with a Parr apparatus, Series 3910, in a 500-ml. pressure bottle. The storage tank was not used, the reaction vessel being charged directly through the valve assembly. 6-Chloropurine purchased from the Sigma Chemical Co. (1 g.) was suspended in 25 ml. of D_2O and shaken for 30 min. with 0.5 g. of 10% palladium-on-charcoal catalyst after the vessel had been charged to 7 p.s.i. with deuterium. After filtering the catalyst, the solution was neutralized by careful addition of sodium peroxide and the solvent was removed by lyophilization. Sublimation of the residue at 140° (1.5 mm.) yielded 490 mg. of material,[18] m.p. 215–216°. It did not depress the melting point of purine.

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(9) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).

(10) R. B. Moodie, T. M. Connor, and R. S. Stewart, *Can. J. Chem.*, **37**, 1402 (1959); T. Schaefer and W. G. Schneider, *ibid.*, **41**, 966 (1963).

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(12) V. R. Saudel and H. H. Freedman, *J. Am. Chem. Soc.*, **85**, 2328 (1963).

(13) Resonance contributions of this type are of course well known. E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt, New York, N. Y., 1959, p. 219.

(14) We have performed calculations of the changes in π-density at the C-2 and C-8 carbons when the purines are protonated, using the constant 10 p.p.m./electron. The results appear tenable, but as there is as yet no evidence whether the constant is also applicable to a five-membered heterocyclic ring, we shall not present them now.

(15) J. T. Arnold and M. G. Packard, *J. Chem. Phys.*, **19**, 1606 (1951). We use hexamethyldisiloxane as reference since it is less volatile than tetramethylsilane. It is 2 c.p.s. downfield from tetramethylsilane.

(16) W. Traube, *Ber.*, **33**, 1371 (1900).

(17) A. Bendich, P. J. Russell, and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(18) This material also was compared with a sample of purine by descending paper chromatography using the solvent systems: 80% satd. $(NH_4)_2SO_4$, 2% isopropyl alcohol, 18% 1 *M* sodium acetate, and butanol saturated with NH_4OH–H_2O (1:4 v./v.). It was found to be identical.

The Synthesis and Proton Magnetic Resonance Spectra of Some Brominated Furans[1]

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The reaction of 3-methylfuran with different molar ratios of N-bromosuccinimide has been studied. One equivalent of N-bromosuccinimide with or without the radical initiator, azobisisobutyronitrile (AIBN), gave 2-bromo-3-methylfuran. Two equivalents of N-bromosuccinimide with azobisisobutyronitrile gave 2,5-dibromo-3-methylfuran with traces of 2-bromo-3-bromomethylfuran. Three equivalents of N-bromosuccinimide with azobisisobutyronitrile gave 2,5-dibromo-3-bromomethylfuran and 2,4,5-tribromo-3-methylfuran. Methyl 3-methyl-2-furoate, N-bromosuccinimide, and azobisisobutyronitrile catalyst gave methyl 3-bromomethyl-2-furoate in good yield. Methyl 3-bromomethyl-2-furoate gave the expected products when allowed to react separately with trimethylamine and with sodium cyanide. 3-Methylfuran in O-deuteriomethanol and a catalytic amount of concentrated hydrobromic acid gave approximately 76% deuterium incorporation into the 2-position with negligible incorporation into the 5-position. Furan (stabilized with hydroquinone) is not readily brominated with N-bromosuccinimide; however, in the presence of a catalytic amount of *p*-toluenesulfonic acid, the bromination proceeds smoothly. The products reported were identified by their proton magnetic resonance spectra. The adjacent ring proton coupling of various 2,3-disubstituted furans was found to be 2.0 ± 0.2 c.p.s.

Ring α-brominated alkylfurans have not previously been recorded, but earlier reports have indicated the sensitivity[3] of these compounds. Buu-Hoï and Lecocq[4] studied the reaction of N-bromosuccinimide (NBS) with 2-methylfuran, and, although they were unable to isolate the pure brominated product, they were able to demonstrate that bromination took place in the methyl group. In contrast, we found that, with N-bromosuccinimide and 3-methylfuran, ring bromination took place exclusively. Reaction of 3-methylfuran with 1 equiv. of N-bromosuccinimide in benzene or carbon tetrachloride under nitrogen, in the presence or absence of the free-radical catalyst, 2,2′-azobisisobutyronitrile (AIBN), gave 2-bromo-3-methylfuran. This compound underwent polymerization with explosive violence within a few minutes at room temperature in contact with the air. The compound was purified by preparative scale gas chromatography on a QF-1 (fluorocarbon silicone) column. The pure compound could be satisfactorily stored for several weeks at liquid nitrogen temperature, or stored over calcium carbonate with a trace of hydroquinone under nitrogen at −20°.

The structure of the 2-bromo-3-methylfuran was confirmed by its n.m.r. spectrum, and by chemical conversion to 3-methyl-2-furoic acid through lithium exchange at −70° followed by carbonation.

The susceptibility of 3-methylfuran to electrophilic attack in the 2- and 5-positions was tested by observing deuterium exchange in O-deuteriomethanol with a trace of hydrobromic acid catalyst. Deuterium was incorporated into the 2-position to the extent of approximately 76% with negligible incorporation into the 4- and 5-positions. This, together with the fact that we were unable to detect 2-bromo-4-methylfuran in the monobromination of 3-methylfuran, suggests that the methyl group has a strong influence promoting electrophilic attack in the 2- rather than the 5-position.

Reaction of 3-methylfuran with 2 equiv. of N-bromosuccinimide in the presence of AIBN catalyst still gave principally ring bromination, with the isolation of 2,5-dibromo-3-methylfuran. By gas chromatography, the presence of a small per cent of a second compound was demonstrated and a small amount of it was isolated. From its n.m.r. spectrum, it was identified as the isomeric 2-bromo-3-bromomethylfuran.

Side-chain bromination of 3-methylfuran dominates only when the 2- and 5-positions in the ring are blocked. When 3-methylfuran is treated with 3 equiv. of N-bromosuccinimide in the presence of AIBN catalyst, the tribrominated product was a mixture of about five parts of 2,5-dibromo-3-bromomethylfuran and one part of 2,4,5-tribromo-3-methylfuran. Thus, the bromination of 3-methylfuran takes a much different course from that of 3-methylthiophene. With 3-methylthiophene and 1 equiv. of N-bromosuccinimide in the presence of a free-radical catalyst, the product is principally 3-thenyl bromide, accompanied by a small amount of the isomeric 2-bromo-3-methylthiophene. Earlier reports used benzoyl peroxide[5] as the catalyst, but recent work[6] indicates that AIBN is a superior catalyst in this reaction.

The presence of a deactivating group on the furan nucleus inhibits ring substitution in favor of side-chain substitution. Thus, methyl 3-methyl-2-furoate reacts with 1 equiv. of N-bromosuccinimide in the presence of AIBN catalyst to give an excellent yield of methyl 3-bromomethyl-2-furoate. This compound shows both lachrymatory and vesicant action.

Although 2-chloromethylfuran underwent rearrangement on reaction with sodium cyanide to give 5-methyl-2-cyanofuran,[7] the potential rearrangement site was blocked in methyl 3-bromomethyl-2-furoate, and this compound gave the expected normal product on reaction with sodium cyanide. The structure of the methyl 3-cyanomethyl-2-furoate was proved by its n.m.r. spectrum. Methyl 3-bromomethyl-2-furoate also reacted with trimethylamine to give the expected quaternary salt. The benzyl-type nitrogen bond in this compound was cleaved with hydrogen and pal-

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(2) Fellow of the American Foundation for Pharmaceutical Education and Josiah Kirby Lilly Memorial Fellow for 1962–1964.

(3) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 90.

(4) N. P. Buu-Hoï and J. Lecocq, *Compt. rend.*, **222**, 1441 (1946).

(5) E. Campaigne and B. F. Tullar, *Org. Syn.*, **33**, 96 (1953).

(6) J. B. Sullivan, Ph.D. thesis, University of Washington, 1963.

(7) T. Reichstein, *Ber.*, **63**, 749 (1930).

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF SUBSTITUTED FURANS[a]

	Compound	Hydrogens 2	3	4	5	$-CH_3$	$-CH_2-$	$-OCH_3$	Coupling constant, $J_{4,5}$
1	Furan[b]	7.38	6.30	6.30	7.38				
2	2-Bromofuran		6.28	6.33	7.37				
3	2,5-Dibromofuran		6.25	6.25					
4	3-Methylfuran	7.11		6.13	7.23	2.02			
5	2-Bromo-3-methylfuran			6.24	7.32	2.00			2.0
6	2,5-Dibromo-3-methylfuran			6.20		1.96			
7	2-Bromo-3-bromomethylfuran			6.36	7.31		4.14		2.1
8	2,5-Dibromo-3-bromomethylfuran[c]			6.32			4.09		
9	2,4,5-Tribromo-3-methylfuran[c]					2.08			
10	Methyl 3-methyl-2-furoate			6.28	7.37	2.28		3.78	1.9
11	Methyl 3-methyl-2-furoate ($DCCl_3$)			6.33	7.40	2.35		3.88	
12	Methyl 3-bromomethyl-2-furoate			6.55	7.46		4.65	3.85	2.1
13	Methyl 3-bromomethyl-2-furoate ($DCCl_3$)			6.61	7.51		4.69	3.90	
14	Methyl 3-cyanomethyl-2-furoate ($DCCl_3$)			6.72	7.66		4.01	3.92	2.1

[a] Chemical shifts are expressed as δ (p.p.m.) values; tetramethylsilane was used as an internal reference. The n.m.r. spectra were measured at 60 Mc. in carbon tetrachloride, with the exception of **11**, **13**, and **14** which were run in $DCCl_3$. Coupling constants are given in c.p.s. $\pm$ 0.2. [b] Value taken from G. V. D. Tiers, "N.M.R. Summary," Central Research Department, Minnesota Mining and Manufacturing Company, St. Paul 19, Minn. [c] Determined on a mixture of these two compounds. [d] The n.m.r. spectra were determined by B. J. Nist, Department of Chemistry, University of Washington.

ladium to give the known methyl 3-methyl-2-furoate. Furan (stabilized with hydroquinone) is not readily brominated by N-bromosuccinimide, but the reaction proceeds efficiently in the presence of catalytic amounts of *p*-toluenesulfonic acid. Thus, it appears likely that, in this reaction, bromination proceeds by an ionic mechanism, with protonated N-bromosuccinimide as the active brominating moiety.

Discussion of N.m.r. Results

The assignments of chemical shifts of the compounds are summarized in Table I. Compounds **2** and **3** were prepared for comparison of their chemical shifts under identical conditions of solvent, concentration, and internal standard. It can be seen that, when one hydrogen of furan is substituted by bromine, the remaining ring protons do not experience much of a change in chemical shift. In 3-methylfuran, however, when a ring hydrogen is replaced by bromine, there is a larger change in the chemical shifts of the remaining protons. This, in conjunction with the small difference in chemical shift between the protons in the 2- and 5-positions of 3-methylfuran, gives ambiguous results for the structure of **5**, if this is to be assigned on the basis of chemical shift alone.

We have found the adjacent-ring proton coupling constants of various 2,3-disubstituted furans to be in the range of 2.0 $\pm$ 0.2 c.p.s. Gronowitz[8] has found the $J_{4,5}$ coupling constants of various 2-substituted furans to be in the range 1.75 to 2.15 c.p.s. and various 3-substituted furans to be in the range 1.75 to 1.90 c.p.s. The cross-ring coupling constants of these 2-substituted furans varies from 0.70 to 1.15 c.p.s. and from 0.70 to 1.00 c.p.s. for the 3-substituted furans. From these data, and from the coupling constant of 2.0 c.p.s. of compound **5**, it is possible to assign the structure 2-bromo-3-methylfuran. This assignment was confirmed by chemical proof of structure.

The assignment of structure to **6** is immediately evident by comparing the chemical shifts and relative areas of the signals with those already discussed. The structure of **7** was assigned on the basis of the chemical shift and coupling constant of the ring protons and the signal at δ 4.14 (equal in area to two protons) which can only be attributed to the methylene protons. In the spectrum of the mixture of **8** and **9**, the signals at δ 6.32 and 4.09, equal in area to one and two protons, respectively, are attributed to the ring proton and methylene protons of **8**. The remaining singlet at δ 2.08 was not equal in area to any possible whole number and had to be attributed to a second compound. Since the elemental analysis was correct for the mixture, the second compound had to have an empirical formula the same as **8**, and, since the chemical shift of 2.08 is similar to the methyl protons of other ring-brominated 3-methylfurans, the only possible structure is 2,4,5-tribromo-3-methylfuran. The ratio of **8** to **9** is approximately 5 to 1. The structure of **12** was easily established by comparing the chemical shifts and relative areas of the signals with those of its parent compound, methyl 3-methyl-2-furoate, and **7**.

Experimental

2-Bromo-3-methylfuran.—A mixture of 16.4 g. (0.2 mole) of 3-methylfuran,[9] 140 ml. of anhydrous benzene, 31.8 g. (0.2 mole) of N-bromosuccinimide, and 0.25 g. of 2,2′-azobisisobutyronitrile was heated under nitrogen, with stirring, to reflux. At this point, an exothermic reaction began, and heating was discontinued. When the rate of reflux began to slow, an additional 0.25 g. of the free-radical catalyst was added and heat was applied to maintain refluxing for 1.5 hr. The reaction mixture was cooled in an ice bath, and the succinimide was removed by filtration. The clear filtrate was washed with cold 1% sodium bicarbonate solution. The product in the benzene layer was protected by the addition of 0.1 g. of hydroquinone and 0.5 g. of calcium carbonate as stabilizers, and this benzene solution then was dried over anhydrous sodium sulfate overnight in the refrigerator. The dried solution was filtered, fresh hydroquinone and calcium carbonate were added, and the benzene was removed by distillation at reduced pressure. The product distilled from 28 to 30° at 12 mm. and was collected in a receiver placed in a Dry Ice bath. The yield was 10.6 g. (33%). This product, protected with hydroquinone and calcium carbonate, could be stored under nitrogen in the freezing compartment of the re-

(8) S. Gronowitz, G. Sörlin, B. Gestblom, and R. A. Hoffman, *Arkiv Kemi*, **19**, 483 (1962).

(9) D. M. Burness, *Org. Syn.*, **39**, 46 (1959).

frigerator for several weeks without decomposition. On exposure to air at room temperature, it polymerized explosively within about 5 to 10 min. Samples for n.m.r. studies and elemental analyses were prepared by preparative scale gas chromatography in a Beckman GC-2 instrument through a 10-ft. column of Dow fluorosilicone QF-1 on Chromosorb W at 40°.

Anal. Calcd. for C_5H_5BrO: C, 37.30; H, 3.13. Found: C, 36.99; H, 2.99.

A low-order explosion occurred during the combustion for analysis but the equipment remained intact, and the analysis was satisfactorily completed.[10]

3-Methyl-2-furoic Acid.—A solution of butyllithium in hexane (3.7 ml. of a 15% solution, 0.0087 mole) was added to 10 ml. of ether under nitrogen at −70°. To this was added, with stirring, a solution of 1.13 g. (0.007 mole) of 2-bromo-3-methylfuran (purified by gas chromatography) in 10 ml. of anhydrous ether. The reaction mixture was stirred at −70° for 30 min. and then poured into a flask containing excess powdered Dry Ice and anhydrous ether. The flask was stoppered with a drying tube and periodically swirled as it was allowed to warm to room temperature. The reaction mixture was shaken with 10 ml. of water and the ether layer was subsequently extracted with sodium carbonate solution. The combined water extracts were acidified with hydrochloric acid and this solution then was extracted with ether. After drying this ether extract over sodium sulfate and evaporation of the solvent, there remained 0.47 g. (53%) of product, m.p. 134–135°. There was no change in melting point after recrystallization from benzene, and there was no depression in a mixture melting point with authentic 3-methyl-2-furoic acid.[9] The infrared spectra, as KBr pellets, of this product and of authentic 3-methyl-2-furoic acid were identical.

2-Deuterio-3-methylfuran.—Deuteriomethanol was prepared from sodium methoxide and deuterium oxide and shown by n.m.r. assay to be approximately 93% deuterated as OD. A mixture of 2.0 ml. (0.048 mole) of this deuteriomethanol, 0.4 g. (0.0048 mole) of 3-methylfuran, and 0.0028 ml. of concentrated (48%) hydrobromic acid was heated under reflux for 45 min. An n.m.r. tube was prepared directly from this reaction mixture, and integration of this spectrum showed that the 3-methylfuran had undergone deuterium exchange to the extent of about 76% in the 2-position, and a negligible amount in the 4- and 5-positions.

2,5-Dibromo-3-methylfuran.—A mixture of 13.2 g. (0.18 mole) of 3-methylfuran, 110 ml. of anhydrous benzene, 50.9 g. (0.36 mole) of N-bromosuccinimide, and 0.20 g. of 2,2′-azobisisobutyronitrile, under nitrogen, was heated to reflux. A vigorous reaction ensued and cooling was necessary to control it. After the vigorous reaction had subsided, 0.25 g. of the free-radical catalyst was added and heat was applied to maintain refluxing for 1 hr. The reaction mixture was cooled in an ice bath, the succinimide was removed by filtration, and the clear filtrate was washed with cold 1% sodium bicarbonate. The organic layer was protected, with 0.1 g. of hydroquinone and 0.5 g. of calcium carbonate added as stabilizing agents, and dried over anhydrous sodium sulfate. The benzene was removed under reduced pressure and the fraction which boiled from 38 to 40° at 1 mm. was collected. Redistillation of this gave 17.9 g. (38%) of product collected at 33° (0.5 mm.). Samples for n.m.r. studies and elemental analyses were further purified by preparative scale gas chromatography at 100° on a 5-ft. QF-1 column.

Anal. Calcd. for $C_5H_4Br_2O$: C, 25.03; H, 1.68; Br, 66.62. Found: C, 25.19, 25.13; H, 1.69, 1.70; Br, 66.62, 66.89.

2-Bromo-3-bromomethylfuran.—In the gas chromatographic purification in the above preparation of 2,5-dibromo-3-methylfuran, the major product peak was followed by a small peak of a secondary product. Enough of this minor secondary product was collected from several runs through the gas chromatograph to identify it from its n.m.r. spectrum as 2-bromo-3-bromomethylfuran. This compound was highly lachrymatory and very irritating to the mucous membranes.

Tribromo-3-methylfuran.—From a mixture of 16.0 g. (0.2 mole) of 3-methylfuran, 280 ml. of anhydrous benzene, 95.4 g. (0.6 mole) of N-bromosuccinimide, and 0.25 g. of 2,2′-azobisisobutyronitrile, worked up as before, there was collected 21.5 g. (34%) of tribrominated product at 72 to 74° (0.5 mm.).

Anal. Calcd. for $C_5H_3Br_3O$: C, 18.84; H, 0.95; Br, 75.20. Found: C, 18.96; H, 1.04; Br, 75.39.

This tribrominated product was shown by its n.m.r. spectrum to be a mixture of approximately one part of 2,4,5-tribromo-3-methylfuran and five parts of 2,5-dibromo-3-bromomethylfuran.

Methyl 3-Bromomethyl-2-furoate.—A solution of 70 g. (0.5 mole) of methyl 3-methyl-2-furoate[11] in 150 ml. of carbon tetrachloride, under nitrogen, was heated to reflux, and to this was added slowly, a mixture of 89 g. (0.5 mole) of N-bromosuccinimide and 1.0 g. of 2,2′-azobisisobutyronitrile. After the addition was complete, the mixture was refluxed for an additional 15 min., then cooled in an ice bath. The succinimide was removed by filtration; the filtrate was washed with cold saturated sodium bicarbonate solution and then dried over anhydrous sodium sulfate. The benzene was removed under reduced pressure, and 76.3 g. (70%) of product was collected from 88 to 90° (0.30 mm.), m.p. 52–55°. The vapors of this compound are extremely irritating to the eyes and mucous membranes, and the solid material or solutions of it exhibit vesicant action in contact with the skin. Recrystallization from anhydrous methanol raised the melting point to 55–56°.

Anal. Calcd. for $C_7H_7BrO_3$: C, 38.38; H, 3.22; Br, 36.48. Found: C, 38.40; H, 3.45; Br, 36.63.

Methyl 3-Cyanomethyl-2-furoate.—A solution of 11 g. (0.05 mole) of methyl 3-bromomethyl-2-furoate in 50 ml. of anhydrous methanol was added with stirring to a solution of 4.9 g. (0.1 mole) of sodium cyanide in 50 ml. of anhydrous methanol. The mixture was heated to 40° for 1 hr. and then refluxed for 0.5 hr. After evaporation of the methanol, the residue was shaken with 50 ml. of water and 100 ml. of ether. The water layer was further extracted with ether, and the ether extracts were combined and dried. After evaporation of the ether, the product was recrystallized from carbon tetrachloride to give a 6.2-g. (75%) yield of white crystals, m.p. 62–63°. Further recrystallization from methanol raised the melting point to 63–63.5°.

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48; O, 29.06. Found: C, 57.87; H, 4.74; N, 8.63; O, 29.00.

2-Carbomethoxy-3-furylmethyl trimethylammonium Bromide.—To a stirred solution of 10.9 g. (0.05 mole) of methyl 3-bromomethyl-2-furoate in 30 ml. of chloroform, cooled to 0°, was added 5.9 g. (0.11 mole) of trimethylamine which had been previously cooled to −70°. A Dry Ice condenser was used on the reaction flask to prevent premature loss of the trimethylamine. The solution was allowed to warm to room temperature, at which point the reaction proceeded rapidly with evolution of heat. The mixture was stirred for an additional hour and then the Dry Ice condenser was replaced with a water condenser and the mixture was heated to reflux to drive off the excess trimethylamine. The reaction mixture was cooled in an ice bath and the crystalline product was collected by filtration to obtain a yield of 13.5 g. (98%), m.p. 205–209°. Four recrystallizations from absolute ethanol failed to raise the melting point.

Anal. Calcd. for $C_{10}H_{16}BrNO_3$: C, 43.18; H, 5.80; Br, 28.73; N, 5.04; O, 17.26. Found: C, 43.07; H, 5.66; Br, 28.61; N, 4.89; O, 17.39.

Methyl 3-Methyl-2-furoate.—2-Carbomethoxy-3-furylmethyl trimethylammonium bromide (10 g., 0.039 mole) was dissolved in 100 ml. of anhydrous ethanol, and 0.2 g. of palladium oxide catalyst was added. The mixture was placed in a hydrogenation bottle under 31-lb. gauge pressure of hydrogen, and shaken for 5 days. At this point, 0.043 mole of hydrogen gas had been absorbed. The alcohol was evaporated and the residue was extracted with ether. The ether extract was evaporated to dryness, and the remaining material was vacuum distilled to give 1.7 g. of a compound melting at 35.5–37°. A mixture melting point with an authentic sample of methyl 3-methyl-2-furoate[11] showed no depression.

2-Bromofuran.—N-Bromosuccinimide (35.6 g., 0.2 mole) and anhydrous *p*-toluenesulfonic acid (0.1 g. dissolved in 17 ml. of benzene) were added to a solution of 40.8 g. (0.6 mole) of furan (Eastman, stabilized with hydroquinone) in 50 ml. of anhydrous benzene. The mixture was maintained at a gentle reflux for 35 min., cooled in an ice bath, and the succinimide was removed by filtration. The solution was extracted with satu-

(10) We wish to acknowledge the kindness of Dr. L. D. Hayward of the University of British Columbia, under whose direction this analysis was performed.

(11) D. M. Burness, *Org. Syn.*, **39**, 49 (1959).

rated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and distilled through a 40-cm. packed column to give 11.7 g. (39%) of 2-bromofuran, collected at 52–54° (180 mm.).

From the higher boiling material there was recovered 1.5 g. of 2,5-dibromofuran, collected at 60–61° (15 mm.). The amount of dibromofuran was substantially increased if only a small excess of furan over N-bromosuccinimide were used.

In a similar run without the *p*-toluenesulfonic acid catalyst, no reaction appeared to occur, and, after refluxing for 45 min., 91% of the N-bromosuccinimide was recovered unchanged.

Preparation and Some Reactions of 2-(1,3-Butadienyl)magnesium Chloride

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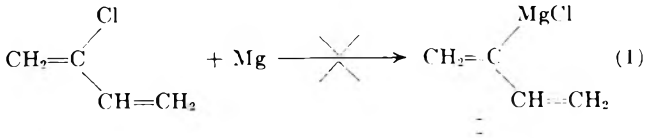
The preparation of 2-(1,3-butadienyl)magnesium chloride (I) from 4-chloro-1,2-butadiene is described. The structure of the Grignard reagent was indicated by its infrared and n.m.r. spectra and by its chemical reactions. Coupling reactions of 2-(1,3-butadienyl)magnesium chloride produce 2-(1,3-butadienyl) metallic derivatives in fair-to-good yields.

Vinyl Grignard reagents[1,2] have been useful for the preparation of a variety of unusual vinyl metallic compounds.[3]

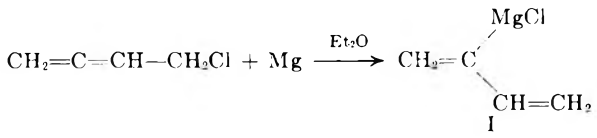
An interest in 2-(1,3-butadienyl) metallic compounds prompted us to attempt the preparation of the Grignard reagent I from chloroprene, 2-chloro-1,3-butadiene. All attempts to carry out the reaction of eq. 1 in diethyl



(1)

ether, tetrahydrofuran, or xylene[4] were unsuccessful. In no case was a positive Gilman test I[5] observed. Polymers of chloroprene were the only products isolated from these experiments.

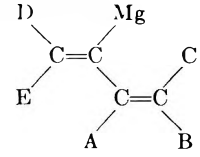
2-(1,3-Butadienyl)magnesium chloride (I) was successfully prepared by reaction of 4-chloro-1,2-butadiene[6] with magnesium in diethyl ether.[7] Under the proper conditions yields of the Grignard reagent are about 95% as shown by Gilman titration.[8] The structure was indicated by the infrared and n.m.r.[9] spectra of the product in diethyl ether.



The infrared spectrum of a *ca.* 1.0 *M* solution of the Grignard reagent *vs.* diethyl ether in the reference beam had strong bands at 1600 (C=C stretching vibration of the conjugated diene), 1000 (vinyl C–H out-of-plane deformation vibration), and 895 cm.$^{-1}$ (methylene out-of-plane deformation vibration). The spectrum was devoid of bands in the region between 1900 and 2000 cm.$^{-1}$, indicative of the absence of the allene group which absorbs strongly near 1950 cm.$^{-1}$.[10] However, since diethyl ether has a weak band at 1960 cm.$^{-1}$, it was necessary to eliminate the possibility of masking by the solvent. For this purpose the infrared absorbances of increasingly dilute solutions of 4-chloro-1,2-butadiene in ether were measured. The allene band at 1959 cm.$^{-1}$ was detectable at concentrations as low as 0.3% 4-chloro-1,2-butadiene. It is concluded that the amount of allenic products in the Grignard solution is very small.

To obtain a reasonably well-resolved n.m.r. spectrum the Grignard reagent was purified by two recrystallizations from ether at −75°. The spectrum of a 1.0 *M* solution of the purified reagent in ether was run on a Varian A-60 n.m.r. spectrometer. The chemical shifts (p.p.m.) downfield from tetramethylsilane and coupling constants (c.p.s.) are summarized in Table I and are fully consistent with the assigned structure. The pattern differs from that of a 10% solution of 4-chloro-1,2-butadiene in ether which possesses three sets of complex multiplets: a ten-line group at 4.07 p.p.m. for the $-CH_2-$ with chlorine attached, a twelve-line group at 4.88

TABLE I
N.M.R. DATA FOR
2-(1,3-BUTADIENYL)MAGNESIUM CHLORIDE[a]



Proton	Chemical shift,[b] p.p.m.	Multiplet	Coupling constant, c.p.s. J_{AB}	J_{AC}	J_{BC}	J_{DE}
A	6.57	Quadruplet	9.2	17.3	...	...
B	4.76	Quadruplet	9.2	...	3.4	...
C	5.05	Quadruplet	...	17.3	3.4	...
D	5.29	Doublet	...	...	...	5.8
E	5.88	Doublet	...	...	...	5.8

[a] *Ca.* 1.0 *M* solution in diethyl ether. [b] Downfield from tetramethylsilane (internal).

(1) H. Normant, *Compt. rend.*, **239**, 1510, 1811 (1954); *Bull. soc. chim. France*, 728 (1957).

(2) H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balint, and R. Cserr, *J. Org. Chem.*, **22**, 1602 (1957).

(3) H. D. Kaesz and F. G. A. Stone, "Organometallic Compound," H. Zeiss, Ed., Reinhold Publishing Corporation, New York, N. Y., 1960, pp. 88–149.

(4) E. T. Blues and D. Bryce-Smith, *Chem. Ind.* (London), 1533 (1960).

(5) H. Gilman and F. Schulz, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(6) This was prepared by 1,4-addition of HCl to monovinyl acetylene: see W. H. Carothers and C. J. Berchet, *ibid.*, **55**, 2807 (1933).

(7) A similar reaction involving the formation of 3-methyl-2-(1,3-butadienyl)magnesium bromide from 4-bromo-3-methyl-1,2-butadiene has been reported recently: see Y. Pasternak, *Compt. rend.*, **255**, 1750 (1962).

(8) H. Gilman, E. A. Zoellner, and J. B. Dickey, *J. Am. Chem. Soc.*, **51**, 1576 (1929).

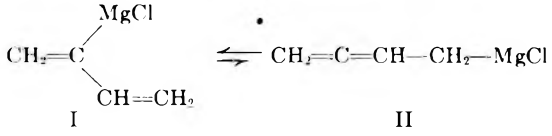
(9) By "structure" is meant that of the carbon skeleton and its position of attachment to the metal.

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p. 61.

p.p.m. for the terminal methylene, and a triplet of triplets at 5.35 p.p.m. for the internal =CH– proton.[11]

The positions of protons D and E are assigned in accordance with the assignments made for the methylene protons of vinylmagnesium chloride[12] and vinylmagnesium bromide.[13] The coupling constant J_{DE} (5.8 c.p.s.) agrees well with the coupling constants (7.5 c.p.s.[12] and 7.4 c.p.s.[13]) reported for the respective methylene protons of the vinylmagnesium halides.

Recent n.m.r. studies[14,15] have indicated the existence of a rapid equilibrium between the allylic isomers of allylmagnesium compounds. An analogous equilibrium involving 2-(1,3-butadienyl)magnesium chloride and its allenic isomer (II) is considered unlikely. The



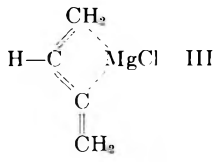
I II

absence of an allene peak in the infrared shows that if II is present its concentration is vanishingly small. The sharpness of the n.m.r. lines at 25° indicates that, if an equilibrium exists, the interconversion rate is slower than 2 or 3 c.p.s. Except for slight changes in the chemical shifts, the n.m.r. spectrum observed at −35° is identical with that observed at room temperature.

Confirmatory chemical evidence against II is found in the hydrolysis of the Grignard reagent, which was performed by adding the ether solution to an excess of 10% aqueous ammonium chloride at 40°. Ether and gaseous products distilled instantly and were condensed at −80°. The condensate, analyzed by gas chromatography, contained 1,3-butadiene in 95% yield based on added I. No 1,2-butadiene was observed, although as little as 0.1% could have been detected. In contrast allylic Grignard reagents, known to exist as equilibrium mixtures, yield isomeric mixtures of olefins when they react with proton donors.[16]

Theoretical arguments can be advanced in support of the view that I is more stable thermodynamically than its allenic isomer II. It is well known that, in general, allenes are unstable with respect to their conjugated isomers, presumably because the latter are stabilized by resonance. Resonance stabilization is probably the main reason for the fact that the Grignard reagent has structure I. Another contributory factor may be the relative bond energy of the C–Mg bond which is probably greater in I (vinylic C–Mg bond) than in II (saturated C–Mg bond).

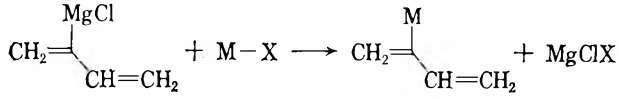
The position (1600 cm.$^{-1}$) of the C=C stretching bond is evidence against a bridged methylene–π-allylic



III

structure such as III. Simple π-allylic complexes with transition metals are reported[17,18] to absorb near 1450 cm.$^{-1}$. It should be mentioned that I has a medium absorption near 1460 cm.$^{-1}$ which has not yet been assigned. However, the presence of the higher frequency band, the fact that π-allylic structures have been considered[14] and discarded[15] in the case of allylmagnesium compounds, and the n.m.r. line positions discussed above lead us to conclude that structure I is more likely than structure III.

Coupling reactions of I proceed normally without rearrangement to yield 2-(1,3-butadienyl) derivatives IV. This is the most convenient route to a variety of



IVa, M = $(C_4H_9)_3Sn$
b, M = $(C_6H_5)_2P$
c, M = ClHg

butadiene monomers substituted in the 2-position with hetero atoms. Examples of this type of monomer which have been prepared are tri-*n*-butyl-2-(1,3-butadienyl)tin (IVa), diphenyl-2-(1,3-butadienyl)phosphine (IVb), and 2-(1,3-butadienyl)mercury(II) chloride (IVc). Compounds IVa and IVb can be polymerized and copolymerized by free-radical initiators.

Preliminary investigations of the condensations of I with carbonyl compounds gave mixtures of isomeric carbinols in moderate yields. The principal products obtained are 2-(1,3-butadienyl)carbinols and 4-(1,2-butadienyl)carbinols. These reactions are under study and will be the subject of a future communication.

Experimental

2-(1,3-Butadienyl)magnesium Chloride (I).—A 100-ml. round-bottomed flask was fitted with a mechanical stirrer, 50-ml. dropping funnel, and reflux condenser. This system was maintained under a nitrogen blanket. The flask was charged with 1.2 g. (0.49 g.-atom) of magnesium turnings and 20 ml. of anhydrous ether, the dropping funnel with a solution of 4.0 g. (0.045 mole) of 4-chloro-1,2-butadiene in 10 ml. of anhydrous ether. Two milliliters of the chloride solution was added, and the mixture was heated to gentle reflux. In a small test tube were placed three magnesium turnings, 10 mg. of mercuric chloride, 1 ml. of ether, 2 drops of 4-chloro-1,2-butadiene, and 2 drops of methyl iodide. An exothermic reaction was induced by crushing the turnings and warming briefly. After the reaction became vigorous, the contents of the test tube were added to the flask. Dropwise addition of the chloride solution was begun, and within a few minutes the reaction became self-sustaining. External heating was removed, and the remainder of the chloride solution was added dropwise at such a rate as to maintain gentle reflux. Addition was completed in 0.5 hr. The clear brown mixture was refluxed for 45 min., then cooled.

Gilman titration[8] showed the presence of 1.44 mequiv. of organomagnesium compound per milliliter of solution. This corresponds to a total of 0.043 equiv. or a yield of 95% based on 4-chloro-1,2-butadiene.

Tri-*n*-butyl-2-(1,3-butadienyl)tin (IVa).—2-(1,3-Butadienyl)-magnesium chloride I was prepared as described above from 82 g. (0.0927 mole) of 4-chloro-1,2-butadiene. Excess magnesium was removed by filtering through glass wool. The ether solution was added dropwise under nitrogen to a vigorously stirred solution of 250 g. (0.419 mole) of bis-(tri-*n*-butyltin) oxide (Metal and Thermit Corp.) in 700 ml. of dry heptane and 250 ml. of dry tetrahydrofuran in a 2-l. round-bottomed flask equipped with a mechanical stirrer, thermometer, and Claisen head.

(11) R. C. Ferguson, *J. Phys. Chem.*, **68**, 1594 (1964).
(12) R. T. Hobgood, Jr., and J. H. Goldstein, *Spectrochim. Acta*, **18**, 1280 (1962).
(13) G. H. Frankel, D. G. Adams, and J. Williams, *Tetrahedron Letters*, **No. 12**, 767 (1963).
(14) J. E. Norlander and J. D. Roberts, *J. Am. Chem. Soc.*, **81**, 1769 (1959).
(15) G. M. Whitesides, J. E. Norlander, and J. D. Roberts, *ibid.*, **84**, 2010 (1962).
(16) R. H. De Wolfe and W. A. Young, *Chem. Rev.*, **56**, 874 (1956).
(17) H. P. Fritz, *Chem. Ber.*, **94**, 1217 (1961).
(18) E. O. Fischer and H. Werner, *Z. Chem.*, **2**, 177 (1962).

During the addition, which required 0.5 hr., the temperature was maintained at 65–75°. The ether was distilled through the Claisen head and collected in a receiver. After the addition was completed, the temperature was allowed to rise to 75°; the Claisen head was replaced with a reflux condenser. The mixture was vigorously agitated at 75–80° for 2.5 hr. and then cooled to 5°. A considerable quantity of magnesium salts had separated. These were dissolved by slowly adding 450 ml. of 8% hydrochloric acid. The layers were separated; the organic layer was washed with 200 ml. of 10% sodium chloride. The NaCl wash was extracted once with 100 ml. of heptane, which was combined with the original organic layer. The solution was filtered through calcium chloride and concentrated *in vacuo* on the stream bath. The cloudy yellow residual oil (293 g.) was fractionally distilled through a 20-in. heated Vigreux column. The product, tri-*n*-butyl-2-(1,3-butadienyltin, b.p. 80–90° (0.4 mm.), weighed 220 g. (76.4% yield).

Anal. Calcd. for $C_{16}H_{32}Sn$: C, 56.01; H, 9.44; Sn, 34.60; mol. wt., 343.1. Found: C, 55.7, 55.6; H, 9 4, 9.4; Sn, 34.8, 34.9; mol. wt., 340, 335 (cryoscopic in benzene).

The infrared spectrum had C=C absorption bands at 1620 and 1575 cm.$^{-1}$, a vinyl CH band at 985 cm.$^{-1}$, and methylene C–H bands at 894 and 910 cm.$^{-1}$. No peaks were present in the allene region 1900 to 2050 cm.$^{-1}$.

The n.m.r. spectrum was consistent showing the presence of saturated C–H and unsaturated CH protons in a ratio of 5.42 (theory requires 5.40). The ultraviolet spectrum (cyclohexane) had an ϵ_{max} of 11,600 at 220 mμ.

Diphenyl-2-(1,3-butadienyl)phosphine (IVb).—A 2-l. round-bottomed flask was equipped with a mechanical agitator, dropping funnel, and reflux condenser under a nitrogen blanket. It was charged with a solution of *ca.* 0.90 mole of 2-(1,3-butadienyl)magnesium chloride in 550 ml. of ether. To the well-agitated solution at room temperature was added a solution of 160 g. (0.724 mole) of diphenylchlorophosphine in 200 ml. of anhydrous ether. The addition required 3 hr. after which the mixture was stirred overnight at room temperature. The flask was cooled to 0°, and 700 ml. of 10% aqueous ammonium chloride was added carefully.

After stirring for 0.5 hr., the two layers were separated, and the aqueous layer was washed with 150 ml. of ether. The ether layers were combined, filtered, and concentrated *in vacuo* on the steam bath. The red-orange residue was taken up in 700 ml. of hot ethanol, filtered to remove about 5 ml. of orange oil, and cooled to 0°. The crude product which separated was collected, decolorized with Darco, and recrystallized from 500 ml. of ethanol. A pale yellow crystalline solid (74.5 g., 43.3%) which melted at 35–36.5° (uncor.) was obtained.

Anal. Calcd. for $C_{16}H_{15}P$: C, 80.65; H, 6.35; P, 13.00. Found: C, 80.3, 80.2; H, 6.0, 5.9; P, 12.77, 12.91.

The infrared spectrum had double bond absorptions at 1620 and 1575 cm.$^{-1}$, a vinyl C–H peak at 985 cm.$^{-1}$, and a methylene C–H band at 910 cm.$^{-1}$. There was no evidence for any allene absorption in the 1900- to 2050-cm.$^{-1}$ region. A very weak band at 1962 cm.$^{-1}$ was attributed to the aromatic rings.

2-(1,3-Butadienyl)mercury(II) Chloride (IVc).—2-(1,3-Butadienyl)magnesium chloride was prepared as described above from 17.4 g. (0.192 mole) of 4-chloro-1,2-butadiene. The Grignard solution was added to a vigorously agitated slurry of 90 g. (0.33 mole) of powdered mercuric chloride in 100 ml. of anhydrous ether. After the exothermic reaction had abated, the mixture was stirred and refluxed for 10 min. The ether was removed in a nitrogen stream. The residual solid was refluxed with 400 ml. of ethanol for 10 min. and filtered hot. The filtrate was diluted with 300 ml. of boiling water, then allowed to cool slowly to 0°. The solid which separated was collected by suction filtration, recrystallized from 600 ml. of 50% aqueous ethanol, and dried in a vacuum desiccator. The product, 2-(1,3-butadienyl)-mercury(II) chloride, a white solid with a soft greenish cast, weighed 17.2 g. (31% yield). It had no melting point but began decomposing at 113°.

Anal. Calcd. for C_4H_5HgCl: C, 16.61; H, 1.74; Hg, 69.46; Cl, 12.26. Found: C, 16.5, 16.5; H, 2.2, 2.0; Hg, 64.7, 64.7; Cl, 11.9, 11.6.

The infrared spectrum was consistent with the assigned structure.

Acknowledgment.—The author wishes to express his gratitude to Dr. R. C. Ferguson for his assistance in interpreting the n.m.r. spectra and to Mr. J. A. Fisher for technical assistance. Helpful discussions with Drs. R. Pariser and A. L. Barney are acknowledged.

Nitrogen Heterocycles. I. Pyrrolidones

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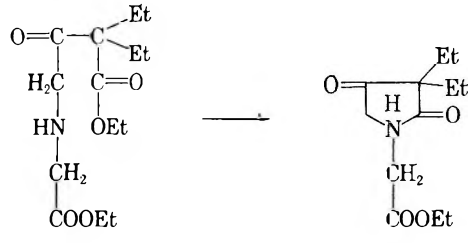
The condensation of ethyl γ-bromodialkylacetoacetate and ethyl glycinate results in pyrrolidine ring formation. The preparation of some derivatives of 3,3-dimethyl-2,4-pyrrolidinedione and of 3,3-diethyl-2,4-pyrrolidinedione is described.

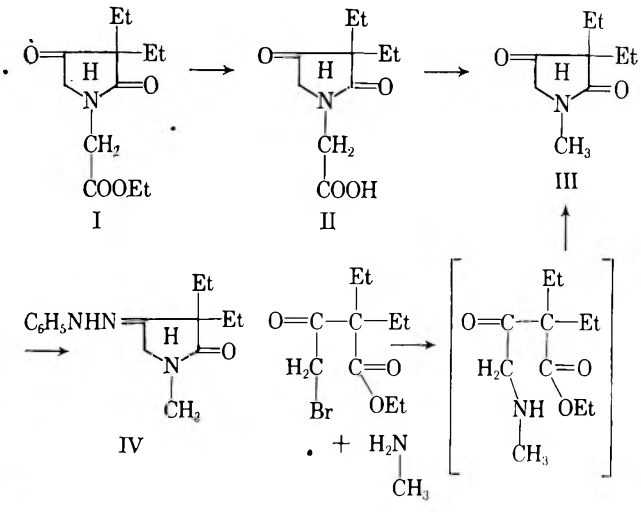
During the course of a study designed to uncover compounds with central depressant activity, ethyl γ-bromo-α,α-diethylacetoacetate[1] was condensed with ethyl glycinate to give 1-(carbethoxymethyl)-3,3-diethyl-2,4-pyrrolidinedione (I).



On saponification followed by decarboxylation 1-(carboxymethyl)-3,3-diethyl-2,4-pyrrolidinedione (II) and 1-methyl-3,3-diethyl-2,4-pyrrolidinedione (III) were obtained. The latter, on treatment with phenylhydrazine, gave the monohydrazine, 1-methyl-3,3-diethyl-4-phenylhydrazono-2-pyrrolidone (IV). The synthesis of 1-methyl-3,3-diethyl-2,4-pyrrolidinedione (III) was also effected by condensing ethyl γ-bromo-α,α-diethylacetoacetate and methylamine. The pyrrolidone structure of these compounds was confirmed by an infrared analysis of the acid (II) which showed a strained carbonyl band at 1765 cm.$^{-1}$ characteristic of carbonyl groups in five-membered rings. That the band was not associated with the carboxyl function was shown by its persistence on conversion of the acid to the triethylamine salt.

The 1-methylpyrrolidinedione (III) on treatment with hydroxylamine gave the monoxime (V) which was catalytically reduced to the amine. The latter was not identified as such but was condensed with benzenesul-

(1) M. Conrad and R. Gast, *Ber.*, **31**, 2954 (1898).



fonyl chloride to give 1-methyl-3,3-diethyl-4-phenylsulfonamido-2-pyrrolidione (VI).

When butylamine and benzylamine were used instead of methylamine in the interaction with the γ-bromacetoacetate, 1-butyl-3,3-diethyl-2,4-pyrrolidinedione (VII) and 1-benzyl-3,3-diethyl-2,4-pyrrolidinedione (VIII) were obtained, respectively.

Replacement of the bromodiethylacetoacetate with ethyl γ-bromo-α,α-dimethylacetoacetate[2] in the reaction with ethyl glycinate gave the dimethyl analog of I, namely, 1-(carbethoxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (IX). Hydrolysis of the ester gave the acid (X) whose pyrrolidone structure was confirmed by infrared analysis in exactly the same way as for the diethyl analog. Decarboxylation of the acid proved difficult. In one successful experiment, the decarboxylation product was treated with phenylhydrazine to give 1,3,3-trimethyl-1,4-phenylhydrazino-2-pyrrolidone (XI), but subsequent attempts to prepare 1,3,3-trimethyl-2,4-pyrrolidinedione (XII) by this method failed. The latter was finally prepared by condensing the bromdimethylacetoacetate with methylamine. As with the diethyl analog, it gave the 4-isonitroso derivative (XIII) on treatment with hydroxylamine. Catalytic reduction of the isonitroso compound and treatment of the product with benzenesulfonyl chloride gave 1,3,3-trimethyl-4-phenylsulfonamido-2-pyrrolidone (XIV).

Substitution of ammonia in place of methylamine in the interaction with the bromacetoacetate derivative gave 3,3-dimethyl-2,4-pyrrolidinedione (XV), a compound previously reported by Conrad and Hock.[3]

The details of synthesis of the compounds not previously reported in the literature are given in the Experimental section.

Experimental[4]

Derivatives of 3,3-Diethylpyrrolidinedione. A. 1-(Carbethoxymethyl)-3,3-diethyl-2,4-pyrrolidinedione (I).—To a solution of 21 g. (0.2 mole) of ethyl glycinate in 25 ml. of benzene was added dropwise, with stirring, 26.5 g. of ethyl γ-bromo-α,α-diethylacetoacetate in 25 ml. of benzene. Heat was evolved and a precipitate of ethyl glycinate hydrochloride appeared. When precipitation was complete, the mixture was filtered and the benzene was removed from the filtrate. The residue was distilled to give the product in the form of a viscous, colorless liquid, b.p. 130–132° (0.55 mm.), $n^{24}D$ 1.4675.

Anal. Calcd. for $C_{12}H_{19}NO_4$ (mol. wt., 241): C, 59.7; H, 7.9; sapon. equiv., 241. Found: C, 59.6; H, 7.9; sapon. equiv., 248.

B. 1-(Carboxymethyl)-3,3-diethyl-2,4-pyrrolidinedione (II).—A mixture of 8.5 g. of the ester (I) and 18 ml. of 2 *N* NaOH was refluxed for 1 hr. The mixture was concentrated to one-half volume under vacuum and was then neutralized with 12 ml. of 3 *N* hydrochloric acid. The oil which separated was extracted with ether. The ether solution was dried with sodium sulfate and filtered; the ether was removed to give a solid residue. The residue on recrystallization from a benzene–carbon tetrachloride mixture gave the product in the form of fine white needles, m.p. 127–129°.

Anal. Calcd. for $C_{10}H_{15}NO_4$ (mol. wt., 213): C, 56.4; H, 7.0. Found: C, 56.3; H, 7.1.

Infrared showed a band for a strained carbonyl at 1765 $cm.^{-1}$. Ammonia passed into an ether solution of the acid gave the ammonium salt which on recrystallization from ethanol was obtained in the form of colorless prisms, m.p. 149–152°.

Anal. Calcd. for $C_{10}H_{18}N_2O_4$ (mol. wt., 230): C, 52.2; H, 7.8. Found: C, 52.4; H, 7.9.

C. 1-Methyl-3,3-diethyl-4-phenylhydrazono-2-pyrrolidone (IV).—Ten grams of the carboxymethyl pyrrolidone (II) was decarboxylated by heating under reflux (270–275°) for 2 hr. It was then distilled to give a viscous yellow liquid, b.p. 90–95° (4 mm.), $n^{27}D$ 1.4675. The distillate was dissolved in dilute ethanol; phenylhydrazine was added in excess and the mixture was heated on a steam bath for 1 hr. to give a precipitate of the phenylhydrazone. Recrystallization from dilute ethanol gave white prisms, m.p. 185–189° with prior softening.

Anal. Calcd. for $C_{15}H_{21}N_3O$ (mol. wt., 259): C, 69.5; H, 8.1; N, 16.2. Found: C, 69.6; H, 8.2; N, 16.2.

The distillate was substantially 1-methyl-3,3-diethyl-2,4-pyrrolidinedione (III), a compound which was subsequently prepared by the method described in D.

D. 1-Methyl-3,3-diethyl-2,4-pyrrolidinedione (III).—To a mixture containing 150 ml. of 30% methylamine in ethanol and 400 ml. of ether was added dropwise, with stirring and cooling, 100 g. of ethyl γ-bromo-α,α-diethylacetoacetate. The mixture was stirred for 4 hr. The precipitated methylamine hydrobromide was filtered off and the solvents were removed under vacuum. The liquid residue was distilled to give a colorless liquid, b.p. 84° (0.65 mm.), $n^{26}D$ 1.4665.

Anal. Calcd. for $C_9H_{15}NO_2$ (mol. wt., 169): C, 63.9; H, 8.9; N, 8.3. Found: C, 64.5; H, 8.8; N, 8.4.

A portion of the product treated with phenylhydrazine in dilute ethanol gave a phenylhydrazone melting at 183–190° with prior softening. A mixture melting point with IV was undepressed.

Anal. Calcd. for $C_{15}H_{21}N_3O$ (mol. wt., 259): C, 69.5; H, 8.1; N, 16.2. Found: C, 69.5; H, 8.4; N, 15.8.

E. 1-Methyl-3,3-diethyl-4-isonitroso-2-pyrrolidone (V).—A mixture of 5 g. of the pyrrolidinedione (III), 6 g. of hydroxylamine hydrochloride, 30 ml. of pyridine, and 25 ml. of ethanol was refluxed for 2 hr. The solvents were removed under vacuum, and the residue was washed with cold water and recrystallized from dilute ethanol to give white prisms, m.p. 125–127°.

Anal. Calcd. for $C_9H_{16}N_2O_2$ (mol. wt., 184): C, 58.7; H, 8.7; N, 15.2. Found: C, 58.5; H, 8.2; N, 15.3.

F. 1-Methyl-3,3-diethyl-4-phenylsulfonamido-2-pyrrolidone (VI).—A solution of 10 g. of the isonitroso compound in methanol was reduced with hydrogen in the presence of Raney nickel at 50 p.s.i. and room temperature. When the reduction was complete, the mixture was filtered and the solvent was removed under vacuum. The liquid residue was treated with 50 ml. of 2 *N* NaOH and 8 ml. of benzenesulfonyl chloride was added with shaking. The mixture was acidified with hydrochloric acid and cooled to give a white precipitate. Recrystallization from dilute ethanol gave white prisms, m.p. 151.5–153.5°.

Anal. Calcd. for $C_{15}H_{22}N_2O_3S$ (mol. wt., 310): C, 58.1; H, 7.1. Found; C, 57.9; H, 7.1.

G. 1-Butyl-3,3-diethyl-2,4-pyrrolidinedione (VII).—To a solution of 58.4 g. of *n*-butylamine in 400 ml. of ether was added dropwise, with stirring and cooling, 106 g. of ethyl γ-bromo-α,α-diethylacetoacetate. The addition took 1 hr. and stirring was continued for 2 hr. after addition was complete. The precipitated salt was filtered off and the ether was removed. Distilla-

(2) M. Conrad, *Ber.*, **30**, 856 (1897).
(3) M. Conrad and K. Hock, *ibid.*, **32**, 1200 (1899).
(4) All melting points are corrected.

tion of the residue gave a pale yellow oil, b.p. 97–102° (0.4 mm.), $n^{23}D$ 1.4645.

Anal. Calcd. for $C_{12}H_{21}NO_2$ (mol. wt., 211): C, 68.3; H, 10.0; N, 6.6. Found: C, 68.4; H, 9.8; N, 6.6.

H. 1-Benzyl-3,3-diethyl-2,4-pyrrolidinedione (VIII).—A solution of 43 g. of benzylamine in 200 ml. of ether was interacted with 53 g. of the bromoacetoacetate in accordance with the procedure described under G to give a colorless liquid, b.p. 145° (0.55 mm.), $n^{26}D$ 1.5235.

Anal. Calcd. for $C_{15}H_{19}NO_2$ (mol. wt., 245): C, 73.5; H, 7.8; N, 5.7. Found: C, 73.8; H, 8.0; N, 5.9.

Derivatives of 3,3-Dimethylpyrrolidinedione. A. 1-(Carbethoxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (IX).—A solution of 30 g. of ethyl glycinate in 25 ml. of benzene was treated with 34.5 g. of ethyl γ-bromo-α,α-dimethylacetoacetate[2] in 25 ml. of benzene in accordance with the procedure described under A above for the diethylacetoacetate. The product was a colorless liquid, b.p. 112° (0.2 mm.), $n^{26}D$ 1.4634, which tended to solidify to a low melting solid.

Anal. Calcd. for $C_{10}H_{15}NO_4$ (mol. wt., 213): C, 56.4; H, 7.0. Found: C, 56.3; H, 7.0; sapon. equiv., 188.

B. 1-(Carboxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (X).—The ester (IX, 5 g.) was hydrolyzed as described for the diethyl analog with 12 ml. of 2 *N* NaOH to give the acid in the form of small white needle clusters (from ethyl acetate), m.p. 128–130°; infrared analysis showed a band for a strained carbonyl at 1765 $cm.^{-1}$.

Anal. Calcd. for $C_8H_{11}NO_4$ (mol. wt., 185): C, 51.8; H, 5.9. Found: C, 52.0; H, 6.1.

C. 1,3,3-Trimethyl-2,4-pyrrolidinedione (XII).—A mixture of 200 g. of methylamine in ethanol (30% solution) was dissolved in 1000 ml. of ether and treated with 200 g. of the bromoacetoacetate according to the procedure previously described for the diethyl analog to give a colorless liquid, b.p. 141–144° (46 mm.), $n^{26}D$ 1.4720. The liquid partially solidified on standing. It was therefore chilled and filtered; the crystalline material was recrystallized from an ether–petroleum ether (b.p. 40–60°) mixture to give soft white crystals, m.p. 47–50°.

Anal. Calcd. for $C_7H_{11}NO_2$ (mol. wt., 141): C, 59.7; H, 7.8; N, 9.9. Found: C, 59.6; H, 7.7; N, 9.9.

The same compound could be made by decarboxylation of 1-(carboxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (X). The product so obtained was treated with phenylhydrazine in the conventional manner to give yellow flakes (from ethanol) of 1,3,3-trimethyl-4-phenylhydrazono-2-pyrrolidone (XI), m.p. 167–173° (with prior softening).

Anal. Calcd. for $C_{13}H_{17}N_3O$ (mol. wt., 231): C, 67.5; H, 7.4. Found: C, 67.8; H, 7.6.

D. 1,3,3-Trimethyl-4-isonitroso-2-pyrrolidone (XIII).—A mixture of 10 g. of the dione (XII), 12 g. of hydroxylamine hydrochloride, 60 ml. of pyridine, and 60 ml. of ethanol was interacted as described for the diethyl analog to give small white needles of the product (from dilute ethanol), m.p. 211–212°.

Anal. Calcd. for $C_7H_{12}N_2O_2$ (mol. wt., 156): C, 53.8; H, 7.7; N, 18.0. Found: C, 53.8; H, 7.2; N, 18.1.

E. 1,3,3-Trimethyl-4-phenylsulfonamido-2-pyrrolidone (XIV).—A solution of 8 g. of the isonitroso compound (XIII) in methanol was reduced, and the reduction product was treated with benzenesulfonyl chloride in the manner previously described for the diethyl analog to give white spires (from dilute ethanol) of the product, m.p. 163–165°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3S$ (mol. wt., 282): C, 55.3; H, 6.4. Found: C, 55.4; H, 6.3.

Acknowledgment.—The authors are indebted to Dr. A. Steyermark and his staff for the microanalyses and to Mr. S. Traiman for the infrared studies.

5*H*-1,4-Benzodiazepin-5-ones. Ring-Closure Reactions of Substituted 2-Aminobenzamides

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Several new 5*H*-1,4-benzodiazepin-5-ones were prepared from 2-aminobenzamides by ring closures involving intramolecular eliminations of alkylsulfonic or arylsulfonic acids, cyclodehydrochlorination, and cyclodehydration reactions. Some chemical transformations of the new compounds are presented.

During recent years, considerable effort has been expended toward the synthesis of 1*H*-1,4-benzodiazepines,[1] a group of compounds having interesting psychopharmacologic properties. In the course of our investigations into the preparation of centrally active drugs, we arrived at several routes for preparing novel 5*H*-1,4-benzodiazepin-5-ones through ring closures involving elimination reactions in suitably substituted 2-aminobenzamides.[2]

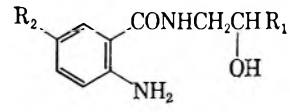
The first method involved the reaction of a 2-amino-*N*-(2-hydroxyalkyl)benzamide (I) with an alkylsulfonyl or arylsulfonyl chloride. The method is illustrated best by the preparation of 1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIj). 2-Amino-*N*-(2-hydroxyethyl)benzamide (Ie), obtained from the reaction of 2-aminoethanol with isatoic anhydride, was treated with 2 molar equiv. of *p*-toluenesulfonyl chloride at 0–5° in pyridine. After several hours, the addition of water to the reaction mixture resulted in the precipitation of a solid which, on heating in ethanol, gave IIIj. It subsequently was shown that the cyclization occurred during the attempted purification of intermediate II, since the solid initially obtained had an infrared absorption spectrum significantly different from IIIj. The spectrum of the rather labile intermediate has an amide II band at 6.4 μ and is compatible with the open-chain structure of the *p*-toluenesulfonate ester of 2-*p*-toluenesulfonamido-*N*-(2-hydroxyethyl)benzamide. The amide II band is absent in the spectrum of IIIj, as expected, since it is a cyclic amide. The same reaction was carried out in stepwise fashion using 1 equiv. of *p*-toluenesulfonyl chloride. The product isolated was *N*-(2-hydroxyethyl)-2-*p*-toluenesulfonamidobenzamide. When the latter product in pyridine was treated with a 2nd molar equiv. of *p*-toluenesulfonyl chloride and the reaction worked up in the customary manner, IIIj again was obtained.

(1) (a) A. Stempel and F. W. Landgraf, *J. Org. Chem.*, **27**, 4675 (1962); (b) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962); (c) S. C. Bell and S. J. Childress, *ibid.*, **27**, 1691 (1962); (d) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Chem.*, **5**, 63 (1962); (e) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962); (f) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

(2) M. Uskoković, J. Iacobelli, and W. Wenner [*ibid.*, **27**, 3606 (1963)] have described the preparation of 3*H*-1,4-benzodiazepin-2,5(1*H*,4*H*)-diones from substituted 2-aminobenzamides.

TABLE I

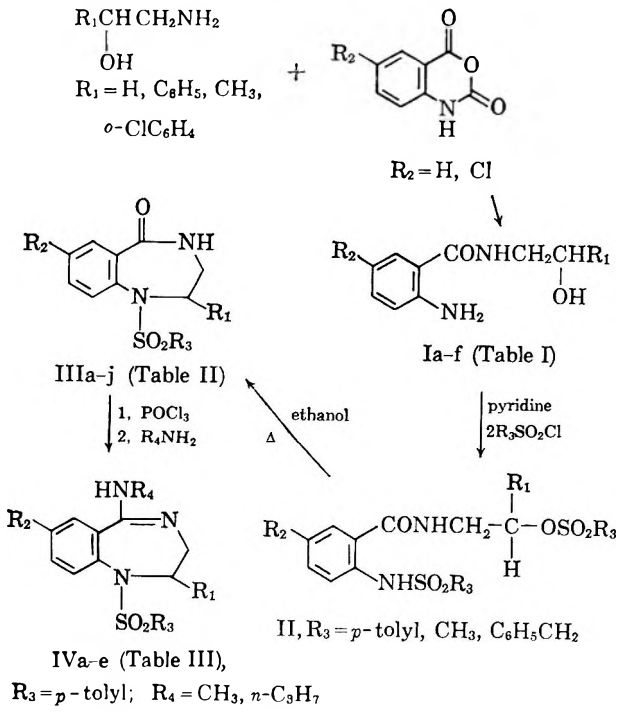
2-AMINO-*N*-(2-HYDROXYALKYL)BENZAMIDES



Compound I	R_1	R_2	M.p., °C.	Recryst. solvent[a]	Yield, %	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
a	H	Cl	120.5–122	C	87	$C_9H_{11}ClN_2O_2$	50.36	5.16	13.05	16.52	50.25	5.25	13.05	16.50
b	C_6H_5	Cl	119–121	A	55	$C_{15}H_{15}ClN_2O_2$	61.96	5.20	9.64	12.19	62.02	5.24	9.38	12.07
c	CH_3	Cl	109–110.5	A	83	$C_{10}H_{13}ClN_2O_2$	52.52	5.73	12.25	15.50	52.72	5.89	12.29	15.50
d	*o*-ClC_6H_4	Cl	105–107	B–A	80	$C_{15}H_{14}ClN_2O_2$	55.40	4.34	8.62	21.80	55.71	4.25	8.38	21.50
e[b]	H	H	90–91	B	38	$C_9H_{12}N_2O_2$	59.98	6.71	15.55		59.76	6.62	15.47	
f	*o*-ClC_6H_4	H	103–105	B–A	55	$C_{15}H_{15}ClN_2O_2$	61.97	5.20	9.63	12.19	62.22	5.00	9.34	11.6

[a] A = benzene, B = cyclohexane, and C = water. [b] D. R. Shridar and K. S. Narang [*J. Indian Chem. Soc.*, **33**, 305 (1956)] reported m.p. 95° for Ie.

CHART I



The compounds Ia–f (Table I) were converted to IIIa–j (Table II) as described above. (See Chart I.)

In each of these cyclization reactions, the formation of a 5*H*-1,4-benzodiazepin-5-one was accompanied by distinct infrared spectral changes. Compounds IIIa–j have only weak absorptions in the normal NH stretching region (3.0 μ) and no amide II band (6.4 μ). These bands are clearly present in the spectra of benzamides Ia–f. Another noticeable change is the appearance of a broad absorption at 3.5–3.6 μ which is not present in the latter compounds.

With the exception of the instance where $R_1 = CH_3$, $R_2 = Cl$, and $R_3 = p$-tolyl in II, none of the intermediates was sufficiently stable to be purified by recrystallization. It was necessary to treat this ester with 1 equiv. of sodium methoxide in boiling methanol before ring closure to 7-chloro-1,2,3,4-tetrahydro-2-methyl-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIc) would occur.

In another experiment, treatment of 2-amino-5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)benzamide (Id) with 2 molar equiv. of *p*-toluenesulfonyl chloride gave 5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)-2-(*p*-toluenesulfonamido)benzamide instead of the expected cyclized product. Apparently, the 2nd equiv. of *p*-toluenesulfonyl chloride did not react with the somewhat sterically hindered hydroxyl group of Id. When a more reactive reagent, methanesulfonyl chloride, was allowed to react with 5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)-2-(*p*-toluenesulfonamido)benzamide, ring closure occurred and resulted in the formation of 7-chloro-2-(*o*-chlorophenyl)-1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIId).

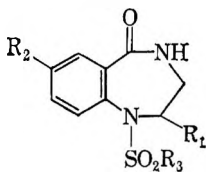
The foregoing experiments make it clear that the amino group of I reacts with the 1st equiv. of sulfonyl chloride, forming a sulfonamide. The 2nd equiv. reacts with the hydroxyl function, resulting in a sulfonate ester (II). Merely heating II in ethanol results in a surprisingly facile elimination of R_3SO_2OH. This elimination probably occurs by a concerted backside displacement of the OSO_2R_3 anion by the sulfonamido nitrogen with simultaneous abstraction of a proton from the same nitrogen atom. In only one experiment was the addition of a strong base, sodium methoxide, necessary to promote this elimination and concurrent cyclization to IIIc. It is difficult to assess the significance of the one exception since, in all other cases, elimination and ring closure occurred merely by heating the intermediate II.

N-Phenylanthranilic acid reacted with ethyl chloroformate to give *N*-phenylisatoic anhydride. Treatment of the anhydride with 2-aminoethanol afforded 2-anilino-*N*-(2-hydroxyethyl)benzamide. The latter compound in pyridine was treated with 1 equiv. of methanesulfonyl chloride. After standing several hours, the reaction mixture was treated with water, resulting in the separation of 1,2,3,4-tetrahydro-1-phenyl-5*H*-1,4-benzodiazepin-5-one. In this reaction the methanesulfonyl chloride reacts preferentially with the hydroxyl group, since the basicity of the amino nitrogen is considerably reduced by the presence of the two aromatic moieties to which it is bonded.

Removal of the *p*-tolylsulfonyl group from compound IIIj was accomplished by sulfuric acid hydrolysis. The product isolated was 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one. In similar fashion, hydrolysis of 7-chloro-1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIa) afforded 7-chloro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one.

TABLE II

1-ALKYLSULFONYL- AND 1-ARYLSULFONYL-1,2,3,4-TETRAHYDRO-5*H*-1,4-BENZODIAZEPIN-5-ONES

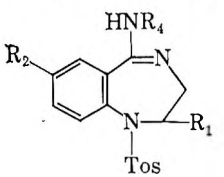


Compound III	R_1	R_2	R_3	M.p., °C.	Recryst. solvent[a]	Yield, %	Formula	Calcd., % C	H	N	Cl	S	Found, % C	H	N	Cl	S
a	H	Cl	C_7H_7[b]	174–176	D	34	$C_{16}H_{15}ClN_2O_3S$	54.78	4.31	7.98	10.10	9.14	54.94	4.37	8.00	10.2	9.16
b	C_6H_5	Cl	C_7H_7	132–133	E	54	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56	8.31	7.51	62.09	4.58	6.74	8.4	7.7
c	CH_3	Cl	C_7H_7	122–124	E	55	$C_{17}H_{17}ClN_2O_3S$	55.96	4.70	7.68	9.72	8.79	55.95	4.59	7.63	9.8	8.99
d	*o*-ClC_6H_4	Cl	C_7H_7	165–166	A–F	40	$C_{22}H_{18}Cl_2N_2O_3S$	57.27	3.93	6.07	15.37	6.95	57.54	3.79	5.90	15.3	7.2
e	H	H	CH_3	164–165.5	D	22	$C_{10}H_{12}N_2O_3S$	49.88	5.03	11.66		13.34	50.08	5.05	11.42		13.4
f	CH_3	Cl	CH_3	114–116	D–C	23	$C_{11}H_{13}ClN_2O_3S$	45.75	4.54	9.70	12.28	11.10	46.00	4.54	9.49	12.36	11.1
g	C_6H_5	Cl	CH_3	157–158	E	75	$C_{16}H_{13}ClN_2O_3S$	54.78	4.31	7.98	10.10	9.14	54.88	4.31	8.29	10.12	9.2
h	C_6H_5	Cl	$CH_2C_6H_5$	139–140	B	63	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56	8.31	7.51	61.71	4.41	6.39	8.3	7.8
i	*o*-ClC_6H_4	H	C_7H_7	152–153.5	D	41	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56	8.31	7.51	61.91	4.68	6.56	8.0	7.6
j	H	H	C_7H_7	197–199	D	78	$C_{16}H_{16}N_2O_3S$	60.74	5.14	8.85		10.14	60.96	5.32	9.11		10.0

[a] A = benzene, B = cyclohexane, C = water, D = ethanol, E = methanol, and F = petroleum ether. [b] C_7H_7 = *p*-tolyl.

TABLE III

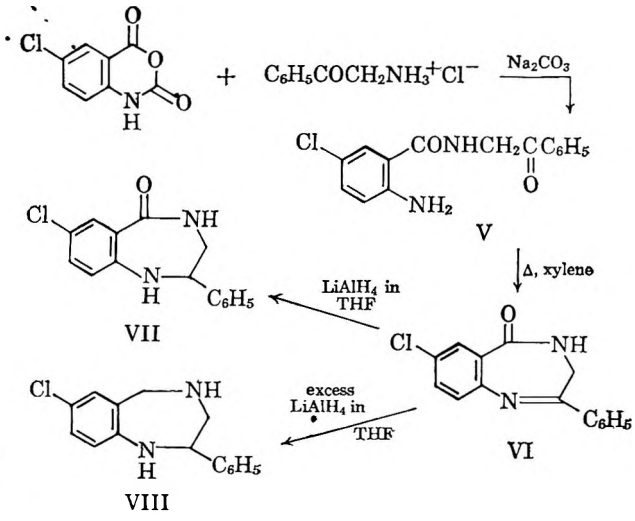
2,3-DIHYDRO-5-ALKYLAMINO-1-*p*-TOLYLSULFONYL-1*H*-1,4-BENZODIAZEPINES



Compound IV	R_1	R_2	R_4	M.p., °C.	Recryst. solvent[a]	Yield, %	Formula	Calcd. % C	H	N	Cl	S	Found, % C	H	N	Cl	S
a	H	H	CH_3	161–164	A	31	$C_{17}H_{19}N_3O_2S$	61.98	5.81	12.76		9.73	62.25	5.94	12.98		9.5
b[b]	H	H	*n*-C_3H_7	145–150	B	17	$C_{19}H_{23}N_3O_2S$	62.25	6.60	11.46		8.79	62.64	7.04	11.2		8.4
c	C_6H_5	Cl	CH_3	198–200	A	57	$C_{23}H_{22}ClN_3O_2S$	62.79	5.04	9.55	8.06	7.29	62.63	4.56	9.49	8.2	7.2
d	*o*-ClC_6H_4	Cl	CH_3	232–234	C	13	$C_{23}H_{21}Cl_2N_3O_2S$	58.23	4.46	8.86	14.94	6.76	57.90	4.52	8.82	14.60	6.95
e	*o*-ClC_6H_4	H	CH_3	172–174	C	23	$C_{23}H_{22}ClN_3O_2S$	62.79	5.04	9.55	8.06	7.29	63.02	5.23	9.46	8.0	7.4

[a] A = benzene, B = cyclohexane, and C = ethanol. [b] Analyzed as hemihydrate.

CHART II



Treatment of IIIj with phosphorus pentasulfide in pyridine gave 1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepine-5-thione.

7-Chloro-2,3-dihydro-5-methylamino-2-phenyl-1-*p*-tolylsulfonyl-1*H*-1,4-benzodiazepine (IVc) was obtained by reaction of 7-chloro-1,2,3,4-tetrahydro-2-phenyl-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIb) with phosphorus oxychloride, followed by treatment of the product with methylamine. Other examples are given in Table III.

Another synthetic route to 5*H*-1,4-benzodiazepin-5-ones was through cyclodehydrochlorination. For example, reaction of 2-amino-5-chloro-*N*-(2-hydroxyethyl)benzamide with thionyl chloride gave 2-amino-5-chloro-*N*-(2-chloroethyl)benzamide. Heating the latter compound in boiling *N*,*N*-dimethylformamide in the presence of sodium carbonate gave 7-chloro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one. Infrared spectral comparison of the latter product with the hydrolysis product of IIIa, previously described, showed the two materials to be identical. A mixture melting point of the two also confirmed this identity.

Treatment of an aqueous solution of ω-aminoacetophenone hydrochloride with sodium carbonate, followed by the addition of 5-chloroisatoic anhydride, afforded 2-amino-5-chloro-*N*-phenacylbenzamide (V). Cyclodehydration of V to 7-chloro-3,4-dihydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (VI) was accomplished by heating V in boiling xylene solution. Lithium aluminum hydride reduction of VI in tetrahydrofuran gave 7-chloro-1,2,3,4-tetrahydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (VII) by reduction of the azomethine bond. When a large excess of hydride was used and the reaction time was extended, both the azomethine and lactam bonds were reduced, giving 7-chloro-2,3,4,5-tetrahydro-2-phenyl-1*H*-1,4-benzodiazepine (VIII). (See Chart II.)

In contrast to the present work, Sulkowski and Childress[3] reported that the lithium aluminum hydride reduction of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, an isomer of VI, left the azomethine bond unchanged but reduced the lactam instead. The product of their reduction was 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine. Sternbach and coworkers[4] reported the same observations but they subsequently were able to reduce the azomethine bond of the latter compound by a second treatment with lithium aluminum hydride. The greater ease with which the azomethine bond in VI is reduced, however, compared with the lactam bond is not unexpected since it is an anilic type. It is well established that anils undergo reduction readily under these conditions. The aromatic lactam carbonyl group, on the other hand, requires slightly more vigorous conditions for reduction.

The pharmacologic properties of these 5*H*-1,4-benzodiazepin-5-ones and their derivatives are currently under investigation.

(3) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **28**, 2150 (1963).

Experimental[5]

1,2,3,4-Tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIj).—To an ice-cold solution of 8.4 g. of 2-amino-*N*-(2-hydroxyethyl)benzamide (Ie) in 30 ml. of dry pyridine was added, in portions, 19 g. of *p*-toluenesulfonyl chloride. After standing overnight in the refrigerator, the reaction mixture was poured into 100 ml. of water. The oily residue was washed several times with water, affording a crystalline product (19.6 g.), m.p. 94–99°. This material (14.5 g.) was added to 50 ml. of ethanol and the mixture was heated for 15 min. on the steam bath. After cooling in ice, the crystalline product was washed with 50 ml. of hot water, affording 8.5 g. of IIIj, m.p. 192–197°. The analytical sample obtained by recrystallization from ethanol had m.p. 197–199°; λ_{max} 6.14 (C=O), 7.51, and 8.65 μ (SO_2).

***N*-(2-Hydroxyethyl)-2-*p*-toluenesulfonamidobenzamide.**—To a cold solution of 2 g. of Ie in 15 ml. of dry pyridine was added 2.1 g. of *p*-toluenesulfonyl chloride. The mixture was allowed to stand 3 hr. in the refrigerator and was then poured into 100 ml. of water. The viscous oil which separated crystallized on cooling to afford 3.0 g. of product, m.p. 115–117°. Two recrystallizations from benzene raised the melting point to 125.5–126.5° and gave λ_{max} 6.15 (C=O), 6.47 (amide II), 7.50, and 8.68 μ (SO_2).

Anal. Calcd. for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.58; H, 5.25; N, 8.47; S, 9.3.

5-Chloro-*N*-(2-hydroxypropyl)-2-(*p*-toluenesulfonamido)benzamide, *p*-Toluenesulfonate Ester.—To an ice-cold solution of 8.4 g. of 2-amino-5-chloro-*N*-(2-hydroxypropyl)benzamide (Ic) in 25 ml. of dry pyridine was added 14 g. of *p*-toluenesulfonyl chloride. The reaction mixture was allowed to stand overnight at room temperature and was then poured into 200 ml. of warm water. The oily residue which was deposited was washed several times with water. The addition of a little methanol resulted in the formation of a crystalline solid (4.7 g.), m.p. 120–123°. The analytical sample obtained by recrystallization from ethanol had a m.p. 116–118°; λ_{max} 6.09 (C=O), 6.52 (amide II), 7.44, and 8.64 μ (SO_2).

Anal. Calcd. for $C_{24}H_{25}ClN_2O_6S_2$: C, 53.67; H, 4.69; Cl, 6.60; N, 5.22; S, 11.94. Found: C, 53.90; H, 4.77; Cl, 6.7; N, 5.47; S, 11.9.

7-Chloro-1,2,3,4-tetrahydro-2-methyl-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIc).—To a solution of 3.5 g. of 5-chloro-*N*-(2-hydroxypropyl)-2-(*p*-toluenesulfonamido)benzamide, *p*-toluenesulfonate ester, in 25 ml. of anhydrous methanol was added 0.5 g. of sodium methoxide. The reaction mixture was heated under reflux for 10 min. and was then cooled in ice. The solid which deposited was washed with water. Recrystallization from methanol gave 1.3 g. of product, m.p. 122–124°; λ_{max} 6.11 (C=O), 7.52, and 8.76 μ (SO_2).

***o*-Chloromandelonitrile Acetate.**—A solution of 134 g. of *o*-chloromandelonitrile in 82 g. of acetic anhydride was heated under reflux for 2 hr. The reaction mixture was distilled *in vacuo* through a Claisen head. The product, which was the fraction distilling between 109 and 111° (0.25 mm.), amounted to 107 g. and had λ_{max} 5.67 μ (C=O).

(4) L. H. Sternbach, E. Reeder, and G. A. Archer, *ibid.*, **28**, 2456 (1963).

(5) Melting points were taken in capillary tubes (Thomas–Hoover melting point apparatus) and are uncorrected. Infrared spectra were determined in potassium bromide pellets using a Perkin-Elmer, Model 21, spectrophotometer.

Anal. Calcd. for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.84; Cl, 16.92; N, 6.68. Found: C, 57.30; H, 3.92; Cl, 17.2; N, 6.47.

o-Chloro-β-hydroxyphenethylamine.—To a cold, stirred suspension of 37.9 g. of lithium aluminum hydride in 800 ml. of dry tetrahydrofuran was added a solution of 107 g. of *o*-chloromandelonitrile acetate in 50 ml. of tetrahydrofuran over a period of 1 hr. The reaction mixture was allowed to stand for 20 min. at room temperature and was then heated under reflux for 2 hr. The aluminum complex was decomposed cautiously, after cooling in ice, by the dropwise addition of 100 ml. of water followed by 200 ml. of 20% sodium hydroxide solution. The reaction mixture was filtered and the filtrate was concentrated by evaporation *in vacuo* on a rotary evaporator. The oily residue was distilled through a Claisen head, affording 56 g. of product, b.p. 108–112° (0.25 mm.). The product was used without further purification.

5-Chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)-2-(*p*-toluenesulfonamido) benzamide.—To an ice-cold solution of 20 g. of 2-amino-5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)benzamide (Id) in 40 ml. of dry pyridine was added 23 g. of *p*-toluenesulfonyl chloride. After standing overnight in the refrigerator, the reaction mixture was poured into 200 ml. of water. The oily layer was washed several times with water. The addition of a little methanol induced crystallization. The crude product amounted to 23 g., m.p. 70–92°. Several recrystallizations from benzene raised the melting point to 165–166° and gave λ_{max} 6.10 (C=O), 6.46 (amide II), 7.42, and 8.61 μ (SO_2).

Anal. Calcd. for $C_{22}H_{20}Cl_2N_2O_4S$: C, 55.12; H, 4.20; Cl, 14.79; N, 5.82. Found: C, 55.28; H, 4.10; Cl, 14.5; N, 5.98.

7-Chloro-2-*o*-chlorophenyl-1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIId).—To an ice-cold solution of 5.2 g. of 5-chloro-*N*-(*o*-chloro-β-hydroxyphenethyl)-2-(*p*-toluenesulfonamido)benzamide in 10 ml. of anhydrous pyridine was added, dropwise, 1.26 g. of methanesulfonyl chloride. The temperature of the reaction was kept below 20° during the addition. After the reaction mixture was allowed to stand 3.5 hr. at room temperature, ice was added. The gummy residue which was deposited was dissolved in benzene. The benzene was removed by evaporation leaving an oily residue. Trituration of the residue with petroleum ether (b.p. 30–60°) gave a crystalline product (2 g.), m.p. 155–163°. Recrystallization from benzene–petroleum ether raised the melting point to 165–166° and gave λ_{max} 6.07 (C=O), 7.48, 7.56 doublet, and 8.61 μ (SO_2).

***N*-Phenylisatoic Anhydride.**—A solution of 5 g. of *N*-phenylanthranilic acid in 20 ml. of ethyl chloroformate was heated under reflux for 10 hr. The excess ethyl chloroformate was removed *in vacuo* on a rotary evaporator. The residual solid amounted to 3.6 g., m.p. 172–179°. Recrystallization of the product from ethanol raised the melting point to 177–179°, and gave λ_{max} 5.64 and 5.76 μ (anhydride).

Anal. Calcd. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.21; H, 3.83; N, 5.65.

2-Anilino-*N*-(2-hydroxyethyl)benzamide.—To a solution of 10 g. of *N*-phenylisatoic anhydride in 50 ml. of absolute ethanol was added 2.6 g. of 2-aminoethanol. The reaction mixture was heated for 10 min. on the steam bath. The ethanol was removed *in vacuo* on a rotary evaporator leaving a solid residue (8.1 g.), m.p. 62–70°. Recrystallization from benzene–cyclohexane raised the melting point to 77–79° and gave λ_{max} 6.16 (C=O), 6.52 μ (amide II).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.04; H, 6.11; N, 10.92.

1,2,3,4-Tetrahydro-1-phenyl-5*H*-1,4-benzodiazepin-5-one.—To an ice-cold solution of 2.6 g. of 2-anilino-*N*-(2-hydroxyethyl) benzamide in 5 ml. of dry pyridine was added, dropwise and with stirring, 1.1 g. of methanesulfonyl chloride, keeping the temperature of the reaction at 0–10°. After the reaction mixture had warmed to room temperature, ice was added. The crystalline product which was deposited amounted to 2.2 g., m.p. 60–64°. Recrystallization from aqueous ethanol raised the melting point to 66–68° and gave λ_{max} 6.10 μ (C=O).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.57; H, 5.92; N, 11.53.

1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-5-one.—A solution of 1 g. of IIIj in 5 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 5 days. The reaction mixture was then poured into 15 ml. of water and the solution was neutralized with 3 *N* sodium hydroxide solution. A crystalline material was deposited (0.2 g.), m.p. 52–54°. Recrystallization from *n*-pentane afforded 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one, m.p. 55°; λ_{max} 6.15 μ (C=O).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27 Found: C, 66.47; H, 5.92; N, 17.06.

1,2,3,4-Tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepine-5-thione.—To a solution of 1 g. of IIIj in 15 ml. of dry pyridine was added 1 g. of phosphorus pentasulfide. The reaction mixture was heated under reflux for 2 hr., cooled in ice, and poured into 50 ml. of hot water. The aqueous solution was neutralized with 30% hydrochloric acid. The crystalline product which was deposited amounted to 1.3 g., m.p. 140–154°. Recrystallization from aqueous pyridine raised the melting point to 160–163° and gave λ_{max} 7.51 and 8.67 μ (SO_2).

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 57.80; H, 4.85; N, 8.43; S, 19.29. Found: C, 57.91; H, 4.84; N, 8.43; S, 19.1.

7-Chloro-2,3-dihydro-5-methylamino-2-phenyl-1-*p*-tolyl-sulfonyl-1*H*-1,4-benzodiazepine (IVc).—A solution of 7.7 g. of 7-chloro-1,2,3,4-tetrahydro-2-phenyl-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIb) in 35 ml. of phosphorus oxychloride was heated under reflux for 2 hr. The excess phosphorus oxychloride was removed *in vacuo* on a rotary evaporator. The residual oil was cooled in ice. A cold solution of methanolic methylamine (10 g. of methylamine in 25 ml. of anhydrous methanol) was added, dropwise, to the residue. The reaction mixture was then heated under reflux for 30 min. After removal of the excess methylamine and solvent by evaporation, 25 ml. of water was added to the residue. A yellow, amorphous substance (9.4 g.) was obtained which, after recrystallization from benzene, gave 4.5 g. of product, m.p. 198–200°; λ_{max} 7.84 and 8.86 μ (SO_2).

2-Amino-5-chloro-*N*-(2-chloroethyl)benzamide.—A solution of 13.4 g. of 2-amino-5-chloro-*N*-(2-hydroxyethyl)benzamide (Ia) in 100 ml. of thionyl chloride was heated under reflux for 1 hr. The excess thionyl chloride was removed *in vacuo* on a rotary evaporator. The residual solid was treated with 10% sodium bicarbonate solution. The solid was recrystallized from cyclohexane, affording 2.4 g. of product, m.p. 115–116°; λ_{max} 6.16 (C=O) and 6.54 μ (amide II).

Anal. Calcd. for $C_9H_{10}Cl_2N_2O$: C, 46.37; H, 4.32; Cl, 30.42; N, 12.02. Found: C, 46.52; H, 4.43; Cl, 30.40; N, 12.01.

7-Chloro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one.—To a solution of 6.2 g. of 2-amino-5-chloro-*N*-(2-chloroethyl)benzamide in 15 ml. of *N*,*N*-dimethylformamide was added 4 g. of finely pulverized sodium carbonate. The reaction mixture was heated under reflux for 1.5 hr. and filtered, and water was added to the filtrate until precipitation of the product was complete. Recrystallization from *n*-hexane afforded 3.2 g. of product, m.p. 76–78°; λ_{max} 6.12 μ (C=O).

Anal. Calcd. for $C_9H_9ClN_2O$: C, 54.97; H, 4.61; Cl, 14.25; N, 18.03. Found: C, 55.26; H, 4.52; Cl, 14.48; N, 18.00.

The identical product, m.p. 77–78°, was obtained by hydrolysis of IIIa in concentrated sulfuric acid for 24 hr. at ambient temperature. A mixture melting point of the two materials gave no depression. The infrared spectra were identical.

2-Amino-5-chloro-*N*-phenacylbenzamide (V).—To a stirred solution of 15 g. of ω-aminoacetophenone hydrochloride in 60 ml. of water was added 17.3 g. of 5-chloroisoatoic anhydride, followed by 4.7 g. of sodium carbonate. The reaction mixture was allowed to stand overnight, with stirring, at room temperature. Filtration afforded 25.1 g. of product, m.p. 130–140°. Recrystallization from cyclohexane–benzene raised the melting point to 148–150° and gave λ_{max} 5.91, 6.09 (C=O) and 6.62 μ (amide II).

Anal. Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54; Cl, 12.28; N, 9.70. Found: C, 62.70; H, 4.51; Cl, 12.2; N, 9.59.

7-Chloro-3,4-dihydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (VI).—A suspension of 5.9 g. of V in 150 ml. of dry xylene was heated, with stirring, to the boiling point. The water liberated was collected in a Dean–Stark water separator. The reaction mixture was then filtered and the filtrate was cooled in ice affording a crystalline product (2.5 g.), m.p. 155–165°. Recrystallization from xylene gave VI, m.p. 160–162°; λ_{max} 6.01 μ (C=O).

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.09; Cl, 13.10; N, 10.35. Found: C, 66.83; H, 4.37; Cl, 12.55; N, 10.16.

7-Chloro-1,2,3,4-tetrahydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (VII).—To a stirred, ice-cold suspension of 1.14 g. of lithium

aluminum hydride in 200 ml. of anhydrous tetrahydrofuran was added, dropwise, a solution of 5.5 g. of VI in 50 ml. of anhydrous tetrahydrofuran. When the addition was completed, the reaction mixture was stirred at room temperature for 2 hr. and then was heated under reflux for 1 hr. The reaction mixture was cooled in ice, and 50% aqueous tetrahydrofuran (30 ml.) was added cautiously, followed by 25 ml. of 10% sodium hydroxide solution. The reaction mixture was filtered and the filtrate was taken to dryness on a rotary evaporator. The oily residue which was deposited was triturated with 15 ml. of ethyl acetate resulting in a crystalline product (1.8 g.), m.p. 159–166°. Recrystallization from ethyl acetate afforded VII, m.p. 170–173°; λ_{max} 6.10 μ (C=O).

Anal. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.05; H, 4.80; Cl, 13.00; N, 10.27. Found: C, 65.88; H, 4.67; Cl, 12.55; N, 10.36.

7-Chloro-2,3,4,5-tetrahydro-2-phenyl-1*H*-1,4-benzodiazepine (VIII).—The reduction of 10.8 g. of VI with 4.6 g. of lithium aluminum hydride in 250 ml. of tetrahydrofuran was carried out as described in the previous example, except that the reaction mixture was heated under reflux for 3.5 hr. before work-up. Recrystallization from methanol resulted in a hygroscopic product (2.5 g.), m.p. 60–68°.

Anal. Calcd. for $C_{15}H_{15}ClN_2$: C, 69.63; H, 5.84; N, 10.83. Found: C, 69.33; H, 6.13; N, 10.43.

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Ethyl Hydantoin-5-carboxylates[1-3]

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Ethyl hydantoin-5-carboxylates have been prepared from ureidomalonates in the presence of sodium ethoxide.

Hydantoins and structurally related compounds, natural and synthetic, are legion in the chemical literature. There are, however, few specific references to derivatives of hydantoin-5-carboxylic acid. This acid, as would be predicted because of its structural relationship to malonic and acetoacetic acids, possesses a reactive substituted methylene group and is difficult to isolate owing to ready decarboxylation. Amides of substituted hydantoin-5-carboxylic acid were isolated by both Fischer[5] and Biltz[6,7] as degradation products of methylated purines. In most cases, attempts to isolate acids from these amides were thwarted by decarboxylation. Biltz,[7] however, isolated 3-methylhydantoin-5-carboxylic acid which was decarboxylated when heated to 130°.

Johnson and Nicolet[8] prepared hydantoin-5-carboxamide (VI) by the ring closure of N-carbethoxyaminomalonamide. The compound was not investigated further except to fuse it with urea in an attempt to prepare uric acid. Johnson and Nicolet also attempted to prepare the intermediate, pseudouric acid, by the reaction of ethyl ureidomalonate (I) and urea in the presence of sodium ethoxide. An alcohol-insoluble precipitate formed which was described as "the sodium salt of ethyl ureidomalonate."

The potential of this latter reaction led us to repeat Johnson's experiment with a variety of ureidomalonates which were readily prepared by the addition of ethyl aminomalonate to the appropriate isocyanate.

When treated with sodium ethoxide, the ureidomalonates cyclize. Under these conditions, ethyl ureidomalonate gave the stable sodium salt of ethyl hydantoin-5-carboxylate (II). The isolation of the parent ester was technically difficult. Initially, ring closure of ethyl ureidomalonate was demonstrated by (1) failure to regenerate ethyl ureidomalonate from the sodium salt on acidification, (2) conversion of the salt to hydantoin (IV) by digestion with concentrated hydrochloric acid, and (3) conversion of the salt to the amide (VI) by cold concentrated ammonium hydroxide.

In alcohol–water solutions, an irreversible change can be observed in the ultraviolet spectrum of I in the region 210–230 mμ on treatment with base followed by acidification. Since no change occurs in the spectrum of I on direct treatment with acid, it was assumed that cyclization occurred on treatment with base. Cyclization occurred so rapidly in basic solution that it was not possible to record the spectrum of the ethyl ureidomalonate anion. Elemental analysis of the sodium salt and successful isolation of the ester III by neutralization with acid-form Dowex-50 resin confirmed ring closure.

The ultraviolet spectra of ethyl hydantoin-5-carboxylates have a strong maximum in the region 290–310 mμ in basic alcohol–water solutions (Table I). The maximum fades rapidly and in this respect these substances have spectral properties similar to those of diethyl malonate and ethyl acetoacetate. Ionization on the 5-position is indicated. The rapid fading of the maximum is due to the saponification of the ester to the corresponding hydantoin-5-carboxylate anion.

Although in sodium ethoxide the cyclization of I occurred at room temperature, reflux was employed to obtain a more easily filtered product. The cyclization of ethyl N′-phenylureidomalonate, however, was a slower reaction and reflux in ethanol was necessary to obtain a good yield of ethyl 3-phenylhydantoin-5-carboxylate (VIII).

Ethyl N′-tetra-O-acetylglucosylureidomalonate formed an insoluble salt when treated with alcoholic

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(3) Abstracted from the dissertation of William Garner which was submitted to the Faculty of the Graduate School of Arts and Sciences of the University of Buffalo in partial fulfillment of the requirement for the degree of Doctor of Philosophy, June, 1959.

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(5) E. Fischer, *Ann.*, **215**, 253 (1882).

(6) H. Biltz, *Ber.*, **43**, 1600 (1910).

(7) H. Biltz, *ibid.*, **46**, 3407 (1913).

(8) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.* **36**, 345, 355 (1914).

TABLE I

ULTRAVIOLET SPECTRA OF SODIUM SALTS OF ESTERS OF HYDANTOIN-5-CARBOXYLIC ACIDS AND OF ETHYL ACETOACETATE IN WATER

Compound	$\lambda_{max.}$ mμ	ϵ_{max} (approximate)
Ethyl hydantoin-5-carboxylate	292	5.5×10^3
Ethyl 3-phenylhydantoin-5-carboxylate	293	1.5×10^4
Ethyl 3-phenyl-2-thiohydantoin-5-carboxylate	305	1.8×10^4
N′-Tetra-O-acetylglucosylureidomalonate (XI) treated with base	291	1.6×10^4
N′-Tetra-O-acetylglucosylthioureidomalonate (XII) treated with base	307	1.8×10^4
Ethyl acetoacetate	272	2.2×10^4

sodium ethoxide. Neutralization of the salt with acid-form Dowex 50 gave a glass which could not be crystallized. The ultraviolet spectrum of the salt, however, gave a characteristic pattern for a hydantoin-5-carboxylate with an absorption maximum at 291 mμ and it is assumed that ring closure was effected.

The simple digestion in boiling water, as well as the treatment with ammonia or sodium ethoxide, was found to convert ethyl N′-phenylthioureidomalonate to ethyl 3-phenyl-2-thiohydantoin-5-carboxylate.

Ethyl N′-tetra-O-acetylglucosylthioureidomalonate when treated with sodium ethoxide and neutralized with acid-form Dowex-50 gave a water-insoluble oil which could not be crystallized. The ultraviolet spectrum of the product indicated that ring closure occurred (Table I).

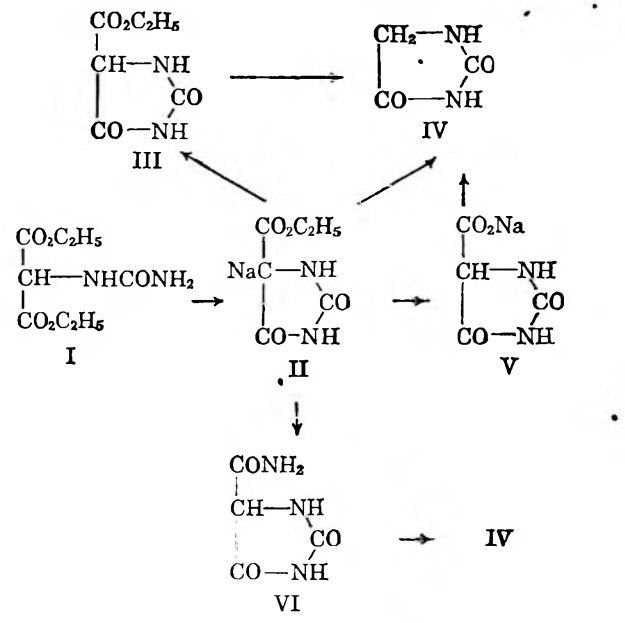
Compound II reduces a variety of mild oxidizing agents including Benedict's solution, Tollens reagent, and potassium triiodide. In experiments where the isolation of III from II was attempted by neutralization with dilute acid followed by multiple extraction with ether, two compounds were isolated in small quantities. These compounds were obtained only when ether was employed and when the reaction mixture was allowed to stand in this solvent. Their elemental analyses corresponded to oxidation products. However, they were not characterized. A reaction employing ether in the isolation procedure which was intended to give ethyl 3-phenylhydantoin-5-carboxylate (VIII) produced in good yield a compound with elemental analyses corresponding to ethyl 5-hydroxy-3-phenylhydantoin-5-carboxylate. This latter compound was degraded with ammonium hydroxide to phenylurea and mesoxalic acid in a manner similar to the "alloxan cleavage" reported by Biltz[6] for the glycol of tetramethyluric acid. No comparable products could be isolated from reactions involving the intentional oxidation of the hydantoin-5-carboxylates with mild permanganate, peroxide, Benedict's solution, or potassium triiodide. In the oxidation products of hydantoin-5-carboxylates, the characteristic ultraviolet absorption at 290 mμ was absent.

Experimental[9]

Ultraviolet Spectra.—Absorption maxima of the anions of the ethyl hydantoin-5-carboxylates faded rapidly owing to hydrolysis. Estimation of the extinction coefficients was accomplished by determining the position of the maxima with an aliquot of alkaline sample. A fresh aliquot of the sample, in which saponification was "quenched" by dilute hydrochloric acid or 1% of ammonium chloride, was placed in the cell. The wave length was set at the maximum and base was added to the cell while absorbance was recorded. The absorbance increased rapidly owing to formation of the anion and then faded rapidly at ambient temperatures as the anion of the ester was hydrolyzed to the hydantoin-5-carboxylate ion. The maximum movement of the pen was used to estimate the extinction coefficient.

SCHEME I

SUMMARY OF REACTIONS OF ETHYL HYDANTOIN-5-CARBOXYLATE



Ethyl Sodiohydantoin-5-carboxylate (II).—Sodium ethoxide solution (0.23 mole), prepared from 5.3 g. of sodium in 300 ml. of absolute alcohol, was added over a period of 2.5 hr. to a stirred refluxing solution of 50 g. (0.23 mole) of ethyl ureidomalonate[11] in 700 ml. of absolute alcohol under nitrogen. After cooling, the solids were collected in a sintered-glass funnel and washed twice with 200-ml. portions of absolute alcohol and once with 200 ml. of absolute ether to give 43.6 g. (98%) of II.

Anal. Calcd. for $C_6H_7N_2O_4Na$: N, 14.4. Found: N, 14.1.

"Autosaponification" and Decarboxylation of II.—A solution of 8.7 g. of II in 500 ml. of water was allowed to stand at room temperature for 48 hr. At the end of this time, the characteristic 292-mμ absorption maximum was absent from the solution. The solution was shaken with 100 ml. of acid-form Dowex-50 and a gas was evolved. The supernatant from this mixture was then passed through a column which contained more of the resin. This effluent plus the column washings was evaporated under reduced pressure to 15 ml. There was deposited 3.6 g. of crystalline hycantoin which without further purification melted at 221–223° (72%).

Ethyl Hydantoin-5-carboxylate (III).—Twenty-five grams of II was dissolved in 200 ml. of ice-cold water. One gram of decolorizing carbon was added; the mixture was shaken for 1 min. The charcoal was removed by filtration and the filtrate was passed rapidly through acid-form Dowex-50 resin in a 25 × 300 mm. column. The total effluent plus washings was evaporated under reduced pressure to a clear sirup. The sirup was dried azeotropically with absolute alcohol and covered with 250 ml. of absolute ether. When this sirup failed to change in appearance after 24 hr., 10 ml. of absolute alcohol was added to the ether. The sirup crystallized after standing an additional 48 hr., m.p. 82°, 13.5 g. (60%). It was very soluble in water, methanol, ethanol, and acetone, and slightly soluble in boiling benzene. The analytical sample was recrystallized from benzene in poor yield, m.p. 87.5–88.5°.

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.8; H, 4.7; N, 16.3. Found: C, 42.0; H, 4.9; N, 16.3.

(9) All melting points were determined by the liquid-bath capillary method with a thermometer which had been calibrated with U.S.P. Melting Point Reference Standards. Hydantoin, after recrystallization from water, melted, then decomposed at 222–223° (lit.[10] m.p. 220°).

(10) C. Harries and M. Weiss, *Ann.*, **327**, 355 (1903).

(11) (a) V. Cerchez, *Bull. soc. chim. France*, [4]**47**, 1287 (1930); (b) J. C. Sheehan and H. K. Bose, *J. Am. Chem. Soc.*, **73**, 1761 (1951).

One gram of III was digested with 10 ml. of concentrated hydrochloric acid and the mixture was evaporated to dryness. The yield of hydantoin on recrystallization from 95% ethanol was 0.35 g. (60%), m.p. 221–222°.

Ethyl 3-Phenylhydantoin-5-carboxylate (VIII).—Sodium ethoxide solution (10 mmoles) was added over a period of 15 min. to a stirred, refluxing solution of 3.0 g. (10 mmoles) of dry ethyl N′-phenylureidomalonate[12] in 25 ml. of absolute alcohol. Reflux was maintained for an additional 15 min. After cooling to room temperature, the solution was diluted with 50 ml. of water and immediately passed through a column containing acid-form Dowex-50. The effluents were then evaporated under reduced pressure. The residual sirup was dissolved in 50 ml. of absolute alcohol and this solution was allowed to evaporate spontaneously. After 3 days, the sirup showed evidence of crystallizing. The mass was covered with 2 ml. of 50% alcohol and triturated. After standing for 24 hr., the entire mass became crystalline. The crystals were collected by filtration, washed with 15 ml. of water, and air dried to give 1.2 g. (47%), m.p. 110°.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.1; H, 4.9; N, 11.3. Found: C, 58.3; H, 5.0; N, 11.6.

A sample of VIII was digested with 6 *N* hydrochloric acid and the mixture was evaporated to dryness. The residue when recrystallized from a small volume of water proved to be 3-phenylhydantoin, m.p. 151–152°, lit.[12,13] m.p. 154–154.5°. A mixture melting point with an authentic sample gave no depression.

In one experiment the reaction mixture of sodium ethoxide and ethyl N′-phenylureidomalonate (20 g.) was acidified with 6 *N* hydrochloric acid in alcohol in lieu of the Dowex-50 column. After cooling, the sodium chloride was removed by filtration. An equal volume of ether was added to the filtrate and on standing a second, much smaller, amount of sodium chloride was obtained. The ether–alcohol filtrate was evaporated under reduced pressure to yield a clear sirup. The sirup was extracted with hot benzene to yield 11.5 g. of crystalline material, the analysis of which corresponded to ethyl 5-hydroxy-3-phenylhydantoin-5-carboxylate, m.p. 116–118° (64%). A mixture melting point with ethyl N′-phenylureidomalonate (m.p. 118–121°) was 95–98°.

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.5; H, 4.6; N, 10.6. Found: C, 54.6; H, 4.5; N, 10.4.

When this substance was treated with ammonium hydroxide, phenylurea was obtained. A second product of this reaction decomposed at 120°. This is the reported decomposition temperature for mesoxalic acid.[14] The reaction mixture also responded to the test of Parrod[15] for mesoxalic acid.

Ethyl N′-Phenylthioureidomalonate (IX).—Phenyl isothiocyanate 18.5 g. (0.137 mole) was added dropwise to 18.5 g. (0.105 mole) of ethyl aminomalonate. The mixture was heated for 10 min. on a steam bath and then cooled in an ice bath. The crystalline mass was then washed by decantation with two 50-ml. portions of ligroin (b.p. 60–90°) and crystallized from absolute alcohol–ligroin to give 24.6 g. (75%), m.p. 98–99°.

Anal. Calcd. for $C_{14}H_{18}N_2O_4S$: C, 54.2; H, 5.8; N, 9.03; S, 10.3. Found: C, 53.9; H, 5.9; N, 9.06 (Dumas)[16]; S, 10.3.

When IX was recrystallized from boiling water, cyclization occurred to give X.

Ethyl 3-Phenyl-2-thiohydantoin-5-carboxylate (X).—An equivalent amount of sodium ethoxide in 100 ml. of absolute alcohol was added dropwise over a period of 0.5 hr. to a stirred, refluxing solution of 15.5 g. of IX in 200 ml. of absolute alcohol. Reflux was maintained for an additional hour. After cooling and neutralization with dilute hydrochloric acid, the mixture was evaporated to dryness under reduced pressure. The boiling absolute alcohol extract of this residue gave on cooling 7.3 g. (55.3%), m.p. 156–157°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.5; H, 4.6; N, 10.6, S, 12.1. Found: C, 53.9; H, 4.4; N, 10.7; S, 12.5.

A sample of the above material was digested with concentrated hydrochloric acid and the mixture was evaporated to dryness. The residue when recrystallized from boiling water proved to be 3-phenyl-2-thiohydantoin.

Ethyl N′-Tetra-O-acetylglucosylureidomalonate (XI).—Ten grams of ethyl aminomalonate was distilled into a chilled receiver which contained 15.7 g. of tetra-O-acetylglucosyl isocyanate.[17] The vessel was kept at ice temperature for an hour. Ten milliliters of chloroform was then added to ensure homogeneity. The mixture was allowed to warm to room temperature and stand for an additional hour. The chloroform was then removed under reduced pressure, and the crude product was recrystallized from equal volumes of absolute alcohol and ligroin to give 14.5 g. (63%), m.p. 157–159°.

Anal. Calcd. for $C_{22}H_{32}N_2O_{14}$: C, 48.2; H, 5.8; N, 5.11. Found: C, 48.0; H, 5.9; N, 5.08.

Ring Closure of XI.—Two milliliters of 1.18 *N* sodium ethoxide solution diluted with 13 ml. of absolute alcohol was added over a period of 15 min. to a stirred, refluxing solution of 1.30 g. (2.36 mmoles) of XI in 35 ml. of absolute alcohol. A precipitate appeared toward the end of the addition. Reflux was maintained for an additional 0.5 hr. After cooling, 20 ml. of water was added to the suspension to give a solution. This solution was passed immediately through a column containing Dowex-50-H^+ and washed with 250 ml. of water. An ultraviolet spectrum of the basicified effluent showed a maximum of 293 mμ. Evaporation under reduced pressure gave a clear glass which did not crystallize.

Ethyl N′-Tetra-O-acetylglucosylthioureidomalonate (XII).—Seven and one-half grams (0.0428 mole) of ethyl aminomalonate was distilled into a chilled receiver which contained 14 g. (0.0361 mole) of tetra-O-acetylglucosyl isothiocyanate.[18] The reaction mixture was allowed to warm to room temperature and the mixture was dissolved in dry benzene to ensure homogeneity. The benzene was removed at reduced pressure and the residue was recrystallized from a mixture of equal volumes of absolute alcohol and ligroin to give 18.0 g. (89%), m.p. 135–137°.

Anal. Calcd. for $C_{22}H_{32}N_2O_{13}S$: C, 46.8; H, 5.7; N, 5.0; S, 5.7. Found: C, 47.1; H, 5.2; N, 4.9; S, 5.6.

Ring Closure of XII.—Two milliliters of 1.18 *N* sodium ethoxide was diluted with 3 ml. of absolute alcohol and added dropwise over a period of 15 min. to a stirred, refluxing solution of 1.33 g. (2.36 mmoles) of XII in 35 ml. of absolute alcohol. Reflux was maintained for an additional 15 min. The solution was allowed to cool to room temperature, and was passed through a column containing Dowex-50-H^+. The column was washed with 200 ml. of 95% alcohol. Evaporation of the effluent at reduced pressure gave a clear, slightly yellow glass which did not crystallize. The ultraviolet spectra of the reaction mixture and the column effluent showed an absorption maximum at 307 mμ.

Hydantoin-5-carboxamide (VI).—Thirty milliliters of frozen concentrated ammonium hydroxide was allowed to warm to a slush and poured on 4 g. of II. After 40 hr. in the refrigerator, the clear solution was evaporated to dryness under reduced pressure. The gummy residue was redissolved in 100 ml. of water and neutralized to a methyl orange end point with dilute hydrochloric acid. After evaporation to dryness under reduced pressure and extraction with cold absolute alcohol, the residue crystallized. It decomposed at 320–325° (1.2 g., 41%).

Anal. Calcd. for $C_4H_5N_3O_3$: N, 29.4. Found: N, 29.4.

Compound VI, prepared by the condensation of carbethoxyaminomalonamide with alcoholic potassium hydroxide, decomposed at 320–325°, and gave an ultraviolet spectrum identical with that of the product of ammonolysis.

(12) E. S. Gatewood, *J. Am. Chem. Soc.*, **47**, 2175 (1925).

(13) J. Guareschi, *Ber.*, **25R**, 327 (1892).

(14) W. Denis, *Am. Chem. J.*, **38**, 561 (1907).

(15) J. Parrod, *Compt. rend.*, **206**, 355 (1938).

(16) This compound, in contrast to several structurally related compounds, was not amenable to Kjeldahl analysis. Several determinations by this method gave a value of 8.00 ± 0.1% nitrogen content.

(17) T. B. Johnson and W. Bergmann, *J. Am. Chem. Soc.*, **54**, 3360 (1932).

(18) K. M. Haring and T. B. Johnson, *ibid.*, **55**, 395 (1933).

Facile Alkyl–Oxygen Ester Cleavage

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Sodium thiophenoxide has been used successfully in an inert solvent (dimethylformamide) at or below room temperature to effect cleavage, at the alkyl–oxygen bond, of certain selected ester functions (principally phenacyl) and to generate as products sodium salts of the corresponding carboxylic acids in good to excellent yields. It is suggested that this procedure is ideally suited for temporarily masking carboxyl functions in synthetic sequences involving sensitive molecules such as the penicillins and peptides.

In synthesis it is frequently desirable to "mask" a carboxyl function, cause a reaction or reactions to occur elsewhere in the molecule, and finally to regenerate selectively the carboxyl function under conditions which will not affect other sensitive features of the molecule. Very few general methods have been devised for accomplishing this sequence. In specific instance, sequences involving the hydrogenolysis of benzyl[2] or *p*-nitrobenzyl[3] esters, the selective saponification of methyl or ethyl esters,[2] and the cleavage under acidic conditions of *t*-butyl ester[4] functions have been successfully employed. More recently, Nefkens[5] has used the phthalimidomethyl group to protect carboxyl functions in a number of peptide syntheses. These methods are limited in scope[2] and generally suffer from the fact that the strong acid or base necessary to effect ester cleavage often destroys other sensitive molecular features. Use of the readily hydrogenolyzed benzyl esters avoids this difficulty; however, problems often arise due to the incompatibility of this method with molecules bearing groups—chiefly sulfur containing—sensitive to catalytic hydrogenation conditions.[2]

We have now developed a simple and effective procedure for the removal of protecting ester functions under very mild and essentially neutral conditions. Phenacyl, phthalimidomethyl,[5] and certain other "active" esters are cleaved at the alkyl–oxygen bond to the corresponding sodium carboxylates by the action of sodium thiophenoxide in an inert solvent at or below room temperature. The literature contains a number of reports[5,6] of formally analogous reactions involving ester cleavage at the alkyl–oxygen bond by nucleophilic agents. These reactions, however, generally require high temperatures and/or prolonged reaction times, conditions much too rigorous for use on highly sensitive molecules. Recently, for example, a series of ester cleavages by mercaptides at temperatures from 79 to 213° with reaction times up to 24 hr. has been reported.[15a] The yields obtained typically were less than 50%. In contrast, using our procedure, phenacyl benzylpenicillinate[16] was cleaved to sodium benzylpenicillinate[17] in 84% yield in 15 min. at room temperature.

In developing this procedure, esters of highly labile[18] benzylpenicillin were chosen as test compounds and the extremely nucleophilic, mildly basic thiophenoxide anion[19] was selected as the cleavage reagent. Dimethylformamide was found to be a satisfactory reaction solvent. Acetone, acetonitrile, and toluene were rejected chiefly owing to the considerably lower solubility of sodium thiophenoxide in these solvents. The methyl,[20] benzyl,[21] and phenacyl[16] esters of benzylpenicillin were prepared and their behavior in the presence of sodium thiophenoxide at various temperatures was studied. The results of these experiments are summarized in Table I.

An examination of the data in Table I demonstrates the critical nature of reaction temperature when dealing with systems containing the labile β-lactam structure. Thus, while no ester cleavage product could be detected when benzyl benzylpenicillinate (2) was stored in the presence of one molar portion of sodium thiophenoxide at 5° for 18 hr., 90% of the unchanged ester was recovered. However, after only 20 min. at 50° only 78% of the ester could be recovered, and after 15 min. at 100° no β-lactam-containing material could be detected. Similarly, phenacyl benzylpenicillinate (3) in the pres-

(1) National Institutes of Health Predoctoral Fellow, 1962–1964.

(2) For references see (a) M. Goodman and G. W. Kenner, *Advan. Protein Chem.*, **12**, 465 (1957); (b) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 928.

(3) H. Swarz and K. Arakawa, *J. Am. Chem. Soc.*, **81**, 5691 (1959); R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **42**, 972 (1959); M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959).

(4) J. C. Sheehan and P. A. Cruickshank, *ibid.*, **78**, 3677 (1956); J. C. Sheehan and K. R. Henery-Logan, *ibid.*, **79**, 1262 (1957); R. W. Roeske, *Chem. Ind.* (London), 1121 (1959); A. Vollmer and M. S. Dunn, *J. Org. Chem.*, **25**, 387 (1960); G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, **82**, 359 (1960).

(5) G. H. L. Nefkens, *Nature*, **193**, 974 (1962); G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. trav. chim.*, **82**, 941 (1963). The phthalimidomethyl ester is readily cleaved under the milder conditions described in this paper (see Table II).

(6) Lithium iodide[7] and other metal halides,[8-10] usually in the presence of a tertiary amine, have been successfully used to effect ester cleavage in a number of examples. Tertiary amines alone cleaved more labile phosphoric acid esters.[11] Fusion of carboxylic acid esters with pyridine hydrochloride[12] produced the corresponding pyridinium carboxylates. Cleavages at the alkyl–oxygen bond of β-lactones,[13] γ-lactones,[14] and certain alkyl esters[15] by alkyl and aryl mercaptides have been reported.

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(9) E. Cherbuliez, J. P. Leber, and M. Bouvier, *Helv. Chim. Acta*, **36**, 1203 (1953).

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(14) H. Plieninger, *Ber.*, **83**, 265 (1950); H. Wenderlein and E. Rager, German Patent 840,996, (June 9, 1952); H. Tani and K. Fudo, *Mem. Inst. Sci. Ind. Research Osaka Univ.*, **6**, 100 (1948); *Chem. Abstr.*, **45**, 10,198 (1951).

(15) (a) W. R. Vaughan and J. B. Baumann, *J. Org. Chem.*, **27**, 739 (1962); (b) J. S. Harding and L. N. Owen, *J. Chem. Soc.*, 1528 (1954); (c) 1536 (1954); (d) L. W. C. Miles and L. N. Owen, *ibid.*, 817 (1952).

(16) H. F. Duffie, Jr., and D. E. Cooper, U. S. Patent 2,650,218 (Aug. 25, 1953).

(17) H. T. Clark, J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 87.

(18) Ref. 17, pp. 86–87.

(19) P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.*, 41 (1956).

(20) Ref. 17, p. 93.

(21) A. W. Chow, N. M. Hall, and J. R. E. Cooper, *J. Org. Chem.*, **27**, 1381 (1962).

TABLE I

$$RCOOR' + PhS^-Na^+ \longrightarrow RCOO^-Na^+ + PhSR'^{a}$$

Ester	Mole ratio PhS^-Na^+/ ester	Reaction time, hr.	Reaction temp., °C.	Yield, %	% ester recovd.
Methyl benzylpenicillinate (1)	1	18	5	0	
Benzyl benzylpenicillinate (2)	1	18	5	0	90
	1	0.33	50	0	78
	1	0.25	100	0	0
Phenacyl benzylpenicillinate (3)	1	18	5	48	
	1	0.17	50	36	
	2	2	5	66	
	2	0.25	25	84	

[a] The isolation and identification of the sulfide coproduct has been previously accomplished.[15a]

ence of one molar portion of sodium thiophenoxide for 18 hr. at 5° was cleaved to the extent of 48%; yet after only 10 min. at 50° only 36% of cleavage product could be isolated. This is indicative of substantial decomposition of the β-lactam system at higher temperature.

In one case (3) an increase in the molar ratio of sodium thiophenoxide markedly increased the yield of reaction product. In other instances a one molar portion of sodium thiophenoxide was adequate to effect cleavage in good yield (see Table II). In general, the sodium carboxylate was isolated by the simple expedient of adding a large excess of acetone to the reaction mixture and after a short time collecting the usually crystalline product by filtration. In order to determine the stability of a sensitive product to the reaction conditions and at the same time to examine the efficiency of the isolation procedure, sodium benzylpenicillinate[17] was stored with one molar portion of sodium thiophenoxide at 5° for 24 hr. Recovery of 85% of unchanged material was achieved. After 10 min. at 25° a similar experiment yielded 88% of unchanged material. These results, when considered with the data in Table I, strongly suggest that the reaction may well be quantitative with the yield loss due to incomplete product isolation. It will be noted in Table II that in certain cases higher yields were obtained, apparently due to more favorable solubility characteristics of the products.

Table II lists several additional examples which help to delineate the scope and versatility of the reaction. While sodium thiophenoxide did not effect cleavage of the less activated benzyl ester (4) at 25°, at 100° cleavage to the extent of 64% was observed, whereas the highly hindered *t*-butyl ester[22] (6) was stable at 100° for 2 hr.

It is noteworthy that sodium thiophenoxide selectively removed phenacyl and similar esters from molecules containing the highly labile[23] phthalimido system (8, 9, 10, and 12) often used for protection of amino functions.[24] Careful examination of the reaction products showed no contamination by material in which ring opening had occurred. That sodium thiophenoxide under mild conditions will effect cleavage of a variety of suitably chosen ester functions is further suggested

(22) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).
(23) Ref. 2b, p. 1249.
(24) Ref. 2b, p. 901.

TABLE II

Ester	Mole ratio PhS^-Na^+/ ester	Reaction time, min.	Reaction temp., °C.	Yield of $RCOO^-Na^+$, %
Benzyl benzoate (4)	1	30	25	0
	1	30	100	64
Phenacyl benzoate (5)	1	30	25	84
	2	30	25	87
t-Butyl benzoate (6)	1	120	25	0
	1	120	100	0
Phenacyl 6-tritylaminopenicillanate (7)	1	30	25	81
Phenacyl 6-phthalimidopenicillanate (8)	1	30	25	76
Phenacyl phthaloylglycinate (9)	2	15	25	99
Benzoin phthaloylglycinate (10)	1	15	25	57
4,4'-Dimethoxybenzoin acetate (11)	1	30	25	91
Phthalimidomethyl acetate (12)	1	30	25	90

by the facile cleavages of benzoin phthaloylglycinate[25] (10) and 4,4'-dimethoxybenzoin acetate[26] (11).

Experimental[27]

Materials.—Sodium thiophenoxide was prepared by the addition of thiophenol to a molar portion of finely dispersed sodium in ether. After 72 hr. of vigorous stirring, sodium thiophenoxide was collected by filtration and stored in a vacuum desiccator until used. The sodium salts of phthaloylglycine,[28] 6-phthalimidopenicillanic acid,[29] and 6-tritylaminopenicillanic acid[29] were prepared by the slow addition of a molar portion of sodium thiophenoxide in a small volume of dimethylformamide to a stirred solution of the appropriate acid in dimethylformamide. When addition was complete, excess acetone[30] was added; after a few minutes the product was collected by filtration.

Action of Sodium Thiophenoxide on Phenacyl Benzylpenicillinate.[16]—A solution of 0.029 g. of sodium thiophenoxide and 0.050 g. of phenacyl benzylpenicillinate[16] in 0.2 ml. of dimethylformamide was allowed to stand at room temperature (25°) for 15 min. To this solution was then added 20 ml. of acetone. This solution was stirred mechanically for 10 min. during which time crystallization occurred. Filtration afforded 0.033 g. (84%) of sodium benzylpenicillin,[17] m.p. 226–227°. The identity of the product was confirmed by mixture melting point and comparison of infrared spectra.

All other ester cleavage reactions were similarly conducted with molar ratios, reaction times, and temperatures as indicated in Tables I and II. In some cases product precipitation occurred before the addition of acetone.[30] In all cases the products were compared spectrally with authentic material and where possible mixture melting points were taken.

Action of Sodium Thiophenoxide on Benzyl Benzylpenicillinate.[21]—A solution of 0.019 g. of sodium thiophenoxide and 0.061 g. of benzyl benzylpenicillinate[21] in 0.3 ml. of dimethylformamide was stored at 5° for 18 hr. To the cold solution was added 10 ml. of pH 7 buffer solution and the resulting solution was extracted three times with 25–50-ml. portions of ether. The dried (magnesium sulfate) ether extract was evaporated to yield 0.055 g. (90%) of a thick oil identified as starting material by infrared spectra.

After 20 min. at 50° a similar experiment yielded 78% of recovered benzyl benzylpenicillinate.[21]

Phenacyl 6-Phthalimidopenicillanate.—A solution of 0.100 g. of 6-phthalimidopenicillanic acid,[29] 0.292 g. (0.04 ml.) of triethylamine, and 0.070 g. of phenacyl bromide in 1 ml. of dimethyl-

(25) J. C. Sheehan and R. M. Wilson, unpublished results.
(26) A. McKenzie and D. J. C. Pirie, *Ber.*, **69**, 861 (1936).
(27) All melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 237 spectrophotometer. We are indebted to Dr. S. M. Nagy and his associates for the microanalytical data.
(28) J. Billman and W. Harting, *J. Am. Chem. Soc.*, **70**, 1473 (1948).
(29) J. C. Sheehan and K. R. Henery-Logan, *ibid.*, **84**, 2983 (1962).
(30) In the case of 6-tritylaminopenicillanic acid, benzene was used to effect isolation.

formamide was refrigerated (5°) for 3 hr. During this time triethylamine hydrobromide crystallized. The mixture was triturated with 10 ml. of ice–water and the resulting precipitate was filtered and dried. This material was suspended in 25 ml. of petroleum ether (b.p. 40–60°) and stirred for 10 min. The crude product (0.117 g.) was then filtered and recrystallized from ethanol to give 0.051 g. of colorless needles, m.p. 144–145°. The infrared spectrum in methylene chloride had strong carbonyl maxima at 1710, 1730, 1760, 1780, and 1800 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{20}N_2O_6S$: C, 62.1; H, 4.32; N, 6.04. Found: C, 61.6; H, 4.35; N, 6.04.

Phenacyl 6-Tritylaminopenicillanate.—A mixture of 0.531 g. of 6-tritylaminopenicillanic acid diethylamine salt[29] and 0.199 g. of phenacyl bromide in 10 ml. of tetrahydrofuran was stirred at room temperature for 18 hr. The precipitated diethylamine hydrobromide (0.117 g., 76%) was removed and the filtrate was evaporated to dryness. The residue was triturated with petroleum ether; the solid material was removed by filtration and recrystallized from a mixture of methylene chloride and ethanol to yield 0.223 g. (39%) of fine colorless platelets, m.p. 184–185°. The infrared spectrum (methylene chloride) exhibits strong carbonyl maxima at 1710, 1760, and 1780 cm.$^{-1}$.

Anal. Calcd. for $C_{35}H_{32}N_2O_4S$: C, 72.7; H, 5.56; N, 4.86. Found: C, 72.6; H, 5.73; N, 5.23.

Phenacyl Phthaloylglycinate.—A mixture of 4.0 g. of phthaloylglycine,[28] 3.1 g. of phenacyl chloride, and 2.0 g. of triethylamine in 150 ml. of 95% ethanol was heated under reflux for 3 hr. and allowed to cool. The product which crystallized was collected and recrystallized from ethanol to yield 2.2 g. of colorless needles, m.p. 149–150°.

Anal. Calcd. for $C_{18}H_{13}NO_5$: C, 66.9; H, 4.02; N, 4.34. Found: C, 67.0; H, 4.01; N, 4.41.

Notes

The Synthesis and Configuration of *cis*- and *trans*-3-Hydroxystachydrine

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The mature fruit of *Courbonia virgata* has been shown to contain the two betaines of 3-hydroxyproline, *cis*- and *trans*-3-hydroxystachydrine.[2] These two isomers, distinguished by the letters a and b, had reported melting points of *ca.* 250° and 209–210°, respectively, with the latter being provisionally assigned the *cis* configuration "because of its greater solubility and slighter tendency to form crystalline salts."[2]

Recently, both *cis*- and *trans*-3-hydroxyproline have been synthesized in this laboratory and the configurations unambiguously assigned by conversion of a precursor, *trans*-3-methoxy-L-proline, to L-methoxysuccinamide.[3]

We have now synthesized *cis*- and *trans*-DL-3-hydroxystachydrine by treatment of the silver salts of *cis*- and *trans*-3-hydroxyproline with methyl iodide in methanol at room temperature. Under these mild conditions epimerization was not observed, in agreement with the analogous 4-hydroxyproline series.[4]

The comparison of the synthetic isomers with authentic samples of stereoisomers a and b revealed that isomer a corresponded to the *trans* configuration and isomer b corresponded to the *cis* configuration. Comparisons were made of melting points, infrared spectra, the relative electrophoretic mobilities, and by paper chromatography in three different solvent systems.

Experimental

Preparation of *cis*-3-hydroxy-DL-stachydrine.—A mixture of 50 mg. (381 μmoles) of *cis*-3-hydroxy-DL-proline, 100 mg. (433 μmoles) of silver oxide, and 125 μl. of water in a 3-ml. centrifuge tube was stirred occasionally at room temperature for 3.25 hr. Approximately one-half of the water was evaporated by means of a stream of nitrogen and 1.0 ml. of methanol was added followed by 50 μl. (113.5 mg., 800 μmoles) of methyl iodide. After 24 hr., an additional 37.5 μl. (85.5 mg., 602 μmoles) of methyl iodide was added and the mixture was stored at room temperature for 48 hr.

The liquor was withdrawn from the centrifuged suspension and the residue washed twice with methanol. Removal of the solvent gave a mixture of pale orange oil and colorless crystals which was triturated with a 2:1 mixture of ethyl alcohol and acetone. The crystalline material was washed twice with a 1:1 mixture of ethyl alcohol and acetone and then dried to give 125 mg. of *cis*-3-hydroxy-DL-stachydrine (41.3%). Two recrystallizations from ethyl alcohol gave small colorless elongated prisms, m.p. 222–222.5°.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.8; H, 8.2; N, 8.8. Found: C, 52.66; H, 8.46; N, 8.31.

Analogous treatment of *trans*-3-hydroxy-DL-proline yielded 47.2 mg. of *trans*-3-hydroxy-DL-stachydrine (77.6%). Recrystallization from ethanol gave colorless prisms, m.p. 232.5–233°.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.8; H, 8.2; N, 8.8. Found: C, 53.47; H, 8.64; N, 8.69.

By comparison, the melting point of isomer a was 251.5–252° dec. and of isomer b was 216.5–217° dec. All melting points were determined under nitrogen in sealed capillaries.

Comparison of *cis* and *trans*-3-Hydroxy-DL-stachydrine with Cornforth's Stereoisomers a and b.—The infrared spectrum of *trans*-3-hydroxy-DL-stachydrine was substantially identical with the spectrum of isomer a with peaks occurring at 3400, 1635, 1468 cm.$^{-1}$ and more than a score in the fingerprint region. The infrared spectrum of *cis*-3-hydroxy-DL-stachydrine was substantially identical with the spectrum of isomer b with peaks occurring at 3530, 1670, 1625, 1485 cm.$^{-1}$ and more than a score in the fingerprint region.

The relative mobilities of the compounds were as follows: paper electrophoresis[5] isomer a, 0.87; *trans*-3-hystach, 0.87; isomer b, 1.00; and *cis*-3-hystach, 1.00.

Paper chromatography was carried out in three different solvent systems [(a) *n*-butyl alcohol–acetic acid–water (4:1:5), 24.5 hr., Whatman No. 1 paper; (b) *n*-propyl alcohol–water (65:35), 19 hr., Whatman No. 1 paper; (c) ethyl alcohol–acetic acid–water (6:1:3), 15.5 hr., Whatman No. 1 paper] on isomer

(1) U. S. Public Health Service Ref. No. 1-F1-GM-14,275-01A1.

(2) J. W. Cornforth and A. J. Henry, *J. Chem. Soc.*, 597 (1952).

(3) J. C. Sheehan and J. G. Whitney, *J. Am. Chem. Soc.*, **84**, 3980 (1962); **85**, 3863 (1963).

(4) A. A. Patchett and B. Witkop, *ibid.*, **79**, 185 (1957).

(5) pH 1.9, 3 kv.; 4 hr.

a (0.19, 0.54, 0.68), *trans*-3-hystach (0.19, 0.54, 0.68), isomer b (0.21, 0.57, 0.70), and *cis*-3-hystach (0.21, 0.57, 0.70).

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Fluoroolefins. X. The Reaction of Propynyllithium with Fluoroolefins

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England and his associates[1] reported briefly that the sodium salt of 1-hexyne and phenylacetylene reacted with tetrafluoroethylene to give, respectively, 30 and 9% of the corresponding difluoroethylene derivative.

$$2R{-}C{\equiv}CNa + CF_2{=}CF_2 \longrightarrow RC{\equiv}CCF{=}CFC{\equiv}CR + 2NaF$$

We now wish to report an extension of this reaction to other fluoroolefins in which propynyllithium was employed as the acetylenic compound and yields of product as high as 73% were realized.

The reactions were carried out by passing the gaseous fluoroolefin into a solution of the acetylide in tetrahydrofuran (THF) at either 0 or −22°. The products were separated by distillation and characterized by elemental analysis and n.m.r. and infrared analysis. The absorption at 4.49 μ served as an indication of the C≡C system while peaks at 5.90 to 6.15 μ showed the C=C group with varying amounts of fluorine.

The infrared absorption due to the triple bond is shifted toward lower wave lengths in the conjugated systems over that in methylacetylene which is noted at 4.67 μ, the values for the C≡C absorption varying from 4.46 to 4.49 μ. On the other hand the absorption in the double-bond region is shifted toward higher wave lengths; thus chlorotrifluoroethylene exhibits C=C absorption at about 5.6 μ whereas 1-chloro-1,2-difluoropent-1-en-3-yne (III) exhibited the double bond stretching absorption at 5.90 μ. Similar shifts were noted for the other enynes. Only one peak in the double-bond region of the spectra was observed in $CH_3C{\equiv}CCF{=}CFCH{=}CH_2$, at 6.01 μ, which presumably is due to the difluoroethylene unit.

Perhalogenated ethylenes reacted readily with the lithium salt to give a mixture of *cis–trans*-substituted ethylenes wherever possible. Tetrafluoroethylene gave only the disubstituted difluoroethylene even with a 50% molar excess of the olefin. Presumably the presence of the triple bond in III causes a drift of electrons away from the difluoromethylene group, thus making it more susceptible to further attack than the difluoromethylene groups in tetrafluoroethylene. Thus no monoelimination product (III) was isolated. In this respect, propynyllithium is different from butyllithium, for Dixon[2] has reported the formation of 80% of 1,1,2-trifluoro-1-hexene in the reaction with tetrafluoroethylene.

$$II + CF_2{=}CF_2 \longrightarrow \underset{III}{CH_3C{\equiv}C{-}CF{=}CF_2} + LiF \xrightarrow{II} \underset{IV}{CH_3C{\equiv}C{-}CF{=}CF{-}C{\equiv}C{-}CH_3} + LiF$$

Trifluorovinyl bromide normally reacts with nucleophilic reagents to give products formed by attack on the difluoromethylene carbon atom. However, methyl- and butyllithium form trifluorovinyllithium and the alkyl halide.[3] It therefore was of some interest to note that propynyllithium attacked in the normal manner to give the bromenyne.

$$CH_3Li + CF_2{=}CFBr \longrightarrow CH_3Br + CF_2{=}CFLi$$

$$C_4H_9Li + CF_2{=}CFBr \longrightarrow C_4H_9Br + CF_2{=}CFLi$$

$$CH_3C{\equiv}CLi + CF_2{=}CFBr \longrightarrow CH_3C{\equiv}CCF{=}CFBr + LiF$$

Neither vinylidene fluoride nor trifluoroethylene gave any of the desired products. Most of the former olefin was recovered. These olefins are lower boiling than most of the others employed, but this is not a contributing factor since tetrafluoroethylene also is volatile. It thus appears that the hydrogen present in these molecules is responsible for their behavior. The compounds may be acid enough to cause the conversion of the propynyllithium to methylacetylene.

Park[4] has recently reported that hexafluorocyclobutene reacts with Grignard reagents to give 75–80% yields of mono- and disubstituted derivatives, and Dixon[2] earlier had found that lithium reagents gave similar results. However, under conditions which gave products with other fluoroolefins, hexafluorocyclobutene gave a black solid product which was not evaluated.

Perfluoropropylene did not give so good a yield of simple products as did the perhalogenated ethylenes. It will be noted that 1,1,2-trifluoro-1,3-butadiene reacted well with propynyllithium to give a conjugated dienyne. A conjugated divnene was obtained from tetrafluoroethylene so that the reaction is a synthetic route to highly conjugated compounds.

The products of the reaction were colorless liquids which generally were thermally unstable. 3,4-Difluorohepta-1,3-dien-5-yne, for example, decomposed at 86° and rapidly turned black at room temperature.

The products from the reaction of propynyllithium and the fluoroolefins are shown in Table I.

It will be noted that increasing the size of the group in $CF_2{=}CFX$ leads to increasing amounts of the less sterically hindered *trans* isomer, thus bromotrifluoroethylene gives a ratio of *trans–cis* isomer of 1:3, whereas the larger substituents, such as $-CF_3$ and vinyl, give exclusively the *trans*-substituted ethylene.

The chemical properties of 1-chloro-1,2-difluoropent-1-en-3-yne (III) were studied. Normally acetylenic compounds react with anhydrous hydrogen fluoride to give a vinyl fluoride or difluoroalkane. Compound III reacted at 85° with hydrogen fluoride to give a mixture of fourteen products. At 25°, no reac-

(1) See D. C. England, L. R. Melby, M. A. Dietrick, and R. V. Lindsey Jr., *J. Am. Chem. Soc.*, **82**, 5112 (1960), for some reactions and references to earlier work.

(2) S. Dixon, *J. Org. Chem.*, **21**, 400 (1956).

(3) P. Tarrant, P. Johncock, and J. Savory, *ibid.*, **28**, 839 (1963).

(4) J. D. Park and R. Fontanelli, *ibid.*, **28**, 258 (1963).

TABLE I

PRODUCTS OF THE REACTION OF PROPYNYLLITHIUM WITH FLUOROOLEFINS

Olefin	Product	Yield, %	*trans*-*cis* (F–F) ratio
$CF_2{=}CCl_2$	$CH_3C{\equiv}C{-}CF{=}CCl_2$	51	
$CF_2{=}CFCl$	$CH_3C{\equiv}C{-}CF{=}CFCl$	73	1:4
$CF_2{=}CFBr$	$CH_3C{\equiv}C{-}CF{=}CFBr$	56	1:3
$CF_2{=}CFCF_3$	$CH_3C{\equiv}C{-}CF{=}CFCF_3$	17	∞
$CF_2{=}CF{-}CH{=}CH_2$	$CH_3C{\equiv}C{-}CF{=}CFCH{=}CH_2$	64	∞
$CF_2{=}CF_2$	$[CH_3C{\equiv}C{-}CF{=}]_2$	35	
$CF_2{=}CHF$		0	
$CF_2{=}CH_2$		0	
$CF_2CF_2CF{=}CF$		0	

tion occurred and at high temperatures, *i.e. ca.* 100°, carbon was the predominant product.

Bromine reacted with an equimolar amount of III to give a 92% yield of product in which bromine added across the triple bond. N.m.r. analysis indicated the presence of each of the four possible isomers with *cis* (F–F) compounds predominantly. The reaction is in contrast to the bromination of hydrocarbon enynes in which addition to the double bonds takes place preferentially.

Water added to III to give a mixture of the two possible ketones.

$$CH_3C{\equiv}C{-}CF{=}CFCl + H_2O \longrightarrow CH_3\overset{O}{\overset{\|}{C}}CH_2CF{=}CFCl + CH_3CH_2\overset{O}{\overset{\|}{C}}CF{=}CFCl$$

The products were characterized by elemental analysis and spectroscopic methods. Infrared analysis indicated α,β-carbonyl conjugation for one while the other had an n.m.r. spectrum which indicated an isolated methyl group. Somewhat more than twice as much unconjugated ketone was obtained. Such results would indicate that the fourth carbon atom bears a larger partial positive charge than the third, since the oxygen appears preferentially on the fourth carbon atom. The contribution of $CH_3{-}\overset{+}{C}{=}\overset{-}{C}{-}CF{=}CFCl$ thus appears more important than $CH_3{-}\overset{-}{C}{=}C{=}\overset{+}{C}F{-}CFCl$ in directing the course of the reaction.

Fluoroolefins such as chlorotrifluoroethylene and tetrafluoroethylene form cyclobutane derivatives with other unsaturated compounds. It was found that chlorotrifluoroethylene reacted with III to give three products. The highest boiling material was not identified but is probably the compound resulting from addition of the two molecules of fluoroolefin to the triple bond and the double bond. The lowest boiling compound has been identified as

$$CH_3C{\equiv}C{-}CF{-}CFCl \quad \text{or} \quad CH_3C{\equiv}C{-}CF{-}CFCl$$
$$\qquad\qquad\quad | \qquad\quad | \qquad\qquad\qquad\quad | \qquad\quad |$$
$$\qquad\quad CF_2{-}CFCl \qquad\qquad\qquad CFCl{-}CF_2$$

since the infrared spectrum showed the presence of the triple bond and the absence of the fluorovinyl structure. The n.m.r. spectrum was complex and not enough comparative data has been published to make a judgment distinguishing one cyclobutane structure from the other. The third component has been identified as

$$CH_3C{=}{=}C{-}CF{=}CFCl \text{ or its cyclobutenyl isomer.}$$
$$\qquad\quad | \qquad\quad |$$
$$\qquad CF_2{-}CFCl$$

This type of structure is indicated by n.m.r. and infrared analysis.

Experimental[5]

Preparation of Propynyllithium.—Methylacetylene from a cylinder was slowly passed into a stirred solution of methyllithium in ether (143 ml., 0.2 mole). A white precipitate of propynyllithium (I) was soon formed and methane was evolved from the solution. The reaction was continued for 6 hr. with the addition of more ether as required.

Reaction of I with Fluoroolefins. General Procedure.—The propynyllithium (see above) was allowed to settle overnight and the supernatent liquid was decanted. Anhydrous tetrahydrofuran (THF, 175 ml.) was then added and was sufficient to dissolve most of I. Reactions were then carried out immediately with this solution since any delay might cause unnecessary cleavage of the THF by I.

The solution of I in THF was cooled to 0 or −22° and slowly treated with the desired fluoroolefin. The reactions were exothermic and the solution immediately turned black. In most of the reactions the olefin was a gas and was passed into the reaction mixture three times in order to ensure complete reaction. Hydolysis of unchanged I was effected by pouring the reaction mixture into ice-cold 3 *N* hydrochloric acid (50 ml.). This whole mixture was steam distilled and a residual black tar was obtained. The organic layer from the steam distillation was separated; the aqueous layer was extracted with three 25-ml. portions of ether. Due to the extreme solubility of THF in water there was still some THF left in the aqueous layer. An analytical v.p.c. check, however, showed that the ether extraction had removed all reaction product from this aqueous portion. The combined organic extracts were dried over calcium chloride and the ether and THF were removed by distillation through either an 18-in. Vigreux or 24-in. Heliplate packed column. The residue consisted of product and THF. The last traces of the latter were removed by repeated washing with water. A check by analytical v.p.c. showed no product to be in the aqueous layer. The organic product was dried over calcium chloride and phosphoric anhydride and was vacuum distilled.

1,1-Dichloro-2-fluoropent-1-en-3-yne (II).—Reaction of 1,1-dichlorodifluoroethylene (40 g., 0.3 mole, 50% excess) with I gave 15.7 g. (51%) of II, b.p. 141.5°, $n^{25}D$ 1.4850.

Anal. Calcd. for: $C_5H_3Cl_2F$: C, 39.25; H, 1.96; F, 12.42. Found: C, 39.16; H, 2.21; F, 12.67.

An infrared spectrum of II had strong bands at 4.49 (C≡C), 7.76, 9.50 (C–F stretching), 10.25, and 12.30, and a medium strong band at 6.15 μ (C=C).

The ultraviolet spectrum (CH_3OH) had λ_{max} 228, 233, and 245 mμ (ε 12,550, 13,730, and 12,060, respectively).

The n.m.r. spectrum was consistent with the structure assigned.

A black tarry material (9.0 g.) was also formed in the reaction.

1-Chloro-1,2-difluoropent-1-en-3-yne (III).—Reaction of chlorotrifluoroethylene (35 g., 0.3 mole, 50% excess) with I gave 20.0 g. (73%) of III, b.p. 97°, $n^{25}n$ 1.4300.

(5) Analyses were by Galbraith Laboratories, Knoxville, Tenn.

Anal. Calcd. for $C_5H_3ClF_2$: C, 44.00; H, 2.20; F, 27.84. Found: C, 44.29; H, 2.42; F, 27.55.

An infrared spectrum of II had strong bands at 4.48 (C≡C), 5.90 (C=C), 7.70, 8.45, 9.51 (C–F stretching), 11.15 μ.

The ultraviolet spectrum (CH_3OH) had λ_{max} 212, 222, and 232 mμ with intensities in the region expected for enynes. The F^{19} n.m.r. spectrum showed peaks corresponding to a mixture of *cis* (F–F) and *trans* isomers in the ratio of 4:1, respectively.

Separation of III into its *cis* and *trans* isomers could be effected to a very limited extent on analytical v.p.c. (dinonyl phthalate on 80–100-mesh Chromosorb, 120°). The two peaks were merged together almost completely and attempts to separate the two compounds by preparative scale v.p.c. were unsuccessful.

A similar reaction was carried out using I (1.3 moles) and chlorotrifluoroethylene (151.5 g., 1.3 moles) and resulted in the formation of 123 g. of III (69.5%) and 10 g. of tar.

1-Bromo-1,2-difluoropent-1-en-3-yne (IV).—Reaction of bromotrifluoroethylene (48 g., 0.3 mole, 50% excess) with I gave 20.0 g. (55.5%) of IV, b.p. 122.0° $n^{25}D$ 1.4590.

Anal. Calcd. for $C_5H_3BrF_2$: C, 33.18; H, 1.66; F, 20.99. Found: C, 32.89; H, 1.86; F, 21.22.

Vapor phase chromatography of IV showed that two compounds, IVa and IVb, were present with very similar retention times. The F^{19} n.m.r. spectrum showed four peaks corresponding to a mixture of *cis* (F–F), and *trans* isomers in the ratio of 3:1, respectively. The *cis* isomer, b.p. 122.0°, $n^{25}D$ 1.4589, was isolated in the pure form by preparative scale v.p.c. by collecting a limited amount of material as it first emerged from the column. An infrared spectrum of IVa had strong bands at 4.48 (C≡C), 5.98 (C=C), 7.72, 8.50 (sh), 8.60, 9.70, 11.20, and 11.40 μ. The ultraviolet spectrum (CH_3OH) had λ_{max} 224 and 234 mμ (ε 14,280 and 10,440, respectively) with a shoulder at 213 mμ.

An infrared spectrum of the mixture of IVa and IVb had strong bands at 4.48 (C≡C), 5.45, 5.74, 5.98 (C=C), 7.72, 8.50, 8.60, 9.70, 11.20, and 11.40 μ. The ultraviolet spectrum of this mixture was essentially the same as obtained from the *cis* isomer.

1,1,1,2,3-Pentafluorohex-2-en-4-yne (V).—Reaction of hexafluoropropene (45 g., 0.3 mole, 50% excess) with I (0.2 mole) at −22° gave 5.7 g. (17%) of V, b.p. 79.5–80°, $n^{21}D$ 1.3591.

Anal. Calcd. for $C_6H_3F_5$: C, 42.36; H, 1.76; F, 55.89. Found: C, 42.55; H, 1.95; F, 56.17.

An infrared spectrum of V had strong bands at 4.46 (C≡C), 5.90 (C=C), 7.25, 7.80, 8.30, 8.49, 8.70, and 9.43 μ. The ultraviolet spectrum (CH_3OH) had λ_{max} 221 mμ (ε 14,880) with a shoulder at 228 mμ. The n.m.r. spectrum was in accord with the above structure with only one *trans* isomer present.

Black tarry material (15 g.) was formed in the reaction. Separation of V from the THF was accomplished using a 24-plate spinning band column and a final purification was carried out using preparative scale v.p.c.

3,4-Difluorohepta-1,3-dien-5-yne (VI).—Reaction of 1,1,2-trifluorobutadiene (27.0 g., 0.21 mole) with I (0.2 mole) gave 16.4 g. (64%) of VI, b.p. 86° dec., $n^{21}D$ 1.4970.

Anal. Calcd. for $C_7H_6F_2$: C, 65.66; H, 4.68; F, 29.67. Found: C, 65.44; H, 4.72; F, 29.92.

An infrared spectrum of VI had strong bands at 4.50 (C≡C), 6.01 (C=C), 7.55, 8.05, 9.22, 9.91, 10.20, and 10.90 μ. The ultraviolet spectrum (CH_3OH) had λ_{max} 260 mμ (ε 24,570). The n.m.r. spectrum showed that only the *trans* form was present.

A black solid (4.5 g.) was also formed in the reaction and was not evaluated.

VI was colorless when pure but rapidly turned black at room temperature in the presence of air.

4,5-Difluoroocta-2,6-diyn-4-ene (VII).—Reaction of tetrafluoroethylene (30 g., 0.3 mole, 50% excess) with I at −22° gave, after removal of the THF by distillation and washing with water, 4.9 g. (35%) of VII, m.p. 76–78°, which was purified by sublimation.

Anal. Calcd. for $C_8H_6F_2$: C, 68.60; H, 4.28; F, 27.13. Found: C, 68.71; H, 4.50; F, 27.44.

An infrared spectrum of VII showed strong bands at 4.50 (C≡C), 7.85, 8.95, 9.50, and 12.41, with a medium strong band at 4.38 μ. No band in the double-bond region was present.

The ultraviolet spectrum (CH_3OH) had λ_{max} 249 and 260 mμ (ε 32,690, and 30,250, respectively) with a shoulder at 240 mμ.

The F^{19} n.m.r. spectrum exhibited a single peak at 65.1 p.p.m. relative to external CF_3COOH. The two fluorines were equivalent and therefore no characteristic *trans* F–F coupling would be shown.

Tar (4.0 g.) was obtained.

Attempted Reactions of I with Other Fluoroolefins. Trifluoroethylene.—Reaction of trifluoroethylene (24.6 g., 0.3 mole) with I (0.2 mole) at 0° gave only 8.0 g. of a black solid.

Hexafluorocyclobutene.—Reaction of hexafluorocyclobutene (18.5 g., 0.114 mole) with I gave 25 g. of a black solid which was not evaluated.

1,1-Difluoroethylene.—No reaction was observed when 1,1-difluoroethylene was passed into a solution of I at either −78, −22, 0, or 25°. No discoloring of the solution occurred and most of the 1,1-difluoroethylene was recovered.

Bromination of III.—III (15.0 g., 0.11 mole) was stirred at room temperature and slowly treated with bromine (17.5 g., 0.11 mole). The red liquid formed was shown by analytical v.p.c. to contain no III. Vacuum distillation gave 30.0 g. of 3,4-dibromo-1-chloro-1,2-difluoropenta-1,3-diene (92.5%), b.p. 182–183°, $n^{21}D$ 1.5192.

Anal. Calcd. for $C_5H_3Br_2ClF$: C, 20.42; H, 1.01; F, 12.82. Found: C, 20.51; H, 1.19; F, 13.09.

An infrared spectrum showed strong bands at 5.85 and 6.15 (C=C) and 7 to 10 μ (C–F stretching). There was no absorption between 4 and 5 μ (C≡C) thus showing that additions had occurred only to the triple bond.

Addition of Water to III.—II (20.0 g., 0.147 mole) was stirred and refluxed for 18 hr. with 100 ml. of 10% aqueous sulfuric acid containing mercuric sulfate (5.0 g.). A brown inorganic solid (4.0 g.) was formed during the reaction. Organic material (16.0 g.) was separated from the water and distilled at reduced pressure (50 mm.) through a 18-in. spinning band column into fraction 1, b.p. 34–37°, 5.2 g.; fraction 2, b.p. 50–58°, 1.3 g.; fraction 3, b.p. 65–75°, 2.5 g.; and a residue of 1.3 g. Fraction 1 was starting material. Fraction 2 was identified as 1-chloro-1,2-difluor-1-en-3-one (VIII, 11%), b.p. 122.0°, $n^{28}D$ 1.4148.

Anal. Calcd. for $C_5H_5ClF_2O$: C, 38.88; H, 3.24. Found: C, 39.12; H, 3.28.

An infrared spectrum showed strong bands at 5.80 (C=C), 6.12 (C=O in α,β-unsaturated ketone), 7.95, 8.45, 9.15, 9.44, and 11.29 μ. C–H stretching showed at 3.35, 3.40, 3.44, and 3.47 μ, indicating CH_3 and CH_2.

Fraction 2 was shown to consist of two components, one of which was VIII. Preparative scale v.p.c. was used to isolate the other component which was identified as 1-chloro-1,2-difluoropent-1-en-4-one, (3.8 g., 23%), b.p. 148–149°, $n^{21}D$ 1.4154.

Anal. Calcd. for $C_5H_5ClF_2O$: C, 38.88; H, 3.24. Found: C, 39.27; H, 3.15.

N.m.r. indicated an isolated methyl group in the molecule with 40% *cis* and 60% *trans* (F–F) structure.

An infrared spectrum showed strong bands at 5.76 (doublet C=C and C=O) and 7.0 to 10.0 μ (C–F stretching).

Some higher boiling material (0.6 g.) was also isolated from fraction 3, but an infrared spectrum gave no indication of the structure.

Reaction of III with Chlorotrifluoroethylene.—A 335-ml. stainless steel autoclave was charged with III (19.5 g., 0.143 mole) and chlorotrifluoroethylene (52 g., 0.446 mole) and was shaken at 190° for 7 hr. Unchanged chlorotrifluoroethylene (35 g.) was vented from the autoclave leaving behind 29 g. of liquid product. Fractional distillation at atmospheric pressure afforded 12.1 g. of 1,2-dichlorohexafluorocyclobutane, b.p. 59–60°, lit.[6] b.p. 59.9°, and 6.7 g. of recovered III (65.5% conversion). The distillate was shown by analytical v.p.c. to contain three components. Preparative scale v.p.c. (silicone elastomer 125°) afforded 1.25 g. of $CH_3-C\equiv C-CF(-CF_2-CFCl)-CFCl$ (6.5%) or its 1,3-dichlorocyclobutyl isomer, b.p. 148.5°, $n^{20}D$ 1.4064.

Anal. Calcd. for $C_7H_3Cl_2F_5$: C, 33.16; H, 1.19; F, 37.55. Found: C, 33.01; H, 1.43; F, 37.79.

An infrared spectrum showed strong bonds at 4.44 (C≡C) and 7.5 to 9.1 μ (C–F).

The second component was isolated and identified as $CH_3-C\equiv C-CF=CFCl$ or its cyclobutenyl isomer (6.7 g., 29%), CF_2-CFCl, b.p. 163.5–164°, $n^{20}D$ 1.4419.

(6) A. L. Henne and R. P. Ruh, *J. Am. Chem. Soc.*, **69**, 279 (1947).

Anal. Calcd. for $C_5H_3Cl_2F_5$: C, 33.16; H, 1.19; F, 37.55. Found: C, 33.09; H, 1.39; F, 37.87.

An infrared spectrum showed strong bands at 4.94 and 6.14 (C=C) and 7.15 to 8.85 μ (C–F).

The third component was not identified.

A similar experiment carried out at 150° for 12 hr. gave very little reaction of III with chlorotrifluoroethylene.

Reaction of III with Hydrogen Fluoride.—III (15.0 g., 0.11 mole) and anhydrous hydrogen fluoride (4.4 g., 0.22 mole) were stirred in a nitrogen atmosphere at −22° for 1 hr. and then kept at 25° for 12 hr. The reaction mixture was then poured onto ice (75 g.), washed with three 10-ml. portions of water, and dried over calcium chloride. Analytical v.p.c. showed that only unchanged III was present.

The same quantities of reactants were sealed in a 335-ml. stainless steel autoclave and heated to 85° for 20 hr. The product was worked up as before to give a black liquid (14.0 g.). This was shown by analytical v.p.c. to consist of at least fourteen components. Some free carbon was deposited on the sides of the autoclave during the reaction.

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Fluoroolefins. XI. The Conversion of Fluoroolefins to Fluoroalkyl Nitroso Compounds *via* Alkylmercury Compounds

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Fluoroalkyl nitroso compounds have been prepared by the reaction of perfluoroalkyl iodides with nitric oxide,[1] by the addition of nitrosyl chloride to a fluoroolefin,[2] or more recently by the thermal decomposition of perfluoroacyl nitrites.[3] We now wish to report that fluoroalkyl nitroso compounds can be made from the reaction of fluoroalkylmercury compounds with nitrosyl chloride. Since the fluoroalkylmercury compounds are made by adding mercuric fluoride across the double bond of the olefin, the over-all reaction involves the addition of nitrosyl chloride to a fluoroolefin in a two-step operation.

$$2CF_2{=}CFCF_3 + HgF_2 \longrightarrow [(CF_3)_2CF]_2Hg \qquad (1)$$

$$[(CF_3)_2CF]_2Hg + 2NOCl \longrightarrow (CF_3)_2CFNO + HgCl_2 \qquad (2)$$

The addition of mercuric fluoride to a series of fluoroolefins was carried out by Krespan's method[4] in which hydrogen fluoride was used as the solvent instead of arsenic trifluoride. Since the completion of our work, Miller[5] has described the addition of mercuric fluoride to $CF_2{=}CHCF_3$ and $CF_2{=}CFCF_3$ in the presence of hydrogen fluoride, while Aldrich[6] has described similar reactions with 1,1-dichlorodifluoroethene and a series of longer chain polyfluoroolefins containing the $-C{=}CF_2$ group.

It appears that the addition of mercuric fluoride to fluoroolefins is limited to those containing a difluoromethylene group, *i.e.*, terminal olefins, since neither hexafluorocyclobutene nor 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene formed an adduct.

The reaction of $(CF_3CFCl)_2Hg$ and nitric oxide was attempted in the gas phase under the influence of ultraviolet radiation. However, the formation of the blue nitroso compound occurred so slowly that this method was judged unsatisfactory. The reaction of nitrosyl chloride with certain fluoroalkylmercury compounds did take place at a reasonable rate in dimethylformamide (DMF) and $CF_3CFClNO$, $(CF_3)_2CFNO$, and CF_3CCl_2NO were prepared from the corresponding fluoroalkylmercury. This type reaction was first used by Baeyer[8] in preparing nitrosobenzene from diphenylmercury and nitrosyl chloride.

The reaction was carried out at room temperature with DMF. Although the reaction seemed to proceed at a comparable rate in dimethyl sulfoxide, the yield of nitroso compound was considerably lower. In the dimethyl ether of diethylene glycol (diglyme) the reaction was much too slow to be useful while in acetone and in benzene the desired reaction did not take place. It is not practical to increase the temperature of the reaction appreciably since nitroso compounds disproportionate rapidly at elevated temperatures.[9]

The great increase in reaction rate with increase in dielectric constant of the solvent seems to indicate that the formation of a charged species is a factor in the over-all rate.

Qualitatively, the order of reactivity of the alkylmercury compounds with nitrosyl chloride is $(CF_3CFCl)_2Hg > [(CF_3)_2CF]_2Hg > (CF_3CCl_2)_2Hg > (CF_3CHF)_2Hg >> (CF_3CFBr)_2Hg$ and $(CF_3CH_2)_2Hg$. No nitroso compound was obtained from the last two mercury derivatives.

The reaction of $(CF_3CHF)_2Hg$ with nitrosyl chloride did not give the expected nitroso compound nor the oxime that might be derived from it. Instead, 1-chloro-1-nitrosotetrafluoroethane, 1,1-dichlorotetrafluoroethane, and 1-chloro-1,3,3,3-tetrafluoroethane were obtained.

$$(CF_3CHF)_2Hg \xrightarrow{NOCl} CF_3CFClNO + CF_3CFCl_2 + CF_3CHFCl$$

Similar results were obtained in another investigation when nitrosyl chloride was added to trifluoroethylene.

$$CF_2{=}CFH + NOCl \longrightarrow CF_2ClCFClNO$$

It seems unlikely that the hydrogen atoms of such dissimilar compounds as $(CF_3CHF)_2Hg$ and $CF_2{=}CFH$ would be replaced by chlorine and the resulting mercury compound and olefin then undergo the cleavage reactions to give $CF_3CFClNO$ and $CF_2ClCFClNO$.

(1) R. N. Haszeldine, *J. Chem. Soc.*, 2075 (1953).

(2) J. D. Park, A. P. Stefani, and J. R. Lacher, *J. Org. Chem.*, **26**, 4017 (1961).

(3) J. D. Park, R. W. Rosser, and J. R. Lacher, *ibid.*, **27**, 1462 (1962).

(4) C. G. Krespan, *ibid.*, **25**, 105 (1960).

(5) W. T. Miller, Jr., M. B. Friedman, J. H. Fried, and H. F. Koch, *J. Am. Chem. Soc.*, **83**, 4105 (1961).

(6) P. E. Aldrich, E. G. Howard, W. J. Linn, W. J. Middleton, and W. H. Sharkey, *J. Org. Chem.*, **28**, 184 (1963).

(7) The reaction of mercuric fluoride and bromotrifluoroethylene in hydrogen fluoride gave a 63% yield of bis(1-bromo-1,2,2,2-tetrafluoroethyl)mercury, m.p. 53–56°. *Anal.* Calcd. for $C_4Br_2F_8Hg$: Br, 28.51. Found: Br, 28.23.

(8) A. Baeyer, *Ber.*, **7**, 1638 (1874).

(9) D. E. O'Connor and P. Tarrant, *J. Org. Chem.*, **29**, 1793 (1964).

A more probable course would involve the replacement of hydrogen in the corresponding oximes and could arise as follows.

$$(CF_3CHF)_2Hg \xrightarrow{NOCl} CF_3CHFNO \rightleftharpoons CF_3CF{=}NOH \xrightarrow{Cl_2 \text{ or } NOCl} CF_3CFClNO$$

$$CF_2{=}CHF + NOCl \longrightarrow CF_2ClCHFNO \rightleftharpoons CF_2ClCF{=}NOH \xrightarrow{Cl_2 \text{ or } NOCl} CF_2ClCFClNO$$

In every reaction of a fluoroalkylmercury compound with nitrosyl chloride that took place, except with bisheptafluoroisopropylmercury, some of the corresponding dichlorofluoroalkane was obtained. These

$$(CF_3CFCl)_2Hg \xrightarrow{NOCl} CF_3CFCl_2\ (5\%)$$

$$(CF_3CCl_2)_2Hg \xrightarrow{NOCl} CF_3CCl_3\ (37\%)$$

compounds could arise either from the displacement of mercury by chlorine or from the decomposition of the resulting α-chloronitroso compound by a free-radical process.[9] Since the last step of the reaction is essentially irreversible, the extent to which the more highly chlorinated product is formed depends on the stability of the free radical. These are $CF_3CCl_2\cdot$ > $CF_3CFCl\cdot$ > $(CF_3)_2CF\cdot$. Since the bisheptafluoroisopropylmercury gave no chloride in the presence of nitrosyl chloride and the other compounds gave polychlorides in amounts proportional to the radical stabilities, the radical process probably operates in this reaction.

$$CF_3CCl_2NO \longrightarrow CF_3CCl_2\cdot \xrightarrow[NOCl]{Cl_2 \text{ or}} CF_3CCl_3$$

Experimental[10]

Reactions of Alkylmercury Compounds with Nitrosyl Chloride.—The general procedure used in preparing the nitroso compounds is as follows. Dimethylformamide and the mercury alkyl were added to a 250-ml., three-necked flask, fitted with a magnetic stirrer, a gas inlet tube, and a take-off leading to a Dry Ice–acetone-cooled condenser. Nitrosyl chloride was bubbled into the solution until it was dark red. The reaction proceeded very slowly, normally requiring from 3 to 4 days. More nitrosyl chloride was added from time to time when the color of the solution had changed from dark red to green. Most of the nitroso compound passed into the Dry Ice trap as it was formed. The flask was swept with nitrogen at the end of the reaction. The product was washed twice with sodium bicarbonate to remove oxides of nitrogen and was then purified by passing it through a preparative scale vapor phase chromatographic column. The 2.5 cm. × 250 cm. column was packed with Celite with dinonyl phthalate used as the liquid phase and was operated at room temperature. This operation was necessary because the boiling point of the major impurity is very nearly the same as that of the nitroso compound. The results are shown in Table I.

TABLE I

PRODUCTS FROM THE REACTION OF FLUOROALKYLMERCURY COMPOUNDS WITH NITROSYL CHLORIDE

Mercury compound formula	Mole	Products, %	
$(CF_3CFCl)_2Hg$	0.095	$CF_3CFClNO$,[a] 79	CF_3CFCl_2,[b] 5
$[(CF_3)_2CF]_2Hg$	0.037	$(CF_3)_2CFNO$, 64	
$(CF_3CHF)_2Hg$	0.057	$CF_3CFClNO$,[c] 14	CF_3CFCl_2[b] CF_3CHFCl[d]
$(CF_3CCl_2)_2Hg$	0.10	CF_3CCl_2NO,[e] 28	CF_3CCl_3,[b] 14

[a] The n.m.r. F^{19} spectrum confirmed the structure $CF_3CFClNO$ which had a b.p. of −5° determined isoteniscopically. *Anal.* Calcd. for C_2ONClF_4: N, 8.46; Cl, 21.43; mol. wt., 165.5. Found: N, 7.65; Cl, 20.63; mol. wt., 165. [b] Identified by comparison of its infrared spectrum with an authentic sample and by its n.m.r. spectrum. [c] The boiling point of this material is −5° and its infrared spectrum was found to be identical with that of an authentic sample of $CF_3CFClNO$. [d] Identified by its n.m.r. and infrared spectra. [e] B.p. 36°, determined isoteniscopically. *Anal.* Calcd. for $C_2ONCl_2F_3$: Cl, 38.96. Found: Cl, 38.60.

(10) Analyses were by Galbraith Laboratories, Knoxville, Tenn.

Acknowledgment.—We are grateful to the U. S. Army Natick Laboratories, Natick, Massachusetts, for financial support of this project. Dr. Juan C. Montermoso acted as the project officer.

1-Deoxy-1-(methylnitrosamino)pentitols[1]

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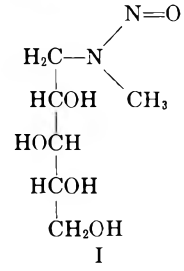
The synthesis of 1,4-dideoxy-1,4-bis(methylnitrosamino)erythritol and the corresponding 1,6-disubstituted mannitol has recently been reported.[3a] Interest in this type of compound is due to the postulate[3b] that alkyl N-nitroso compounds are metabolized to diazoalkanes which can alkylate essential cell constituents and result in an altered metabolic pattern.

The isolation of a small proportion of 1-deoxy-1-(methylnitrosamino)-D-xylitol during the synthesis of the 1,4-anhydrides of D-iditol and D-gulitol[4] led to the present study. The synthesis of the anhydrides involved nitrous acid deamination of the 1-amino-1-deoxyalditols derived from the condensation of nitromethane[5] with D-xylose. The nitrosamine (I) is the



I

product expected from the treatment of a methylglycamine (1-deoxy-1-methylaminoalditol) with nitrous acid[6] and the methylglycamine could have arisen from the condensation of nitromethane, or a reduction product thereof, with D-xylose so as to have resulted in the

(1) Supported by a grant from the Atlas Chemical Industries, Wilmington, Del.

(2) Department of Biochemistry, State University of Iowa, Iowa City, Iowa.

(3) (a) F. Berger, S. S. Brown, C. L. Leese, G. M. Timmis, and R. Wade, *J. Chem. Soc.*, 846 (1963); (b) D. F. Heath, *Nature*, **192**, 170 (1961).

(4) R. Barker, *J. Org. Chem.*, **29**, 869 (1964).

(5) J. C. Sowden and H. O. L. Fischer, *J. Am. Chem. Soc.*, **69**, 1963 (1947).

(6) A. I. Vogel, "Practical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 426.

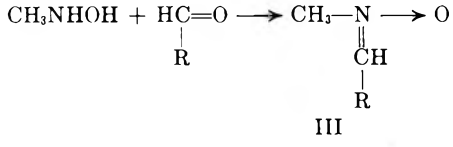
formation of a new C–N bond rather than the usual C–C bond.

The reductive amination of reducing sugars in the presence of amines,[7] ammonia,[8] and hydrazine[9] has been reported, as has the reduction of sugar oximes.[10] Since, in the preparation from which I was isolated,[4] a reduction was performed in which one would expect there to be small amounts of reducing sugar (D-xylose) and nitromethane as contaminants, a mixture of D-xylose and nitromethane was hydrogenated over platinum black in an aqueous acetic acid medium. The product of the hydrogenation was treated with nitrous acid and from that reaction I was isolated in high yield (70–80% based on D-xylose).

Similar yields of the corresponding products from D-ribose, D-lyxose, and D-arabinose were obtained using the same procedure.

Nitromethane does not appear to condense with reducing sugars under acidic conditions; therefore, the condensation probably involves a reduction product of nitromethane which is formed *in situ*. The final reduction product of nitromethane, methylamine, under the conditions used in the reduction does not give an appreciable yield of 1-deoxy-1-methylamino-D-xylitol (II). The yield of II after a greatly extended period of reduction was less than 20%. This finding is interpreted as indicating that a different condensation product is formed and reduced in the two cases.

The product of the second step in the reduction of nitromethane is probably methylhydroxylamine. Under acidic conditions the latter would condense with an aldehyde to form a nitrone (III) which on further reduction would form a methylamine derivative such as II.



III

In support of this hypothesis is the finding that, whereas a mixture of hydroxylamine and D-xylose is reduced to give a high yield of a basic nitrogenous derivative which can be deaminated with nitrous acid with the formation of 1,4-anhydro-D-xylitol, the substitution of ammonia for hydroxylamine gives essentially no condensation product.

The nitroso compounds derived from the pentoses are readily crystallizable, slightly yellow compounds. They consume 3 molar equiv. of periodate with the release of 2 molar equiv. of formic acid and 1 of formaldehyde. They give a typical Liebermann nitroso test. They have absorption maxima at 292 mμ and molar extinction coefficients of 27 ± 1. They can be reduced readily over platinum to the corresponding secondary amine.

Preliminary testing data from the Cancer Chemotherapy National Service Center indicates that the compounds described here are neither carcinostatic nor toxic.

(7) F. Kagen, M. A. Rebenstorf, and R. V. Heinzehman, *J. Am. Chem. Soc.*, **79**, 3541 (1957).

(8) F. W. Holly, E. W. Peel, R. Mozingo, and K. Folkers, *ibid.*, **72**, 5416 (1950).

(9) R. U. Lemieux, U. S. Patent 2,830,983 (1958); *Chem. Abstr.*, **52**, 14,668 (1958).

(10) L. Maquenne and E. Roux, *Compt. rend.*, **132**, 980 (1901).

Experimental[11]

1-Deoxy-1-(methylnitrosamino)-D-xylitol.[12]—To a solution of 10 g. (66 mmoles) of D-xylose and 10 ml. (185 mmoles) of nitromethane in 200 ml. of 25% aqueous acetic acid in a pressure bottle was added 1 g. of platinum oxide. The air in the system was displaced with hydrogen to a pressure of 30 lb.[13] and the bottle was shaken vigorously. The hydrogen uptake was complete in 24 hr. at which time 14.0 l. (0.60 mole) had been taken up. The catalyst was removed by filtration and washed with water. The combined filtrates were concentrated to dryness *in vacuo* at 60°. The residue was taken up in water and passed over a column containing 200 ml. of IR 120 (H^+). The column was washed until the eluate was neutral. Concentration of this acidic eluate gave 1.1 g. of a mixture of D-xylose and xylitol (determined by chromatography).

The column was then eluted at the rate of 5 ml. per minute[14] with 11.2% aqueous ammonia. The first 300 ml. of alkaline eluate was collected and concentrated *in vacuo* at 40° to give 8.6 g. of a slightly yellow sirup which was dissolved in 200 ml. of 25% aqueous acetic acid and 7 g. of sodium nitrite added. After 4 hr. the reaction was boiled to remove the excess nitrous acid, and then concentrated at 60° *in vacuo*. The residue was taken up in water, and after deionization with IR 120 (H^+) and IR 45 a pale yellow solution was obtained. Concentration *in vacuo* gave 8.0 g. of crystalline material which was taken up in hot isopropyl alcohol (50 ml). On cooling 7.4 g. of pale yellow crystals was obtained with m.p. 120–121°. A second crop of 0.8 g. was obtained from the mother liquors. Recrystallization from the same solvent gave 6.3 g. of material, m.p. 121–122°, $[\alpha]_D$ −16.5° (*c* 3, water), and mol. wt. 193 ± 2 (by osmometry).

Anal. Calcd. for $C_6H_{14}N_2O_5$ (194.2): C, 37.1; H, 7.28; N, 14.45. Found: C, 36.9; H, 7.39; N, 14.19.

Similar yields were obtained when D-xylose, D-arabinose, and D-ribose were used instead of D-xylose. The product from the D-ribose preparation was recrystallized from ethyl acetate containing a small proportion of methanol.

The derivatives had the properties shown in Table I.

TABLE I

1-Deoxy-1-(methylnitrosamino)-	M.p., °C.	$[\alpha]^{25}D$ (*c* 3, water)	Analysis, % C	H	N
D-ribitol	85–87	−17.2°	37.0	7.46	14.20
D-lyxitol	102–103	+ 3.7°	36.9	7.18	14.41
D-arabitol	142–144	+16.5°	37.1	7.19	14.63

(11) Melting points are corrected. Paper chromatograms (descending) were run on Whatman 31 with butanone–water (25:2 v./v.).

(12) The assumption is made that the configuration of the starting material is retained in the product.

(13) The reaction proceeds equally well at atmospheric pressure.

(14) The column must be eluted slowly to allow time for the heat of reaction of the ammonia with the resin to dissipate.

The Assignment of Configurations to Three Aminodeoxyheptulosans by Proton Magnetic Resonance

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In a recent communication,[1] the syntheses of three stereoisomeric 2,7-anhydro-4-nitro-4-deoxy-β-D-heptulopyranoses and of their reduction products, the corresponding amine hydrochlorides, was described. On the basis of experiences derived from analogous syntheses, it was assumed that the new compounds bear

(1) H. H. Baer, *J. Org. Chem.*, **28**, 1287 (1963).

their nitrogen functions in equatorial disposition. This would place the compounds into any three of the *allo*, *altro*, *gulo*, and *ido* series. Comparison of molecular rotation data lent support to that assumption and, in fact, made it possible to suggest tentatively the *gulo* configuration for one and the *altro* configuration for a second one of the stereoisomeric amino sugar derivatives. No such assignment was made for the third isomer.[1]

A study of the proton magnetic resonance (p.m.r.) spectra of the fully acetylated amino sugars has now served to confirm unequivocally the hitherto tentative *gulo* and *altro* configurations of the respective isomers, and to establish the *allo* configuration for the remaining isomer. The crystalline acetates prepared for the purpose of this investigation are 4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-alloheptulopyranose (I),[2a] 4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-guloheptulopyranose (II),[2b] and 4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-altroheptulopyranose (III).[2c]

It has been found by Lemieux, Kullnig, Bernstein, and Schneider[3] that in carbohydrates of pyranose structure axial acetoxy substituents resonate at lower field (τ-value) than equatorial substituents, and that the coupling constant between adjacent diaxial ring hydrogens is greater than that between axial–equatorial or equatorial–equatorial ring hydrogens. These findings have since been confirmed by many workers and have been used extensively to determine unknown configurations of carbohydrates. Of particular relevance to the present investigation was the study[4] of numerous 2,3,4-tri-*O*-acetyl- and 3-acetamido-3-deoxy-2,4-di-*O*-acetyl-1,6-anhydro-β-D-hexopyranoses. The fact that the precise stereochemistry of these hexosan derivatives could be determined by the p.m.r. method lent confidence to the deductions made herein on the closely related heptulosan system.

The chemical shifts for the substituent resonances and where possible for the ring hydrogens of I, II, and III are shown in Table I. The ring-hydrogen resonances are shown in Fig. 1. Although the assignments of the H-3 and H-5 hydrogens are unequivocal in all cases, the remaining assignments are only tentative and are based on the band widths calculated from the splittings of the H-3 and H-5 multiplets. For all three compounds the resonance of highest field in the acetate region was assigned to the equatorial acetamido group.[5,6] One of the compounds (I) showed acetoxy resonances at τ 7.81, 7.84, and 7.91, which indicated that it had two axial and one equatorial acetoxy groups and hence that it had the D-*allo* configuration. Both the other compounds exhibited one axial and two equatorial acetoxy resonances so that they were evidently the D-*altro* and D-*gulo* isomers. A differentiation between the two had yet to be provided.

TABLE I

CHEMICAL SHIFTS[a] OF SOME HEPTULOSAN DERIVATIVES

Compound (configuration)	H-3	H-5	OAc-1	OAc-3	Ac-4	OAc-5	NH
I (D-*allo*)	4.77	5.13	7.91	7.84	8.02	7.81	4.38
II (D-*gulo*)	4.71	4.89	7.94	7.88	8.11	7.94	4.11
III (D-*altro*)	4.89	4.97	7.93	7.93	8.08	7.83	4.03
IV (D-*altro*)	4.71	4.71	8.03	7.92	7.96	7.83	

[a] In τ-values.

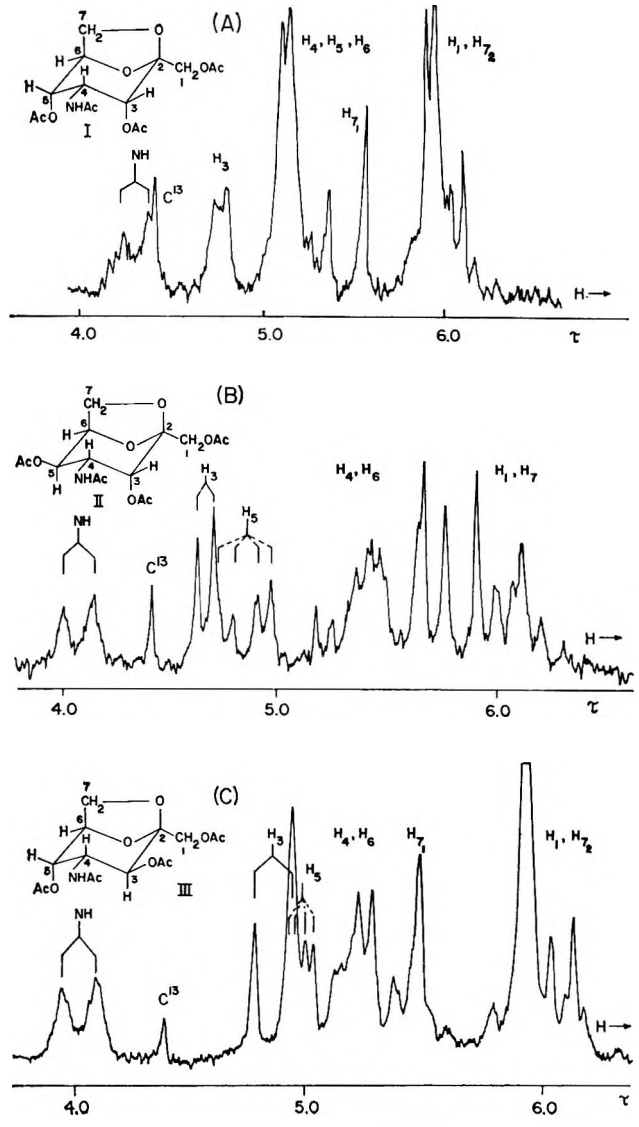

Fig. 1.—The ring hydrogen resonances of the tetraacetyl-aminodeoxyheptulosans I, II, and III. The peaks designated "C^{13}" arise from coupling of the solvent chloroform protons with the chloroform-C^{13} in natural abundance.

It was possible to distinguish between the isomers II and III by a study of the ring-hydrogen resonances. For reasons pointed out previously[1] it was assumed at this stage that the acetamido substituent at C-4 was oriented equatorially in these compounds. Consequently, H-4 was to be regarded as axial. Direct proof of the correctness of this assumption came from the observation of large couplings (*ca.* 10 c.p.s.) both in II and in III. These indicated the presence of neighboring, diaxial hydrogens, a condition requiring H-4 to be axial. With an axial H-4, then, the isomer bearing an axial

(2) Prepared from the aminodeoxyheptulosan hydrochlorides referred to in ref. 1 as (a) compound IVa, $[\alpha]_D$ −55°; (b) compound IVb, $[\alpha]_D$ +39°; and (c) compound IVc, $[\alpha]_D$ −126°.

(3) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(4) L. D. Hall and L. Hough, *Proc. Chem. Soc.*, **382** (1962); a detailed account of this work is in preparation (L. D. Hall, L. Hough, and K. A. McLaughlan).

(5) A. C. Richardson and K. A. McLaughlan, *J. Chem. Soc.*, 2499 (1962).

(6) F. A. L. Anet, R. A. B. Bannard, and L. D. Hall, *Can. J. Chem.* **41**, 2331 (1963).

acetoxy at C-3 (*i.e.*, the *gulo* isomer II) should show a small splitting (*ca.* 2 c.p.s.) for the H-3 doublet, whereas the isomer having an equatorial C-3 acetoxy substituent (*i.e.*, the *altro* isomer III) should show H-3 as a doublet with a large splitting (*ca.* 10 c.p.s.). Additional proof of these assignments should follow from the measurements of the splittings of the H-5 resonance if these could be observed. It was indeed fortunate that the downfield shift of H-3 and H-5, caused by the adjacent acetoxy substituents, was sufficient for both these hydrogens to be resolved, and hence for II and III to be distinguished. One isomer exhibited a doublet, which could only be H-3, at τ 4.71 (splitting, 4.6 c.p.s.) and three lines of a partially concealed quartet, which must be H-5, at τ 4.89 (splittings, 3.5 and 10.4 c.p.s.); clearly, this must be the *gulo* isomer II. The remaining isomer showed the H-3 doublet at τ 4.89 (splitting, 9.9 c.p.s.) and a partially concealed quartet for II-5 at τ 4.97 (splittings, 2.1 and 4.4 c.p.s.), all of which is consistent with the *altro* configuration (III).

Although the ring hydrogens of the *allo* isomer I were not well resolved, they were consistent with the assigned configuration. H-3 occurred as a poorly resolved doublet at τ 4.77 (splitting, *ca.* 4 c.p.s.), and while H-5 overlapped with the resonances of two other hydrogens the total band width was insufficient to accommodate an axial–axial coupling of *ca.* 10 c.p.s.

Also included in Table I are the acetoxy resonances of fully acetylated 2,7-anhydro-β-D-altroheptulopyranose (sedoheptulosan, IV), although this product could not be obtained in crystalline condition. However, the resonances were as expected, showing one axial and three equatorial substituents.

Experimental

The 60-Mc./sec. p.m.r. spectra were measured in a Varian V-4302B spectrometer for chloroform solutions. A Varian V-3521 integrator was used for base line stabilization. Calibration was by the usual side-band technique with tetramethylsilane as internal reference. The chemical shifts and multiplet splittings in Table I are averaged values from at least three spectra.

Acetylation of Aminodeoxyheptulosans.—Aminodeoxyheptulosan (about 100 mg.) in pyridine (2 ml.) was treated with acetic anhydride (2 ml.) at room temperature for 2 days. Excess anhydride was destroyed by the addition of methanol and the solution was evaporated *in vacuo*. The sirupy residue was taken up in 15 ml. of chloroform which was then extracted once with 6 ml. of *N* sulphuric acid and twice with 6 ml. of a saturated sodium hydrogen carbonate solution. After drying over anhydrous sodium sulfate and evaporation of the chloroform solution, the crystalline acetylated aminodeoxyheptulosan was obtained from, and recrystallized with, chloroform–ether. The three isomers were obtained in yields of 50–65% and had the following properties: **4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-alloheptulopyranose** (**I**, from compound IVa[1]), oblong flat platelets, m.p. 213–214° dec., $[\alpha]^{22}D$ −60.9° (*c* 1, chloroform); **4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-guloheptulopyranose** (**II**, from compound IVb[1]), thin prisms, m.p. 128–129°, $[\alpha]^{22}D$ +43.7° (*c* 1, chloroform); **4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-altroheptulopyranose** (**III**, from compound IVc[1]), fine needles, m.p. 189–190°, $[\alpha]^{22}D$ −145.5° (*c* 1, chloroform).

Anal. Calcd. for $C_{13}H_{21}NO_9$ (359.3): C, 50.13; H, 5.89. Found for I: C, 50.07; H, 5.72. Found for II: C, 49.74; H, 5.78. Found for III: C, 50.36; H, 5.56.

Acknowledgment.—Support from the Ontario Research Foundation and from the National Institute of Allergy and Infectious Diseases, United States Public Health Service (Grant AI 4697), is gratefully acknowledged. L. D. H. wishes to thank Dr. F. A. L. Anet for a postdoctoral fellowship.

2-Deoxy Sugars. VI. Concurrent One-Step Formation of Both Anomeric Monodigitoxosides of Digitoxigenin[1]

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This paper deals with the direct coupling of digitoxose (2,6-dideoxy-β-D-*ribo*-hexose, I) with digitoxigenin [3β,14β-dihydroxy-5β-card-20(22)-enolide, II] to give not only the α-monodigitoxoside (III) but the β-anomeric form (IV) as well. The β-, or "natural," anomer was obtained originally by a controlled, partial hydrolysis of digitoxin,[3] but when we attempted to synthesize the material by coupling 2,6-dideoxy-3,4-di-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl chloride with digitoxigenin (II), we obtained the alternate anomeric form (III) instead (see Scheme I).[4]

The presently described reaction was carried out by treating a solution of digitoxigenin (II) and an excess of digitoxose (I) in pure dioxane with a small quantity of hydrogen chloride–dichloromethane solution. After neutralizing the acid, the reaction products were dissolved in aqueous methanol and were extracted with chloroform to remove all extraneous carbohydrate materials. Thin-layer chromatograms disclosed two major spots corresponding chromatographically to the α- and β-monodigitoxosides III and IV, respectively.

The extracted material was resolved by first chromatographing on formamide–cellulose powder[5] which brought about an incomplete separation of II, III, and IV. The fractions containing the latter were recombined and were chromatographed on silicic acid giving a complete separation, from which the monosides III and IV were obtained in a combined yield of 10% based on the genin II.

The formation of an α-glycoside (III) is of interest and may be accounted for satisfactorily in terms of the "anomeric" effect (structure A)[6] which allows for an attraction between the axially oriented α-glycosidic oxygen atom and C-5 which carries a partial positive charge. Such an attraction would overcome, at least in part, the conformational instability imposed by the erected oxygen atom. In the case of pyranosides which are not deoxygenated at C-6, the added electron-

(1) This work was supported in part by U.S. Public Health Service Grant HE-05839.

(2) (a) To whom all enquiries concerning this paper should be addressed; (b) U. S. Public Health Service Predoctoral Fellow; (c) visiting scientist, Georgetown University, 1961–1963.

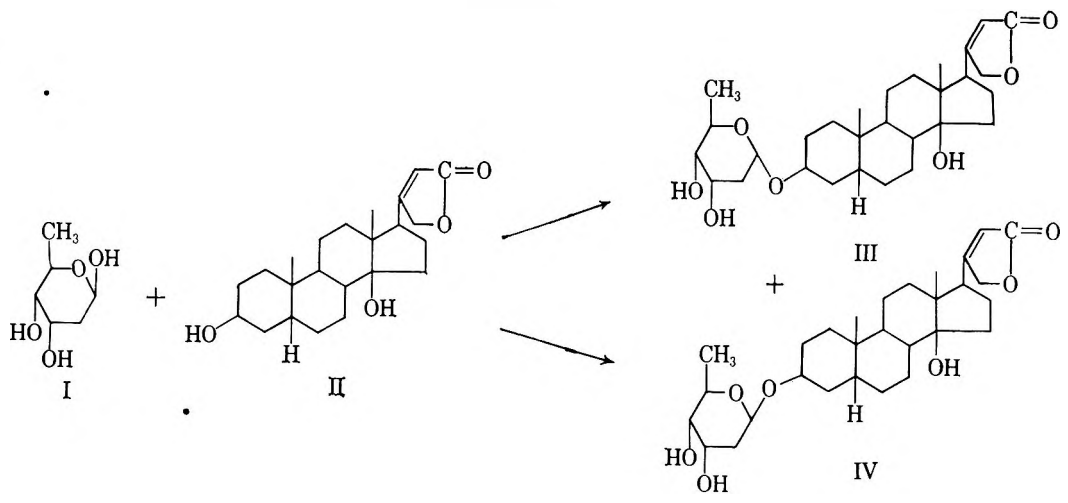
(3) F. Kaiser, E. Haack, and H. Spingler, *Ann. Chem.*, **603**, 75 (1957).

(4) (a) W. W. Zorbach and T. A. Payne, *J. Am. Chem. Soc.*, **81**, 1519 (1959); (b) **82**, 4079 (1960).

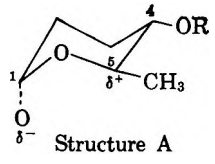
(5) E. Haack, F. Kaiser, and H. Spingler, *Chem. Ber.*, **89**, 1353 (1956).

(6) R. U. Lemieux and P. Chu, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April, 1958, p. 31N. The suggestion that the formation of α-cardenolides is due most likely to this effect was communicated privately by Professor Lemieux to whom the authors are most grateful.

SCHEME I



withdrawing power of the C-5 hydroxymethyl (or acyloxymethyl) group should increase the charge on C-5, thus favoring even more α-glycoside formation.[7] In the present case (structure A, R = H) this attraction is not strong enough to offset to a large degree the conformational instability with the result that substantial amounts of the conformationally more stable β-digitoxoside (IV) were formed.



Structure A

Support for this argument is given in the coupling of 2,6-dideoxy-3,4-di-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl chloride with digitoxigenin (II)[4] which was carried out under equilibrating conditions in the absence of an acid acceptor. Under these conditions, an α-glycoside was formed exclusively, and it is suggested that the powerful electron-withdrawing capacity of the C-4 *p*-nitrobenzoyl group (structure A, R = p-$O_2NC_6H_4\overset{\overset{O}{\|}}{C}$–) was sufficient to offset conformational instability to a point where β-glycoside formation was excluded.

Experimental

All melting points were determined using a Kofler hot stage. Diagnostic thin-layer chromatograms were carried out on Fluka No. D5 TLC silica gel and were developed employing the upper phase separating from an ethyl acetate–pyridine–water (5:1:4) mixture as described by Steinegger and van der Walt.[8]

α- and β-Monodigitoxosides (III and IV) of Digitoxigenin (II).—To a solution of 748 mg. (2.0 mmoles) of digitoxigenin (II) and 592 mg. (4.0 mmoles) of digitoxose (I) in 10 ml. of anhydrous dioxane was added 2 ml. of a solution of dichloromethane containing 0.1 mequiv./ml. of anhydrous hydrogen chloride. After standing for 24 hr., the solution was neutralized by stirring for a short time with an excess of silver carbonate. The filtered solution was then evaporated to dryness at 30° and the sirup was dissolved in 400 ml. of methanol followed by the addition of 1 l. of water. The aqueous solution was shaken thoroughly with 60 ml. of chloroform and, after separating, the chloroform extract was washed three times with small portions of water. After drying over sodium sulfate, the extract was evaporated to dryness at 30°, giving 1.0 g. of sirup containing only Kedde-positive material.

The latter material was placed on a column (4 × 40 cm.) of 200 g. of cellulose powder (Whatman No. 1) previously treated with a 40% (v./v.) solution of formamide in acetone and which was thoroughly dried to remove the acetone prior to packing. Elution was carried out in 2.5-ml. fractions using tetrahydrofuran–cyclohexane (2:3) saturated with formamide. Fractions 62–130, amounting to 330 mg., were combined and were placed on a column (3 × 35 cm.) of 250 g. of silicic acid. The column was eluted with tetrahydrofuran–cyclohexane (2:3), 2.5-ml. fractions being collected. Fractions 241–280 contained 90 mg. of material which, on recrystallization from ether–tetrahydrofuran, gave pure digitoxigenin (II), m.p. 250–254°, $[\alpha]^{30}D$ +20.2° (*c* 0.962, methanol). Fractions 291–360 contained 40 mg. (5.4%) of the α-monodigitoxoside (III) which, after recrystallization from ether–tetrahydrofuran, gave pure III, m.p. 252–256°, $[\alpha]^{30}D$ +87.0° (*c* 0.361, methanol); lit.[4,5] m.p. 251–255°, $[\alpha]^{20}D$ +85.1° (in methanol). Fractions 441–500 amounted to 34 mg. (4.5%) of material which, after recrystallization from absolute ether, gave pure β-monodigitoxoside (IV), m.p. 204–209°,[9] $[\alpha]^{30}D$ −7.1° (*c* 0.446, methanol). The ultraviolet and infrared absorption spectra of the two monosides (III and IV) were identical in all respects with the spectra prepared from corresponding authentic samples. Because the analytical data thus presented for III and IV were unambiguous, combustion analyses were considered unnecessary.

Acknowledgment.—The authors wish to thank Mr. H. K. Miller and Mrs. Anne Wright, Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland, for preparing the infrared spectra.

(7) J. T. Edward, P. E. Morand, and I. Puskas [*Can. J. Chem.*, **39**, 2069 (1961)] suggest, for hexopyranoses not deoxygenated at C-6, that through an inductive effect both the C-4 and C-6 hydroxyl groups serve to augment the positive charge on C-5.

(8) E. Steinegger and J. H. van der Walt, *Pharm. Acta Helv.*, **36**, 599 (1961).

(9) The melting point recorded herein does not agree with the value of 181–184° originally reported[8] by Kaiser and co-workers. In a private communication Dr. F. Kaiser pointed out that, when larger amounts of the β-monoside are isolated from *D. lanata*, he obtains m.p. 205–208° which agrees closely with m.p. 202–208° of some material he had sent us previously. The authors wish to take this opportunity to thank Dr. Kaiser for his generous gift of β-monodigitoxoside.

2-Deoxy Sugars. VIII. Nucleosides Derived from 2-Deoxy-D-allopyranose (2-Deoxy-D-*ribo*-hexopyranose)[1]

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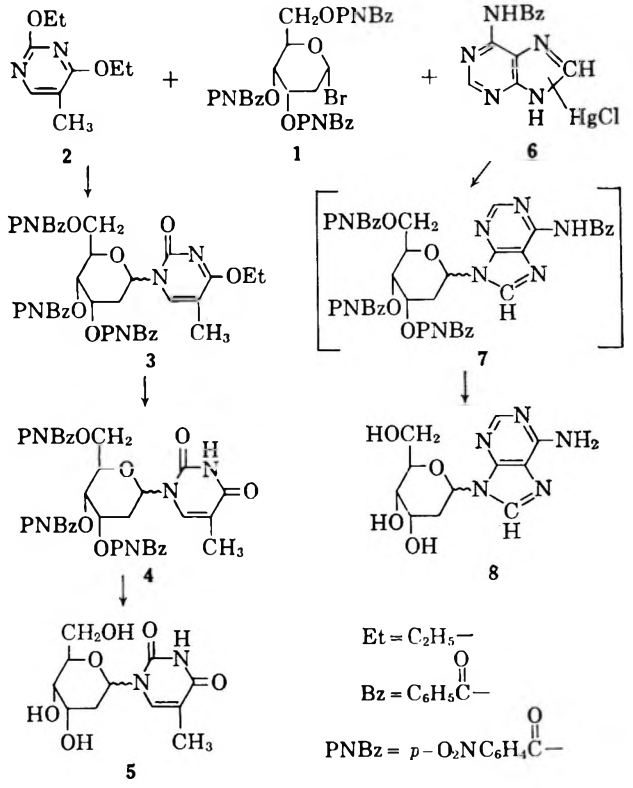
As a continuation of our earlier work[3] on the direct synthesis of potential, anticancer nucleosides using stable crystalline *p*-nitrobenzoylglycosyl halides of 2-deoxy sugars, we investigated the preparation of additional nucleosides to contain as the carbohydrate component 2-deoxy-D-allopyranose (2-deoxy-D-*ribo*-hexopyranose). This paper deals with the preparation of 9-(2-deoxy-D-*ribo*-hexopyranosyl)adenine (**8**) and 1-(2-deoxy-D-*ribo*-hexopyranosyl)thymine (**5**). The latter nucleoside is of especial interest owing to a recent discovery[4] that 1-(2-deoxy-D-*arabino*-hexopyranosyl)thymine, prepared for the first time in this laboratory,[3] is a powerful and apparently specific inhibitor of pyrimidine nucleoside phosphorylase, obtained from Ehrlich's ascites tumor cells. Because the new nucleoside (**5**) and "2-deoxyglucosyl thymine"[3,4] differ only with respect to the configuration of the hydroxyl group about C-3 of the sugar moiety, it is considered that **5** might display an equivalent or even superior biological activity.



The coupling of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexosyl bromide (**1**)[5] and 2,4-diethoxy-5-methylpyrimidine (**2**) took place readily to give crystalline, protected nucleoside **3** which was de-ethylated to give the nitrobenzoylated intermediate **4**, which was likewise crystalline. Deacylation of **4** by means of ethanolic ammonia gave amorphous, hygroscopic 1-(2-deoxy-D-*ribo*-hexopyranosyl)thymine (**5**) in 18% yield based on the bromide **1**.

The bromide reacted also with chloromercuri-6-benzamidopurine (**6**) which resulted in amorphous, protected nucleoside **7**, a fraction of which was insoluble in chloroform. The chloroform extract was purified by column chromatography and, after deacylation with ethanolic ammonia, gave crude nucleoside **8** which was further purified *via* its picrate salt. This resulted in 8.4% (based on **1**) of pure 9-(2-deoxy-D-*ribo*-hexopyranosyl)adenine hemihydrate (**8**), having $[\alpha]_D$ +74.9°.

The chloroform-insoluble material obtained from the protected nucleoside **7** was treated in a similar manner and gave 3.2% (based on **1**) of nucleoside **8** as a monohydrate, having $[\alpha]_D$ +49.5°. Because the ultraviolet absorption spectra and the chromatographic behavior of the two adenine nucleosides are the same, additional studies will be required to determine whether the latter material is the alternate anomeric form of **8**.

Experimental

All melting points were determined using a Kofler hot stage. All paper and t.l.c. chromatograms were carried out by an ascending technique employing saturated aqueous ammonium sulfate–2-propanol–water (2:28:70).

1-(2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-D-*arabino*-hexopyranosyl)-4-ethoxy-5-methyl-2(1*H*)-pyrimidone (3).—An intimate mixture of 750 mg. (1.11 mmoles) of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexopyranosyl bromide (**1**) and 750 mg. (4.03 mmoles) of 2,4-diethoxy-5-methylpyrimidine (**2**) was heated at 55° for 24 hr. under a reduced pressure of 20 mm. After cooling, the melt was crushed and extracted five times with 50-ml. portions of ether. The crude, protected nucleoside **3** amounting to 500 mg. was recrystallized from chloroform–ethanol (1:1), giving 335 mg. of pure **3**, m.p. 276–276.5°.

Anal. Calcd. for $C_{34}H_{29}NO_{15}$: C, 54.61; H, 3.91; N, 9.37. Found: C, 54.37; H, 4.28; N, 8.92.

1-(2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-D-*ribo*-hexopyranosyl)-thymine (4).—To a solution of the 335 mg. of protected nucleoside **3** obtained in the preceding preparation in 40 ml. of chloroform–ethanol (1:1) was added 6 ml. of 20% methanolic hydrogen chloride. The mixture was stirred under the exclusion of moisture overnight, after which the solvent was evaporated *in vacuo*. Recrystallization of the residue from chloroform–ethanol gave 270 mg. of pure **4**, m.p. 317–320°.

Anal. Calcd. for $C_{32}H_{25}N_5O_{15}$: C, 53.41; H, 3.50; N, 9.73. Found: C, 53.55; H, 3.92; N, 8.60.

1-(2-Deoxy-D-*ribo*-hexopyranosyl)thymine (5).—The 270 mg. of de-ethylated, acylated nucleoside **4** obtained in the preceding experiment was dissolved in 27 ml. of absolute ethanol saturated with ammonia at 0°, and the solution was stirred for 24 hr. in a closed flask. The clear solution was evaporated to dryness and the residue was washed three times with 50-ml. portions of ether. It was then dissolved in 50 ml. of water and was extracted with three 50-ml. portions of chloroform. After separating, the aqueous layer was evaporated to dryness, giving 54 mg. of pure nucleoside **5** as an amorphous, hygroscopic powder, m.p. 116–126°, $[\alpha]^{25}_D$ +68.7° (*c* 2.73, methanol), $\lambda_{max}^{H_2O}$ 267 mμ (log ε 3.80), ν_{max}^{KBr} 1665 cm.$^{-1}$ (—NHCO—). When chromatographed on paper the nucleoside **5** traveled as a single spot ($R_{thymine}$ 1.07).

9-(2-Deoxy-D-*ribo*-hexopyranosyl)adenine (8).—To a solution of 2.28 g. (3.38 mmoles) of the bromide (**1**) in 50 ml. of dry dichloromethane was added 1.44 g. (3.04 mmoles) of chloromercuri-6-benzamidopurine (**6**) and the mixture was stirred for 24 hr. at room temperature. After filtering the mercury salts, the filtrate was evaporated under reduced pressure giving 2.2 g. of crude, pro-

(1) This work was supported largely by U. S. Public Health Service Grant CY-4288.

(2) Postdoctoral research associate, Georgetown University, 1961–1963.

(3) W. W. Zorbach and G. J. Durr, *J. Org. Chem.*, **27**, 1474 (1962).

(4) P. Langen and G. Etzold, *Biochem. Z.*, **339**, 190 (1963).

(5) W. W. Zorbach and W. Bühler, *Ann. Chem.*, **670**, 116 (1963).

tected nucleoside **7** which was then treated with chloroform, leaving 1.0 g. of insoluble material. After evaporation of the solvent, the chloroform-soluble material was placed on a column (3 × 26 cm.) of 80 g. of silicic acid (Fisher reagent grade, activated for 1 hr. at 105°) and was eluted with chloroform–methanol (95:5), 2.5-ml. eluates being collected. The desired material, amounting to 240 mg., appeared in fractions 141–200, and was then dissolved in 40 ml. of absolute ethanol saturated with ammonia at 0°. After stirring in a closed flask for 24 hr., the insoluble material was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 10 ml. of methanol, 100 mg. of picric acid was added, and, after standing for 5 hr., the resulting yellow salt was collected. It was next treated in water for 18 hr. with 10 ml. of Amberlite IR-45 ion-exchange resin and, after filtering, the clear solution was evaporated to dryness at 30°. Recrystallization of the residue from 95% ethanol gave 80 mg. (8.4% based on 1) of pure 9-(2-deoxy-D-*ribo*-hexopyranosyl)-adenine (**8**) as a hemihydrate, m.p. 159–164°, $[\alpha]^{23}D$ +74.9° (*c* 0.833, methanol), $\lambda_{max}^{H_2O}$ 259.5 mμ (log ε 4.22). When chromatographed on paper the nucleoside **8** traveled as a single spot ($R_{adenine}$ 1.11). On t.l.c. chromatograms the R_f value was 0.75.

Anal. Calcd. for $C_{11}H_{15}N_5O_4 \cdot 0.5\ H_2O$: C, 45.51; H, 5.55; N, 24.12. Found: C, 45.43; H, 5.97; N, 24.29.

Anomeric (?) Nucleoside 8.—The chloroform-insoluble fraction of the protected nucleoside **7** obtained in the preceding experiment was placed on a column (3 × 26 cm.) of 60 g. of silicic acid (activated for 1 hr. at 105°) and 40 g. of Celite 505, similarly dried. Elution, in 2.5-ml. fractions, was carried out using ethyl acetate, and from fractions 21–36 there was obtained 500 mg. of material which was deacylated and treated in the same manner as that described in the foregoing experiment. The white powder obtained was recrystallized from 95% ethanol giving 30 mg. (3.2% based on 1) of hydrated nucleoside, m.p. 143–150°, $[\alpha]^{23}D$ +49.5° (*c* 0.370, methanol), $\lambda_{max}^{H_2O}$ 260 mμ (log ε 4.10). When chromatographed on paper, the material traveled as a single spot ($R_{adenine}$ 1.11). On t.l.c. chromatograms the R_f value was 0.75.

Anal. Calcd. for $C_{11}H_{15}N_5O_4 \cdot H_2O$: C, 44.14; H, 6.72; N, 23.40. Found: C, 44.87; H, 6.00; N, 23.54.

Acknowledgment.—For the elemental analyses the authors are indebted to Miss Paula Parisius, Microanalytical Laboratory, LC, NIAMD, National Institutes of Health, Bethesda, Maryland, under the direction of Mr. H. G. McCann.

3,3′-Diphenyl-1,1′-bibenzo[c]thienyl

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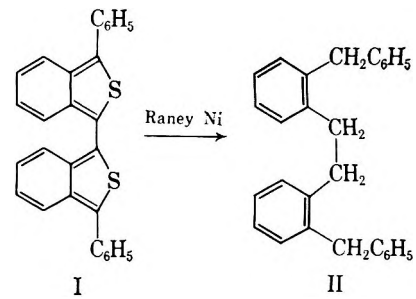
Received September 12, 1963

In a survey of known derivatives of benzo[*c*]thiophene[1] our attention was directed to a red compound, m.p. 237°, obtained by heating *o*-benzoylbenzoic acid with phosphorus pentasulfide,[2] which was reported to be 1-phenylbenzo[*c*]thiophene. Since 1,3-diphenylbenzo[*c*]thiophene, for which the structure is firmly established,[3] is yellow and melts at 118–119°, the color and melting point of the supposed 1-phenylbenzo[*c*]thiophene seemed out of line. Investigation has shown this compound to be 3,3′-diphenyl-1,1′-bibenzo[*c*]thienyl (I).



I II

Structure proof was accomplished by desulfurization of I to *o,o′*-dibenzylbibenzyl (II).

This structure assignment was supported by examination of the mass spectrum, which had a parent peak at 418 (98%) and a peak at mass 354 ascribable to the loss of two sulfur atoms. This shows that the original molecular weight determination (223 and 239 found[2]) must have been in error.

Experimental[4]

3,3′-Diphenyl-1,1′-bibenzo[*c*]thienyl (I).—This compound was prepared as described by O'Brochta and Lowy[2] (termed 2-phenyl-3,4-benzothiophene). Deep red needle-like crystals of I, m.p. 236–237°, were obtained in 15% yield; infrared spectrum: 3.28, 6.26, 6.69, 6.92, 7.34, 7.57, 8.29, 9.23, 9.68, 10.80, 11.70, 11.89, 13.1 (broad), 13.4 (very broad), and 14.4 (very broad) μ; mass spectrum: parent peak at 418 (98%) and peak at 354, due to loss of both sulfur atoms. No peaks attributable to (isotopic) oxygen.

Anal. Calcd. for $C_{28}H_{18}S_2$: C, 80.37; H, 4.33; S, 15.30. Found: C, 79.67; H, 4.31; S, 15.50. Reported in ref. 2: C, 80.01, 80.29; H, 4.72, 4.73; S, 15.02.

Desulfurization of I with Raney Nickel.—A mixture of 1.7 g. (4.1 mmoles) of I, approximately 20 g. of Raney nickel, and 50 ml. of 95% ethanol was refluxed for 2 days. The insoluble residue was removed by filtration, and the filtrate was concentrated until solid material crystallized. Recrystallization from 95% ethanol afforded 1.0 g. (68%) of a white crystalline compound, m.p. 97–98°, identified as *o,o′*-dibenzylbibenzyl (II) by comparison with an authentic sample, synthesized as described below. The infrared spectra were identical in all respects, and the mixture melting point was undepressed.

***o*-Benzylbenzyl Alcohol** (IV).—This compound was prepared from *o*-benzylbenzoic acid[5] as described by Speeter.[6] IV was obtained as a colorless liquid, b.p. 147–148° (1 mm.), $n^{20}D$ 1.5942, lit.[6] b.p. 148–151° (3 mm.). Upon standing at room temperature, the alcohol solidified. Recrystallization from hexane gave white needle-like crystals of IV, m.p. 37–38°; infrared spectrum: broad O–H at 3.0, 6.22, 6.70, 6.89, 9.6–10.0 (broad bands), 13.2–13.7 (broad bands), and 14.5 μ.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 85.26; H, 7.18.

The **phenylurethan derivative** melted at 60–61°, lit.[6] m.p. 77–78°; infrared spectrum: 3.08 (N–H), 5.92 (C=O), 6.25, 6.56, 6.94, 7.62, 8.05, 8.16, 9.43, 13.16, 13.85, and 14.50 μ.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 80.16; H, 6.33; N, 4.56.

***o*-Benzylbenzyl Bromide** (V).—To a solution of 12.8 g. (64.6 mmoles) of IV in 20 ml. of benzene, cooled in an ice bath, was added dropwise 6.0 g. (22 mmoles) of phosphorus tribromide over a 15-min. period. The mixture was stirred overnight while coming to room temperature and allowed to stand until a total reaction time of 24 hr. had elapsed. Work-up in the *usual* manner afforded 17.0 g. of a crude oily product which crystallized when placed in a Dry Ice–acetone bath. Recrystallization from hexane gave 13.0 g. (77.1%) of white needle-like crystals of V, m.p. 40–42°. Further recrystallization from hexane gave the analytical sample, m.p. 42–43°. V gave an immediate

(1) The parent compound has been synthesized recently by R. Mayer, *et al.*, *Angew. Chem.*, **74**, 118 (1962); *Angew. Chem., Intern. Ed. Eng.*, **1**, 115 (1962).

(2) J. O'Brochta and A. Lowy, *J. Am. Chem. Soc.*, **61**, 2765 (1939).

(3) See H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954, pp. 169–170.

(4) Carbon, hydrogen, and nitrogen analyses were by Miss Hilda Beck. Sulfur analysis was by Micro-Tech Laboratories, Skokie, Ill. All infrared spectra were taken in potassium bromide pellets.

(5) E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1441 (1936).

(6) M. E. Speeter, U. S. Patent 2,759,934; *Chem. Abstr.*, **51**, 2044 (1957).

precipitate of silver bromide with alcoholic silver nitrate; infrared spectrum: 3.28, 3.33, 6.23, 6.71, 6.90, 6.98, 8.13, 8.23, 13.2 (broad), 13.6–13.9 (very broad), and 14.5 μ.

Anal. Calcd. for $C_{11}H_{13}Br$: C, 64.38; H, 4.98. Found: C, 64.76; H, 4.99.

***o,o'*-Dibenzylbibenzyl (II).**—To 2.6 g. (10 mmoles) of V was added 0.3 g. (13 mg.-atoms) of sodium, freshly cut into small slices, and the mixture was heated at about 100° for 4 hr. under nitrogen. After the addition of 95% ethanol to consume unchanged sodium, water was added, and the solution was concentrated. Ether extraction gave a fluorescent oily product which partially crystallized on standing overnight. Addition of pentane and cooling in a Dry Ice–acetone bath caused further crystallization. The crude, oily solid, m.p. 92–93°, was recrystallized several times from pentane, eventually yielding 0.2 g. (11%) of II, m.p. 96–97°, as white crystals; infrared spectrum: 3.26, 3.32, 3.43, 6.22, 6.70, 6.88, 9.15, 9.29, 9.47, 12.65, 12.98, 13.44, 13.71, and 14.47 μ. This spectrum was identical in every respect with that of the product of the Raney nickel desulfurization of I.

Anal. Calcd. for $C_{28}H_{26}$: C, 92.77; H, 7.23. Found: C, 93.22; H, 7.17.

The oily residues appeared to consist primarily of II, which was probably contaminated by small amounts of isomeric hydrocarbons that could not be separated by repeated crystallizations or by elution chromatography. The infrared spectrum of this oil in chloroform was essentially identical with that of II in chloroform.

Acknowledgment.—This work was supported by the American Petroleum Institute under Project 48B. We wish to thank Dr. G. P. Hinds of the Shell Oil Company, Deer Park, Texas, for the determination of the mass spectrum.

Electrophilic Attack at the 2-Methyl Group of 2,3-Dimethylbenzo[*b*]thiophene

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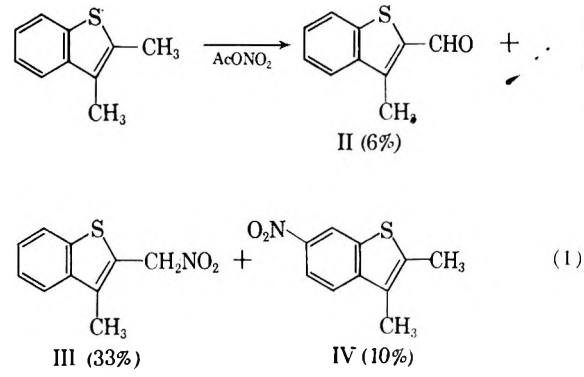
Received September 12, 1963

Benzo[*b*]thiophene undergoes electrophilic substitution preferentially in the 3-position, the 2-position being somewhat less active.[1] One of our objectives in studying the nitration of 2,3-dimethylbenzo[*b*]thiophene was to determine what position(s) in the benzene portion of the molecule would be attacked when the active 2- and 3-positions were blocked by methyl groups. Surprisingly enough, reaction occurred chiefly at the 2-methyl group, rather than on the aromatic nucleus. Thus, addition of 2,3-dimethylbenzo[*b*]thiophene to acetyl nitrate in acetic anhydride–acetic acid solution at 0° with a reaction time of 20 min. gave the results shown in eq. 1 (the remainder of the material appeared to be polymeric).

The yields of these three products were lowered on prolonged contact with the reaction mixture. Inverse addition gave 18% of II and very small amounts of nitro compounds.

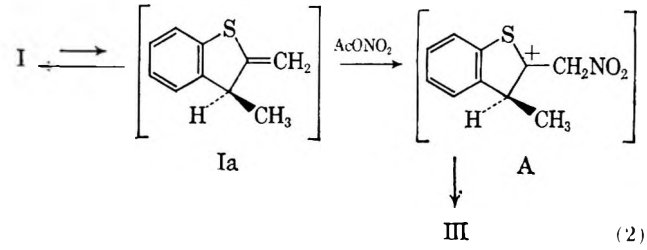
The structure of II was established by reducing it to the known 3-methyl-2-hydroxymethylbenzo[*b*]thiophene. The structure of III followed from its conversion to the same alcohol by reduction and diazotization



(1)

of the resulting amine. The structure of IV was assigned by virtue of the identity of its 1,1-dioxide with that obtaining by nitrating 2,3-dimethylbenzo[*b*]thiophene 1,1-dioxide. The latter will almost certainly substitute in the 6-position by analogy with the behavior of benzo[*b*]thiophene 1,1-dioxide.[2]

The unusual course of this nitration must be a consequence of the tendency of I to exist to some extent in a tautomeric form (Ia), which should be much more subject to electrophilic attack than is I.[3] Although formation of Ia requires loss of aromaticity in the thiophene ring, this is offset to some degree by the relief of strain between the two methyl groups and between the *peri* hydrogen (4-position) and the 3-methyl group. Formation of III from Ia by attack of NO_2^+, or the like, would be anticipated *via* intermediate A. Several mechanisms for the formation of II can be imagined, but there is no experimental evidence on this point yet.



(2)

To our knowledge this is the first report of the preferential attack of an electrophilic reagent at an alkyl group attached to an aromatic nucleus. It is to be expected, however, that other examples will be found in polyalkyl aromatics where tautomerism is favored by relief of alkyl–alkyl oppositions and/or a relatively low degree of aromaticity in the system.[4] Work in this area is continuing.

Experimental[5]

2,3-Dimethylbenzo[*b*]thiophene (I).—In a variation of Werner's method[6] a mixture of 47.5 g. (0.264 mole) of 3-phenylthio-2-butanone, 400 g. of polyphosphoric acid, and 20 g. of phosphorus pentoxide was heated to 120° for 4 hr. with occasional stirring.

(1) See H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954, pp. 45–50, 116.

(2) F. Challenger and P. H. Clapham, *J. Chem. Soc.*, 1615 (1948).

(3) The n.m.r. spectrum of I in carbon tetrachloride shows two methyl absorptions of equal intensity at τ 7.67 and 7.87, and a multiplet at τ 2.38 to 2.97. Since there is no indication of the presence of Ia in the n.m.r. or infrared spectrum of I, the reactivity of Ia must be several powers of ten greater than that of I, but this is to be expected.

(4) Other examples of side-chain nitrations of alkyl benzenes have been recorded, but these are probably radical reactions (see A. V. Topchiev, "Nitration of Hydrocarbons and Other Organic Compounds," Pergamon Press, Inc., New York, N. Y., 1959, pp. 157–160, 168–177.)

(5) Microanalyses were by Miss Hilda Beck. N.m.r. spectra were recorded at 60 Mc. by Larry Shadle.

(6) E. G. G. Werner, *Rec. trav. chim.*, **68**, 509 (1949).

After processing,[6] there was obtained 35.0 g. (82%) of colorless material, b.p. 96–98° (1.5 mm.), $n^{20}D$ 1.6165. Upon refrigeration crystals, m.p. 9°, were obtained.

Nitration of I.—A solution of 1.8 g. (0.011 mole) of I in 5 ml. of acetic anhydride was cooled to 5° and added rapidly with stirring to a nitrating solution, prepared at room temperature by adding (with cooling) 0.70 ml. (0.011 mole) of 70% nitric acid to 5 ml. of acetic anhydride and cooling to −5°. Despite ice–salt cooling, the temperature rose to 35° before slowly returning to 0°. After 20 min. the mixture was poured into ice–water. After hydrolysis, the solution was neutralized with sodium bicarbonate and extracted with ether. The 1.8 g. of yellow solid obtained on concentration of the ether layer was chromatographed on silica gel, eluting with hexane and finally ether–hexane. In this manner there was obtained, in order of elution, 0.22 g. (9.6%) of IV, m.p. 124–125°; 0.75 g. (32.6%) of III, m.p. 103–104°; 0.12 g. (6.1%) of II, m.p. 88–89°; and 0.45 g. of polymeric material. From a similar run, except that the nitration mixture was allowed to stand overnight at 0° prior to processing, the yields were much lower, larger amounts of polymeric material being formed. In this run a small amount of an additional product, m.p. 159–160°, crystallized from the hexane solution being prepared for chromatography. When the nitrating solution was added to a solution of I at 0° and the mixture was allowed to stand overnight at 0° and processed as before, the yields of IV and II were 2% and 18%, respectively; no III was isolated, the major amount of material was polymeric.

3-Methyl-2-benzo[*b*]thiophenecarboxaldehyde (II) was obtained as pale yellow needles, m.p. 88–89°. In addition to a strong C=O band at 6.02 μ, it had an aldehydic C–H band at 3.50 μ, and other infrared peaks at 3.25, 3.42, 6.23, 6.36, 6.52, 6.96, 7.23, 7.40, 7.55, 7.87, 8.20, 8.58, 9.25, 9.40, 10.64, 13.19, 13.72, 13.92, 14.83, and 15.15 μ. The n.m.r. spectrum in carbon tetrachloride showed a singlet at τ −0.23 for the aldehydic proton, a multiplet from τ 2.12 to 2.67 for the aromatic protons, and a singlet at τ 7.32 for the methyl group.

Anal. Calcd. for $C_{10}H_8OS$: 68.18; H, 4.58. Found: 68.02; H, 4.49.

The **oxime**, recrystallized from hexane, melted at 161–162°.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.66; H, 5.01; N, 7.29.

3-Methyl-2-nitromethylbenzo[*b*]thiophene (III) was obtained as nearly colorless crystals, m.p. 103–104°. It dissolved slowly in warm dilute sodium hydroxide and was recovered by acidification. The infrared spectrum showed strong unconjugated nitro peaks at 6.45 and 7.30 μ, and other peaks at 3.35, 3.51, 6.99, 7.45, 7.66, 8.24, 8.52, 8.63, 8.80, 9.41, 9.82, 10.82, 12.47, 12.70, 13.19, 13.70, 14.00, and 14.89 μ. The n.m.r. spectrum showed a multiplet from τ 2.18 to 2.77 for the aromatic protons, a singlet at τ 4.48 for the methylene α to the nitro, and a singlet at τ 7.60 for the methyl group.

Anal. Calcd. for $C_{10}H_9NO_2S_2$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.85; H, 4.56; N, 6.32.

2,3-Dimethyl-6-nitrobenzo[*b*]thiophene (IV) was obtained as bright yellow needles, m.p. 124–125°. The infrared spectrum showed strong conjugated nitro peaks at 6.60 and 7.48 μ, and other peaks at 3.20, 3.40, 6.22, 6.42, 6.82, 7.10, 7.16, 8.46, 8.77, 8.89, 9.56, 1.12, 11.25, 11.92, 12.18, 12.59, 13.27, and 13.88 μ. The n.m.r. spectrum (τ) in carbon tetrachloride showed the aromatic protons individually as follows: a doublet at τ 1.67 (J = 2 c.p.s.) for the 7-*H*; a pair of doublets at 2.10 (J_1 = 9 c.p.s., J_2 = 2 c.p.s.) for the 5-*H*; and a doublet at 2.67 (J = 9 c.p.s.) for the 4-*H*. The methyl groups gave two singlets of equal intensity at 7.53 and 7.77.

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.39; H, 4.53; N, 6.47.

3-Methyl-2-hydroxymethylbenzo[*b*]thiophene (V).—A solution consisting of 10 ml. of 95% alcohol, 0.40 g. (0.0025 mole) of II, and 0.05 g. (0.0013 mole) of sodium borohydride was allowed to stand for 1 hr. A pellet of sodium hydroxide was added, and the alcohol was removed by distillation, adding water to maintain the volume. The crude alcohol, which separated on cooling, was recrystallized from ether–hexane to give 0.22 g. (54%) of material, m.p. 90–91°, lit.[7] m.p. 90.6–91.6°. Infrared peaks were at 3.05, 3.40, 3.48, 6.82, 6.95, 7.22, 7.33, 8.47, 8.60, 8.77, 10.0 broad, 10.65, 13.20, 13.67, 14.00, and 14.55 μ. The n.m.r. spectrum in carbon tetrachloride showed a multiplet from τ 2.38 to 2.98 for the aromatic protons, a singlet at 5.40 for the methylene group, a singlet at 6.83 for the hydroxylic proton, and a singlet at 7.83 for the methyl group.

3-Methyl-2-aminomethylbenzo[*b*]thiophene Hydrochloride.—A solution of 0.1 g. of lithium aluminum hydride and 0.20 g. (0.0010 mole) of III in 25 ml. of ether was refluxed overnight, and water was added dropwise to decompose the excess reducing agent. Excess dilute sodium hydroxide was added to dissolve the aluminum hydroxide, and the solution was extracted with ether. The amine was extracted from the ethereal solution with dilute hydrochloric acid, the acid extract was neutralized, and the amine, 0.1 g. (56%), m.p. 59–60°, was recovered by ether extraction. On drying *in vacuo*, it was converted to a brown oil. The latter was treated with dilute hydrochloric acid to give a sparingly soluble hydrochloride, which was collected on a filter and washed with ether and with water; the solid melted at 220° with decomposition.

Anal. Calcd. for $C_{10}H_{11}NS\cdot HCl$: N, 6.56. Found: N, 6.43.

An excess of cold aqueous sodium nitrite was added to a cold solution of the amine hydrochloride dissolved in dilute hydrochloric acid. After standing at room temperature for an hour, the solution was warmed briefly on the steam bath, cooled, and extracted with ether. After crystallization from pentane, V, m.p. 91–92°, was recovered from the ether solution (identity was established by its infrared spectrum and a mixture melting point determination).

2,3-Dimethyl-6-nitrobenzo[*b*]thiophene 1,1-Dioxide.—Oxidation of 1.0 g. of I with 2.5 ml. of 40% peracetic acid in 10 ml. of acetic acid gave 0.95 g. (79%) of the 1,1-dioxide, m.p. 150–151°, lit.[6] m.p. 149–150°. The n.m.r. spectrum in 1,1,2,2-tetrachloroethane showed a multiplet at τ 2.38 to 2.60 and a singlet at 7.87 for the two methyl groups. A 0.85-g. sample of the dioxide was dissolved in 5 ml. of concentrated sulfuric acid, the solution was cooled to 0°, and a solution of 0.27 ml. of concentrated nitric acid in 1 ml. of concentrated sulfuric acid was added dropwise. Processing in the usual manner gave a product, m.p. 199–200° after two crystallizations from 95% alcohol. This material had an infrared spectrum identical with that of a sample of 2,3-dimethyl-6-nitrobenzo[*b*]thiophene 1,1-dioxide, m.p. 201–202°, obtained in 71% yield by oxidation of IV with 40% peracetic acid, and a mixture melting point determination showed no depression. The n.m.r. spectrum in 1,1,2,2-tetrachloroethane showed a singlet (1.5) at τ 1.48 and a doublet (0.5) at τ 1.64 (J = 2. c.p.s.), which probably resulted from superimposition of a doublet at τ 1.48 (J = 2 c.p.s.) for the 7-*H* aromatic proton with a pair of doublets centered at 1.57 (J_1 = 9 c.p.s., J_2 = 2 c.p.s.) for the 5-*H* aromatic proton. There was a doublet (1) at τ 2.47 (J = 9 c.p.s.) for the 4-*H* aromatic proton and a singlet (6) at 7.80 for the two methyl groups.

Anal. Calcd. for $C_{10}H_9NO_4S$: C, 50.21; H, 3.79; N, 5.86. Found: C, 50.64; H, 3.72; N, 5.94.

Acknowledgment.—This work was supported by the American Petroleum Institute under Project 48B.

(7) R. Gaertner, *J. Am. Chem. Soc.*, **74**, 2185 (1952). The isomer, 2-methyl-3-hydroxymethylbenzo[*b*]thiophene, is reported to melt at 145.8–147.4° [**74**, 766 (1952)].

Preparation of 5-Dinitromethyltetrazole from Salts of Dinitroacetonitrile

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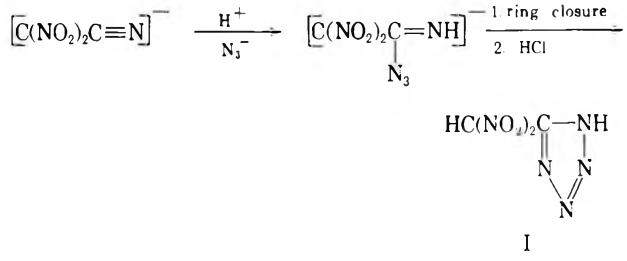
Received October 7, 1963

A general method for preparing tetrazoles by the reaction of nitriles with sodium azide in the presence or absence of ammonium ion in dimethylformamide has recently been described.[1,2] We attempted to extend

(1) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).

(2) W. P. Norris, *J. Org. Chem.*, **27**, 3248 (1962).

this to the preparation of the previously unknown dinitromethyltetrazole by the reaction of dinitroacetonitrile and sodium azide in water but with negative results, probably due to generation of the sodium salt of dinitroacetonitrile and the highly associated hydrazoic acid. It has now been found that the product can be obtained using salts of dinitroacetonitrile (sodium or ammonium, but not potassium) in refluxing water but not in dimethylformamide. This appears to be the first example of the use of an organonitrile salt[3] to form a tetrazole and the product is the first example of a 5-nitroalkyltetrazole. The reaction may be represented as shown.

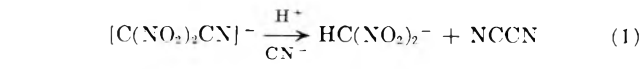


I

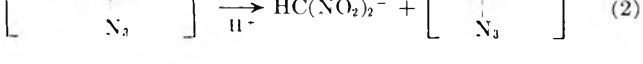
It would appear that the strong electron-withdrawing effect of the *gem*-dinitro group would greatly enhance nucleophilic attack by the azide ion on the carbon of the nitrile group.[4] The product, however, was obtained in only 8–12% yields after purification. This may have been partly due to hindrance of the reaction by repulsion of the negative azide ion by the dinitroacetonitrile anion, or sterically by the bulky dinitromethyl group.

Over 70% of the dinitroacetonitrile salt was recovered after 24 hrs. of refluxing, starting with either the sodium or ammonium salt. In the reaction of sodium dinitroacetonitrile, however, most of the nitrile was recovered as the ammonium salt and the yield of product was somewhat reduced apparently because of depletion of available ammonium ion. A much lower yield of 5-dinitromethyltetrazole was obtained using one-tenth the original amount of ammonium chloride catalyst in the reaction of azide ion with ammonium dinitroacetonitrile. Available ammonium ion may also be depleted by formation of ammonium salts of the products.

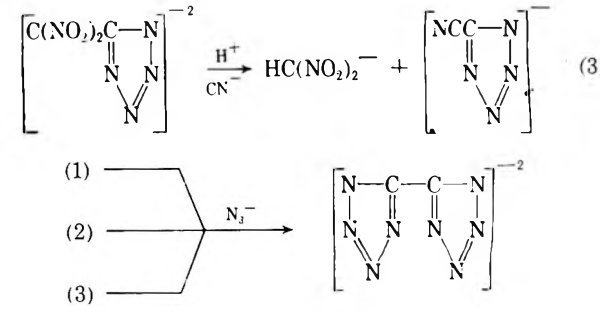
The yield of dinitromethyltetrazole obtained after 48 hr. of refluxing was nearly the same as that obtained after 24 hr., while that of diammonium bitetrazole (II), a by-product of the reaction, increased threefold. Decomposition products also increased considerably. Cyanide ion formed as a breakdown product was shown to be present in the reaction mixture after 24 hr. of refluxing (see Experimental). However, it is not clear how the cyanide ion arises. Cyanide ion, in turn, may react to produce bitetrazole in any one of these ways.



(1)



(2)



(3).

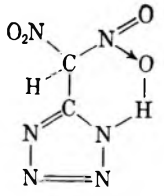
Nucleophilic displacement by cyanide ion appears to be related to a previously reported[5] example of displacement by hydroxyl ion on the nitrile carbon of methyl 4,4-dinitro-4-cyanobutyrate.

The reaction of sodium dinitroacetonitrile with sodium azide and ammonium chloride in dimethylformamide appeared to produce only decomposition products. No product was obtained with potassium dinitroacetonitrile in refluxing water or in dimethylformamide at 110–120° during 48 hr. It has been observed that potassium dinitroacetonitrile is unchanged in alkylation, addition, and other reactions contrary to the more normal behavior of the sodium and other salts of dinitroacetonitrile.[6]

Mono- and disodium, monoammonium, and monoguanidine salts of 5-dinitromethyltetrazole also were prepared from the free dibasic acid. The disodium salt was found to be much more thermally stable than the monosodium salt. This may be attributed to a pronounced resonance stabilization of the tetrazole ring in the dianion by release of an electron pair to the ring.

Infrared bands of dinitromethyltetrazole and its salts attributed to NH stretching, the tetrazole ring, and the nitro groups are summarized in Table I.

The shift in frequency for the nitro groups from 1590 cm.$^{-1}$ for dinitromethyltetrazole, to 1570 cm.$^{-1}$ for the monosodium salt, and to 1530 cm.$^{-1}$ for the disodium and monoammonium salts, may be due to a change in character from nitro to nitronate.[7] The absence of the NH band in the disodium salt, and its presence in the monosodium salt of dinitromethyltetrazole shows that the stronger of the two acidic hydrogens of dinitromethyltetrazole is in the dinitromethyl group. The occurrence of N–H stretching below 3300 cm.$^{-1}$ is indicative of hydrogen bonding and is probably due to intramolecular hydrogen bonding. For the free acid this may be illustrated as shown.



Intramolecular hydrogen bonding also has been observed for 2,2-dinitroethylamine.[9]

(3) Trimethylammonium cyanide has been used to prepare tetrazole.[1]

(4) Electronegative groups attached to the nitrile facilitate tetrazole formation.[1]

(5) C. O. Parker, W. D. Emmons, A. S. Pagano, H. A. Rolewicz, and K. S. McCallum, *Tetrahedron*, **17**, 89 (1962).

(6) C. O. Parker, W. D. Emmons, H. A. Rolewicz, and K. S. McCallum, *ibid.*, **17**, 79 (1962).

(7) A similar shift is shown by α,α-dinitronitriles compared with salts of 1,1-dinitroparaffins.[8]

(8) L.W. Kissinger and H. E. Ungnade, *J. Org. Chem.*, **25**, 1471 (1960).

(9) M. J. Kamlet and J. C. Dacons, *ibid.*, **26**, 3005 (1961).

TABLE I

INFRARED BANDS OF 5-DINITROMETHYLTETRAZOLE AND ITS SALTS[a]

Compound	Infrared, cm.$^{-1}$ NH[b]	Tetrazole ring[c]	*gem*-Dinitro group[d]	Others[e]
5-Dinitromethyltetrazole	3130	1070, 1048, 1016, 997	1590, 1330	1518, 1407, 1350
Monosodium-5-dinitromethyltetrazole	3170	1070 .. 1018, 1005	1570, 1350	1485, 1412 ..
Disodium-5-dinitromethyltetrazole	..	.. 1032, 1015 ..	1530, 1365	.. .. ..
Monoammonium-5-dinitromethyltetrazole	3230	.. 1045, 1022 ..	1530, 1360	.. 1400 ..

[a] All spectra were obtained on Nujol mulls (Perkin-Elmer spectrophotometer Model 321). [b] Bands corresponding to hydrogen bonded NH (3230–3030 cm.$^{-1}$) [R. A. Braun and W. A. Mosher, *J. Am. Chem. Soc.*, **80**, 4919 (1958)]. [c] In general, the tetrazole ring absorbs between 1100–1000 cm.$^{-1}$ [E. Lieber, D. R. Levering, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951)]. [d] In general, *gem*-dinitro absorbs near 1580 and 1330 cm.$^{-1}$ [J. F. Brown, *J. Am. Chem. Soc.*, **77**, 6341 (1955)]. [e] Possibly due to nitro.

Experimental[10]

Potassium dinitroacetonitrile[11] was treated with decolorizing charcoal and recrystallized from water. Sodium and ammonium dinitroacetonitrile were prepared from the potassium salt according to a previously described method.[6] The salts were dried at 100° for 2 hr., and kept in a desiccator over Drierite.[12] Sodium dinitroacetonitrile had m.p. 224–226° (lit.[6] m.p. 224–226°) and ammonium dinitroacetonitrile had m.p. 175–176° dec. (lit.[6] m.p. 182° dec.). Sodium azide was treated with decolorizing carbon and crystallized from water. Ammonium chloride and guanidine carbonate were reagent grade and were used without further treatment.

Reaction of Sodium Dinitroacetonitrile, Sodium Azide, and Ammonium Chloride.—A solution of sodium dinitroacetonitrile (15.30 g., 0.100 mole), sodium azide (6.65 g., 0.102 mole), and ammonium chloride (5.50 g., 0.102 mole) in 50 ml. of water in a round-bottomed flask fitted with a condenser and magnetic stirrer was stirred and refluxed for 24 hr.[13]

Isolation of Diammonium Bitetrazole and Its Conversion to Bitetrazole.—The solution was cooled and kept at 5° for several hours; the yellowish solid was collected on a filter, washed with cold water, and dried at 110°. The yield of the salt was 0.59 g. (7.0%). In another run using half the quantities, the yield after 48 hr. of refluxing was 0.90 g. (21.2%). Crystallization from water gave white needles which did not melt up to 300°.

Anal. Calcd. for $C_2H_8N_{10}$: C, 13.95; H, 4.65; N, 81.40. Found: C, 13.78, 13.98; H, 4.88, 5.02; N, 81.50, 82.03.

The diammonium bitetrazole was dissolved in an excess of hot 10% hydrochloric acid (1 g. of salt in 10 ml. of acid). The solution was filtered hot and the filtrate cooled to 5° causing bitetrazole to precipitate as a white, crystalline solid. The product was highly acidic in aqueous solution. For analysis, a sample was recrystallized twice from water and dried at 110°, m.p. 255.0–255.5° dec. (lit.[14] m.p. 254–255° dec.).

Anal. Calcd. for $C_2H_2N_8$: C, 17.38; H, 1.45; N, 81.16; neut. equiv., 69.0. Found: C, 17.33, 17.36; H, 1.46, 1.51; N, 82.40, 82.43; neut. equiv., 69.1.

Isolation of 5-Dinitromethyltetrazole.—The pH of the ammonium bitetrazole filtrate was adjusted to less than 1 (measured with a pH meter) with concentrated hydrochloric acid. Hydrazoic acid and water were removed under water aspiration on the steam bath. The remaining solids were extracted with boiling acetone and the insoluble salts were removed by filtration and discarded. The acetone was evaporated under reduced pressure, the remaining dry solid was extracted several times with ethyl ether totaling several hundred milliliters, and insoluble solids were reserved for recovery of dinitroacetonitrile salt. Removal of the ether gave 2.26 g. of crude product. Crystallization from methyl alcohol gave 1.39 g. (8.0%) of white, crystalline product which produced intensely yellow, highly acidic aqueous solutions. The yield after 48 hr. of refluxing using half the quantities was 0.77 g. (8.8%). For analysis a sample was recrystallized from methyl alcohol.

Anal. Calcd. for $C_2H_2N_6O_4$: C, 13.80; H, 1.16; N, 48.28; neut. equiv., 87.0. Found: C, 14.01, 14.04; H, 1.50, 1.24; N, 48.10, 48.20; neut. equiv., 87.7; pK_1, 1.65, and pK_2, 3.60 (water, 25°).[15]

The free acid, on heating fairly rapidly in a capillary tube produced nitrogen dioxide fumes at about 100°, gradually darkened above 150°, and went abruptly from dark brown to black, without melting, at about 180°.

Recovery of Ammonium Dinitroacetonitrile.[16]—The ether-insoluble solids were extracted several times with small quantities of hot ethyl acetate leaving 5.3 g. of ammonium dinitroacetonitrile which was collected on a filter. The filtrate was evaporated to a small volume (approximately 25 ml.) and cooled to 5°; an additional 3.9 g. of ammonium dinitroacetonitrile was collected. Evaporation of the final filtrate left 2.1 g. of ammonium dinitroacetonitrile containing a small amount of the sodium salt. The total recovered salt was 11.3 g. (76.4%). Total recovered salt from the reaction mixture refluxed 48 hr. using half quantities was 5.2 g. (70.7%). The ammonium salt was recrystallized twice from alcohol giving white crystals whose infrared spectrum was identical with that of a known sample prepared as described.

Preparation of Monoammonium 5-Dinitromethyltetrazole.—5-Dinitromethyltetrazole was dissolved in sufficient 10% aqueous ammonia to give a solution having a pH greater than 9. The water and excess ammonia were evaporated and the product was crystallized from ethyl alcohol. The monoammonium salt darkened above 195°, and abruptly decomposed without melting at 214°. Several attempts to prepare the diammonium salt gave monoammonium salt.

Anal. Calcd. for $C_2H_5N_7O_4$: C, 12.56; H, 2.62; N, 51.36. Found: C, 12.69; H, 2.70; N, 51.55.

Preparation of Monosodium and Disodium 5-Dinitromethyltetrazole.—5-Dinitromethyltetrazole was titrated electrometrically to either the first or second end points with 0.1 *N* sodium hydroxide. The water was removed and the dry salts were washed with alcohol, with acetone, and then dried. The disodium salt appeared to be unchanged up to 310°, and the monosodium salt exploded violently at approximately 160°.

Anal. Calcd. for $C_2HN_6O_4Na$: C, 12.21; H, 0.76; N, 42.73; Na, 11.76. Found: C, 12.24; H, 0.51; N, 42.86; Na, 11.73.

Anal. Calcd. for $C_2N_6O_4Na_2$: C, 11.13; N, 38.39; Na, 21.30. Found: C, 11.01; H, 0.00; N, 38.53; Na, 21.10.

Preparation of the Monoguanidine Salt of 5-Dinitromethyltetrazole.—5-Dinitromethyltetrazole (0.075 g.) and guanidine carbonate (0.098 g.) were dissolved in 2 ml. of water. The pH of the solution was adjusted to about 3 with concentrated hydrochloric acid. The light yellow, crystalline precipitate was filtered, after cooling to 5°, and recrystallized twice from water. It decomposed without melting at 164.0–164.5°.

Anal. Calcd. for $C_3H_6N_9O_4$: C, 15.52; H, 2.61; N, 54.30. Found: C, 15.56, 15.26; H, 3.57, 3.37; N, 54.41, 54.20.

Reaction of Ammonium Dinitroacetonitrile with Sodium Azide and Ammonium Chloride.—Ammonium dinitroacetonitrile (7.40 g., 0.050 mole), sodium azide (3.33 g., 0.051 mole), and ammonium chloride (2.75 g., 0.051 mole) in 25 ml. of water were refluxed for 24 and 48 hr. Both reaction mixtures then were treated as described for the reactions with sodium dinitroacetonitrile except that the ether-insoluble solids were not extracted with ethyl acetate. Yields are summarized in Table II.

(10) All melting points are uncorrected.

(11) Obtained from the Rohm and Haas Co., Redstone Arsenal Research Division.

(12) Sodium dinitroacetonitrile absorbs moisture from the atmosphere and forms a stable monohydrate.[5]

(13) Highly alkaline fumes escaped from the condenser after approximately 0.5 hr. of refluxing. The absorbed fumes in dilute hydrochloric acid gave a negative test for ammonium ion with Nessler's reagent.

(14) F. R. Benson, *Chem. Rev.*, **41**, 1 (1947).

(15) A. Weissberger, "Physical Methods of Organic Chemistry," Vol. I, Part II, 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1946, pp. 1747, 1748.

(16) Salts of dinitroacetonitrile are recovered unchanged from concentrated hydrochloric acid and, therefore, were recovered from the reaction mixture after adjusting the pH to less than 1.

TABLE II

Reflux time, hr.	Bitetrazole, g. (%)	5-Dinitromethyltetrazole, g. (%)	Recovered ammonium dinitroacetonitrile, g. (%)
24	0.68 (8.0)	1.07 (12.3) from 2.1 g. of crude	5.37 (71.8)
48	1.80 (21.9)	0.80 (9.2) from 2.7 g. of crude	2.64 (35.2)

A reaction using 0.05 mole of ammonium dinitroacetonitrile, 0.051 mole of sodium azide, and 0.0051 mole of ammonium chloride (10 mole % of the sodium azide) in 25 ml. of water refluxed for 24 hr. gave 0.34 g. (4.0%) of bitetrazole and 0.2 g. (2.3%) of crude 5-dinitromethyltetrazole.

After 24 hr. of refluxing, the reaction mixture gave a positive test for the presence in large concentration of cyanide ion with benzidine–copper acetate reagent.[17]

Elementary analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Acknowledgment.—The author gratefully acknowledges the many helpful suggestions made by Dr. G. P. Sollott of this laboratory in reviewing this paper and the helpful discussions with Drs. R. A. Henry and W. G. Finnegan of the Naval Ordnance Test Station.

(17) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1957, pp. 174, 175.

The Synthesis of 1-Aryl 3-Cyano-5-pyrazolones

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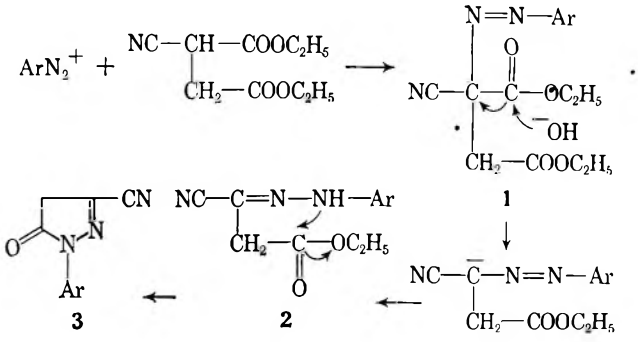
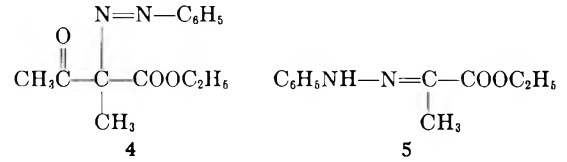
Kendall and Fry[1] reported a method for the preparation of certain 1-aryl 3-substituted pyrazolones by the reaction of diazotized aromatic amines with the appropriately substituted diethyl succinates in an alkaline medium. While this suggested a convenient procedure for 3-cyanopyrazolones, in the single example describing the use of diethyl cyanosuccinate,[2] only the 3-carboxy compound was isolated, presumably because the alkaline conditions used for the ring closure also led to hydrolysis of the cyano group.[3]

As suggested by Kendall and Fry, the reaction may be considered to be a three-step process. The initially formed azo compound **1** loses the carbethoxyl group to give an intermediate which tautomerizes to the phenylhydrazone **2**. This then cyclizes to the pyrazolone **3** (see col. 2).

Recently Yao and Resnick[4] have reported the isolation and spectral properties of intermediates analogous to **1** and **2**. Thus, ethyl α-phenylazo-α-methylacetoacetate (**4**) had a λ_{max} of 272 mμ and ethylpyruvate phenylhydrazone (**5**) had absorption maxima at 290 and 312 mμ. These findings suggested that the reaction of diazonium salts with diethyl cyanosuccinate



could be followed by ultraviolet spectroscopy, and that, thereby, sufficiently mild conditions for the ring closure might be found which would permit the isolation of the desired 3-cyanopyrazolones.



When diazotized *p*-toluidine was added to diethyl cyanosuccinate in pyridine, an immediate yellow color appeared. Examination of the ultraviolet spectrum in ethanol of samples obtained by precipitating aliquots of the solution into aqueous hydrochloric acid showed the presence of strong absorption at 296 mμ, presumably due to **1**. Even on several hours standing, the reaction mixture showed no further changes. Addition of triethylamine caused the very slow, but never complete, diminution in the intensity of the 296 mμ peak, and the slow increase of broad absorption at 300–350 mμ (2?). However, addition of a mixture of triethylamine and 2% sodium hydroxide solution caused a rapid drop in the 296-mμ peak, transient broad absorption at 300–350 mμ, and the appearance of a new strong band centered at 254 mμ due to **3**. After 1 hr., no further significant changes were observed.

The procedure as described below appears to be a general one for the preparation of 1-aryl 3-cyanopyrazolones in reasonable yields from the corresponding aryl amines. The crude products made by this procedure were usually contaminated with traces of a yellow impurity. This is believed to be due to the presence of small amounts of aryl azopyrazolone formed by the reaction of **3** with traces of unconsumed diazonium salt. The use of an excess of diethyl cyanosuccinate suppresses the formation of this impurity which is easily removed during the work-up.

Experimental[5]

1-*p*-Tolyl-3-cyano-5-pyrazolone.—To a solution of 0.0375 mole of diethyl cyanosuccinate[6] in 175 ml. of pyridine was added a solution of the diazonium salt prepared by diazotizing, at 0–5°, 0.025 mole of *p*-toluidine in 50 ml. of water and 6 ml. of concentrated hydrochloric acid with 1.75 g. of sodium nitrite dissolved in 10 ml. of water. After the mixture had been stirred at 20° for 20 min., 50 ml. of triethylamine and 100 ml. of 2% aqueous

(1) (a) J. D. Kendall and D. J. Fry, British Patent 585,780 (1947); *Chem. Abstr.*, **42**, 224*b* (1948). (b) See also U. S. Patent 2,459,226 (1949); *Chem. Abstr.*, **43**, 3042*h* (1949).

(2) Ref. 1a, example 8 in patent.

(3) This may also have resulted *via* displacement of the cyano group rather than the carbethoxyl group from the intermediate azo compound.

(4) H. C. Yao and P. Resnick, *J. Am. Chem. Soc.*, **84**, 3514 (1962).

(5) Melting points are uncorrected and were obtained on a Mel-Temp capillary melting point apparatus. Elemental analyses were by Dr. S. M. Nagy of the Microchemical Laboratory, Massachusetts Institute of Technology. Ultraviolet spectra were determined using a Cary Model 11 spectrophotometer. Infrared spectra were determined on potassium bromide disks using a Perkin-Elmer Model 421 spectrophotometer.

(6) A. Haller and L. Barthe, *Compt. rend.*, **106**, 1413 (1888).

sodium hydroxide was added. The solution was stirred for 1.5 hr. and then poured into 400 ml. of concentrated hydrochloric acid and 1 kg. of ice. The resulting creamy solid was collected by suction filtration, washed with water, dissolved in 125 ml. of cold 2% sodium hydroxide solution, and extracted with three 50-ml. portions of ether to remove traces of an orange impurity. The solid obtained on acidification of the aqueous solution with 5% hydrochloric acid was collected and crystallized from acetic acid to give 3.15 g. (64%) of light tan crystals, m.p. 209–210° dec.; ultraviolet spectrum: λ_{max} 255 mμ (ε 16,000), shoulder at *ca.* 310 mμ (EtOH); infrared spectrum: very sharp absorption at 2248 cm.$^{-1}$ (C≡N).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.10. Found: C, 66.41; H, 4.52; N, 20.98.

In a similar fashion, the following aromatic amines were converted to the corresponding 1-aryl 3-cyanopyrazolones: *p*-ethylaniline (58%), m.p. 172–173° dec. (benzene); *p*-aminophenethyl alcohol (47%), m.p. 147–148° dec. (nitromethane); and *m*-aminobenzotrifluoride (64%), m.p. 117–120° (1,2-dichloroethane). Satisfactory analyses were obtained for all compounds.

Acknowledgment.—We wish to thank Dr. T. W. Milligan for helpful discussions and suggestions made during the course of this work.

Reactions of Cupric Bromide in Dioxane. Formation of ω-Bromo-o-hydroxyacetophenone

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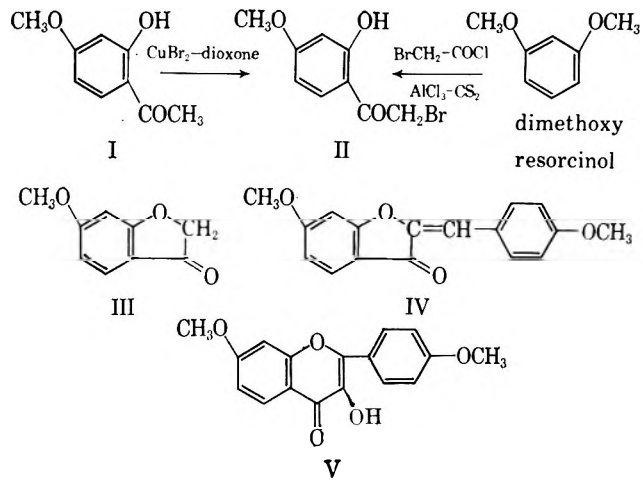
That cupric bromide acts as a brominating agent is not new to the organic chemists. Aliphatic ketones,[1] aliphatic aldehydes,[2] and cyclohexanone[3] have been successfully brominated with cupric bromide in methanol, aqueous methanol, or toluene at the α-carbon atom. Recently, 17-oxoandrostane or its 17-enol acetate has been shown to give 16-α-bromo-17-oxoandrostane[4] with cupric bromide.

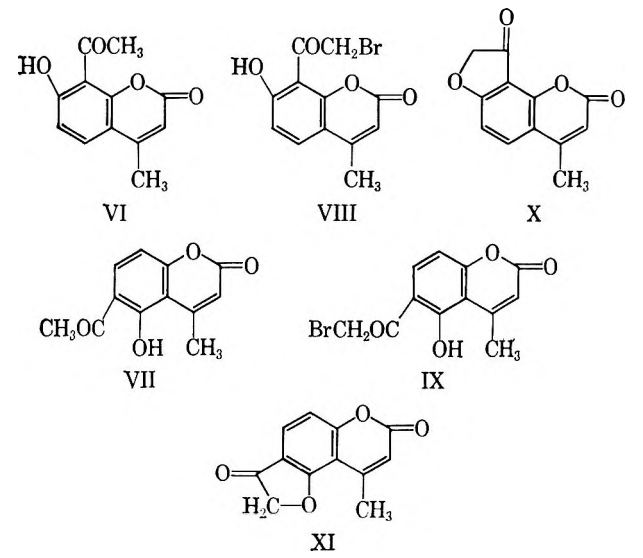
The present work deals with the action of cupric bromide in dioxane on *o*-hydroxyacetophenone and on some of its derivatives. When *o*-hydroxyacetophenone is brominated with reagents like bromine in acetic acid, ether, carbon tetrachloride, dioxane,[5] or aqueous acetic acid,[6] or with N-bromosuccinimide (NBS) or pyridine bromine complex,[7] nuclear bromination takes place. 4-Methoxy-2-hydroxyacetophenone (I) with cupric bromide in dioxane under reflux temperature gave a bromo compound (II), m.p. 161°. On analysis, II was found to be $C_9H_9BrO_3$. It was not identical with 5-bromo-4-methoxy-2-hydroxyacetophenone, m.p. 82°.

II gave I on treatment with zinc dust in an aqueous medium,[8] an acetoxy derivative *via* an iodo derivative, coumaran-3-one (III) with base,[9] benzal coumaran-3-one (IV) or flavonol V on condensation with an aromatic aldehyde in an alkaline medium,[10] and a rose red color with alcoholic potash. (Rose red coloration with alcoholic potassium hydroxide indicates a labile bromine atom which effects ring closure with an elimination of hydrogen bromide giving a benzofuran-3-one derivative.) These reactions clearly show that bromination has taken place at the ω-position and II is ω-bromo-4-methoxy-2-hydroxyacetophenone. This was further supported by its unambiguous synthesis[11] from dimethoxyresorcinol and bromoacetyl chloride.



I II III IV V

Similarly, 8-acetyl-7-hydroxy-4-methylcoumarin (VI) and 6-acetyl-5-hydroxy-4-methylcoumarin (VII) with cupric bromide in dioxane provided ω-bromo derivatives VIII and IX, respectively. VIII and IX gave the corresponding cyclic derivatives X and XI in alkaline medium.



VI VIII X VII IX XI

Bromination of 4-methylhydroxycoumarins with the usual brominating agents (as mentioned earlier) gave nuclear brominated products. The protection of hydroxyl group by acetylation leads to the formation of 4-bromomethyl derivatives with NBS[12] and the pyridine bromine complex.[13] However, cupric bromide in

(1) J. K. Kochi, *J. Am. Chem. Soc.*, **77**, 5274 (1955).
(2) C. E. Castro, *J. Org. Chem.*, **26**, 4183 (1961).
(3) A. W. Fort, *ibid.*, **26**, 765 (1961).
(4) E. R. Glazier, *ibid.*, **27**, 2937 (1962).
(5) A. V. Dombrovskii, *Russ. Chem. Rev.*, **30**, 635 (1961).
(6) M. G. Marathey, *J. Sci. Ind. Res.* (India), **20B**, 40 (1961).
(7) B. J. Ghiya and M. G. Marathey, *ibid.*, **20B**, 41 (1961); **21B**, 28 (1962).
(8) P. N. Wadodkar, *Indian J. Chem.*, **1**, 122 (1963).
(9) (a) P. Friedlander and J. Neudoerfer, *Ber.*, **30**, 1077 (1897); (b) K. Auwers, *ibid.*, **45**, 975 (1912); **47**, 3307 (1914).
(10) J. E. Gowan, P. M. Hayden, and T. S. Wheeler, *J. Chem. Soc.*, 5887 (1955).
(11) K. Auwers and P. Pohl, *Ann.*, **405**, 264 (1914).
(12) J. M. Sehgal and T. R. Seshadri, *J. Sci. Ind. Res.* (India), **12B**, 346 (1953).
(13) B. J. Ghiya, Ph.D. thesis, Nagpur University, 1962.

dioxane gives the ω-bromo derivative whether the hydroxyl group is protected by acylation or kept as such. This gives cupric bromide–dioxane a decided advantage over other brominating agents. Whether the hydroxyl group is protected or otherwise, bromination proceeds to take place at the carbon atom activated by the >C=O group. In compounds VI and VII, the second >C=O group in the pyrone ring has less activity owing to lactonization with oxygen, and such bromination takes place at the ω-position at the acetyl group in preference to C-3.[14,15]

Experimental

Preparation of ω-Bromo-4-methoxy-2-hydroxyacetophenone (II).—4-Methoxy-2-hydroxyacetophenone (1.7 g., 0.01 mole) and cupric bromide (4.5 g., 0.02 mole) in dioxane (50 ml.) were refluxed for 3 hr. The white cuprous bromide was filtered off at the pump and dioxane was removed under reduced pressure. The gummy greenish product was extracted with ether, the ethereal layer was dried with anhydrous sodium sulfate, and the ether was removed. The residue was crystallized repeatedly from petroleum ether–benzene to obtain shining white, hard crystals (1.1 g.), m.p. 161°.

Anal. Calcd. for $C_9H_9BrO_3$: C, 44.08; H, 3.67; Br, 32.65. Found: C, 43.98; H, 3.69; Br, 33.22.

Preparation of 6-Methoxybenzofuran-3-one (III).—II (1 g.) was dissolved in ethanol and treated with potassium hydroxide solution (10 ml., 40%). On slight warming the mixture turned rose red. After 2 hr. the mixture was acidified with hydrochloric acid. The rose red solid was filtered off and was crystallized repeatedly from methanol (0.5 g.), m.p. 170–171°. The ethanolic ferric chloride color was violet.

Anal. Calcd. for $C_9H_8O_3$: C, 65.86; H, 4.87. Found: C, 65.43; H, 4.92.

Preparation of 4′,6-Dimethoxybenzylidenecoumaran-3-one. (IV).—II (3.3 g.) was dissolved in hot ethanol (15 ml.) and anisaldehyde (3 ml.) was added to it. The mixture was heated to boiling and sodium hydroxide solution (10 ml., 40%) was added with stirring. The mixture was brought to boiling again. The yellowish shining solid was filtered off after 1 hr. and was crystallized repeatedly from 60% ethyl alcohol to obtain shining wooly crystals (1.5 g.), m.p. 135–136°. The ethanolic ferric reaction was negative.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.35; H, 4.96. Found: C, 72.08; H, 4.99.

The filtrate after removing compound IV, m.p. 135°, was diluted with water and kept overnight. It was acidified with hydrochloric acid, and the gummy yellow solid was fractionally crystallized from ethyl acetate. The first fraction gave 0.3 g. of IV, and the second fraction, m.p. 188° (acetic acid), was found to be 4′,7-dimethoxyflavonol (V).

Anal. Calcd. for $C_{17}H_{15}C_5$: C, 68.45; H, 4.7. Found: C, 68.15; H, 4.81.

Direct Formation of Flavonol V.—To II (1.5 g.) in hot ethyl alcohol (15 ml.) anisaldehyde (1.5 ml.) was added, and the mixture was boiled. After 15 min. sodium hydroxide solution (25 ml., 5%) was added with stirring and the reaction mixture was kept overnight. It was acidified with hydrochloric acid. The yellow solid was fractionally crystallized to give two fractions: one, m.p. 135° (0.2 g.), was IV; and the second, m.p. 188–189° (0.5 g.), was the flavonol V.

ω-Bromo-4-methoxy-2-hydroxyacetophenone (II). From Dimethoxyresorcinol and Bromoacetyl Chloride.—A solution of resorcinol dimethyl ether (2 g.) and bromoacetyl chloride (2.5 g., obtained from bromoacetic acid and thionyl chloride) in carbon disulfide (20 ml.) was treated with anhydrous aluminum chloride (5 g.) as described previously[11] to form ω-bromo-4-methoxy-2-hydroxyacetophenone (0.8 g.), m.p. 158–159°, identical with II obtained in the first experiment.

8-(Bromoacetyl)-7-hydroxy-4-methylcoumarin (VIII).—8-Acetyl-7-hydroxy-4-methylcoumarin (VI, 3.38 g.) and cupric bromide (9.2 g.) were dissolved in dioxane (100 ml.) in a round-bottom flask (250 ml.), and the contents of the flask were refluxed for 4–5 hr. The white cuprous bromide was filtered off at the pump and the solvent was removed under reduced pressure. A greenish yellow solid was extracted with ethyl acetate and dried over anhydrous sodium sulfate. The solvent was removed and the yellow solid was crystallized from ethyl alcohol to yield 3.0 g. of yellowish white shining crystals, m.p. 135°. It gave a positive test for halogen and a phenolic group. It gave a depression of mixture melting point with 8-acetyl-7-hydroxy-4-methyl-3-bromocoumarin, m.p. 210°.

Anal. Calcd. for $C_{12}H_9BrO_4$: C, 48.49; H, 3.03; Br, 26.94. Found: C, 48.25; H, 3.12; Br, 26.98.

6-(Bromoacetyl)-5-hydroxy-4-methylcoumarin (IX).—6-Acetyl-5-hydroxy-4-methylcoumarin (VII, 3.38 g.) and cupric bromide (9.2 g.) were dissolved in dioxane (100 ml.) and treated as above. The solid was crystallized fractionally from ethyl alcohol to yield yellowish white crystals (2.5 g.), m.p. 146°. It showed a depression of mixture melting point with 6-acetyl-5-hydroxy-4-methyl-3-bromocoumarin, m.p. 226°, and also with 8-bromo-6-acetyl-5-hydroxy-4-methylcoumarin, m.p. 204°.

Anal. Calcd. for $C_{12}H_9BrO_4$: C, 48.49; H, 3.03; Br, 26.94. Found: C, 48.15; H, 3.21; Br, 27.24.

Action of Alcoholic Alkali on Compounds VIII and IX.—VIII (1.5 g.) was dissolved in hot ethyl alcohol and potassium hydroxide (10 ml., 40%) was added to it with stirring. The mixture was heated for 5 min. and was kept overnight. The red-colored mixture on acidification with dilute hydrochloric acid gave a red solid. It was crystallized from ethyl alcohol to yield red shining crystals (0.8 g.) of X, m.p. 153–154°.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.7. Found: C, 66.26; H, 3.75.

IX on similar treatment as above gave a reddish crystalline compound (XI), m.p. 157–159°.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.7. Found: C, 66.22; H, 3.76.

Action of Zinc Dust and Water on Compound II.—A mixture of II (0.5 g.), zinc dust (1 g.), and water (20 ml.) was refluxed for 8 hr. The mixture was extracted with ether and dried over anhydrous sodium sulfate. The ether was removed and a gummy residue obtained on crystallization with 60% ethyl alcohol gave 0.3 g. of shining white crystals, m.p. 50°, which remained undepressed when mixed with 4-methoxy-2-hydroxyacetophenone.

(14) K. B. Doifode, *J. Org. Chem.*, **27**, 2665 (1962).

(15) When this article was under revision a paper by E. R. Glazier was published [*ibid.*, **27**, 4397 (1962)], dealing with bromination of a steroidal ketone in the presence of an olefinic bond using cupric bromide in tetrahydrofuran instead of in dioxane, effecting a similar bromination at the acetyl group.

The Rate of Oxidation of Alicyclic Ketones with Perbenzoic Acid[1a]

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Contribution No. 167 from the Instituto de Química de la Universidad Nacional Autónoma de México, México 20, D. F.

Received September 23, 1963

The oxidation of ketones with peracids to obtain esters or lactones has been thoroughly studied from the preparative[1b] kinetic and mechanistic points of view. The results of Criegee,[3] Friess,[2] and Doering[4,5] on the mechanism were explained on the basis of a slow, rate-controlling addition of the peracid to the ketone group. This is followed by cleavage of the oxygen–oxygen bond leaving an electron-deficient atom to which the more appropiate alkyl group shifts with a concerted release of the proton. In the steroid field the oxidation

(1) (a) Presented in part at the 8th Latin American Congress of Chemistry, Buenos Aires, Sept., 1962; (b) L. H. Sarett, *J. Am. Chem. Soc.*, **69**, 2899 (1947).

(2) S. L. Friess and N. Farnham, *ibid.*, **72**, 5518 (1950).

(3) von R. Criegee, *Ann.*, **560**, 127 (1948).

(4) W. von E. Doering and L. Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950).

(5) W. von E. Doering and E. Dorfman, *ibid.*, **75**, 5595 (1953).

of 20-keto steroids[6] to produce androstane derivatives is of particular value. In preparative work, Δ^5-3-ketones and 3-,[7,9] 7-,[8] 17-,[9,10] and 20-ketones[6] have been oxidized to the corresponding lactones, but no kinetic study measuring the rate of oxidation of these ketones has been reported.

Therefore, the rates of oxidation of some simple alicyclic ketones were measured in order to investigate the effect of alkyl substituents located at different sites in the ring. Compounds examined included substituted cyclopentanones and cyclohexanones, α-halo ketones, and steroid ketones. The results obtained are reported in Table I.

TABLE I

OXIDATION OF KETONES WITH PERBENZOIC ACID

Cyclopentanones	$k_2 \times 10^4$ l. mole^{-1} sec.$^{-1}$
Cyclopentanone	2.15 ± 0.1
3-Methylcyclopentanone	1.39 ± 0.01
Camphor	0.245 ± 0.05
Fenchone	0.198 ± 0.07
1-Indanone	0.17 ± 0.04
5-Methoxyindanone	0.917 ± 0.04
Cyclohexanones	
Cyclohexanone	15.8 ± 0.04
2-Methylcyclohexanone	7.53 ± 0.08
2,2-Dimethylcyclohexanone	5.04 ± 0.1
3-Methylcyclohexanone	12.2 ± 0.03
4-Methylcyclohexanone	19.2 ± 0.05
4-*t*-Butylcyclohexanone	27.7 ± 0.09
1-Tetralone	0.11 ± 0.06
6-Methoxy-1-tetralone	0.65 ± 0.01
α-Halo and steroid ketones	
2-Chlorocyclohexanone	0.425 ± 0.001
2-Bromocholestan-3-one	1.26 ± 0.03
2,2-Dibromocholestan-3-one	33.2 ± 0.08
Cholestan-3-one	16.2 ± 0.05
3β-Hydroxyandrostan-17-one	0.352 ± 0.01
3β-Acetoxyestrone	0.22 ± 0.009
17α-Methyl-17β-hydroxyandrostan-3-one	10.0 ± 0.01
3β-Acetoxypregnan-20-one	0.119 ± 0.005
Cyclodecanone	0.145 ± 0.002

Experimental

The oxidation study was made at 25 ± 0.02° using a thermoregulated constant temperature bath. The concentration ratio of perbenzoic acid to ketone was 1.25 (0.05 *M* for ketone and 0.0625 *M* for the perbenzoic acid). Each experiment was started by mixing a measured volume of the perbenzoic acid solution of known concentration with chloroform in a dark volumetric flask and allowing it to reach the working temperature. The ketone dissolved in chloroform was added to the mixture and the volume was brought up to 100 ml. At convenient times aliquots were withdrawn and treated with an excess of potassium iodide in acid medium. The iodine liberated was titrated with 0.1 *N* sodium thiosulfate. At the same time a blank reaction was run to measure the autodecomposition of perbenzoic acid.[11]

All the samples used were purified specimens but, since all of them are known, only their physical constants are reported here, together with a brief description of the preparation of some of them.

Cyclopentanone, cyclohexanone, 3-methylcyclohexanone, 4-methylcyclohexanone, 4-*t*-butyl-cyclohexanone, 1-indanone, 1-tetralone, camphor, and fenchone were Eastman Kodak samples purified by distillation or through their semicarbazones. Hydrolysis of the latter and further distillation gave samples possessing the following constants: cyclopentanone, $n^{25}D$ 1.4356; cyclohexanone, b.p. 143° (585 mm.), $n^{20}D$ 1.4501; semicarbazones, m.p. 164–165°; 3-methylcyclohexanone, $n^{25}D$ 1.4473; 4-methylcyclohexanone, $n^{25}D$ 1.4454; 4-*t*-butylcyclohexanone, m.p. 66.5°; 1-indanone, m.p. 41°; semicarbazone, m.p. 241–242°; 1-tetralone, $n^{26}D$ 1.5679; semicarbazone, m.p. 220–222°; camphor, m.p. 179°; fenchone, b.p. 82–84° (25 mm.), $n^{26}D$ 1.4610; cholestan-3-one, m.p. 130–131°; eq. 2-methylcyclohexanone, prepared by oxidation of 2-methylcyclohexanol with sodium dichromate in acid medium had b.p. 63–66 (23 mm.), $n^{26}D$ 1.4442; semicarbazone, m.p. 188°; 3-methylcyclopentanone was obtained by oxidation of 4-methylcyclohexanone with nitric acid and pyrolysis of the resultant methyladipic acid with barium hydroxide for 5 hr. at 300° and had b.p. 46–49° (15 mm.), $n^{25}D$ 1.4320; 2,2-dimethylcyclohexanone, b.p. 153–155° (585 mm.), $n^{26}D$ 1.4453, was prepared from 2-methylcyclohexanone by treatment of the latter with sodamide and methyl iodide. Ring enlargement of cyclononanone by the action of diazomethane and purification of the product through the semicarbazone, m.p. 210–211°, gave after hydrolysis the desired cyclodecanone, b.p. 85–87° (10 mm.).

2-Chlorocyclohexanone was prepared by direct chlorination of cyclohexanone at 0° and had b.p. 87–89° (14 mm.).

2-bromocholestan-3-one, from bromination of cholestan-3-one in acetic acid at 15° was recrystallized from chloroform and had m.p. 168–170°. 2,2-Dibromocholestan-3-one was prepared by the same procedure, m.p. 143.5–145°.

Δ^5-Cholesten-3-one, m.p. 124–124.5°, was obtained by oxidation of 5,6-dibromocholesterol followed by debromination with zinc.

3β-Acetoxy-Δ^5-cholesten-7-one, m.p. 158–160°, was prepared by oxidation of cholesteryl acetate with *t*-butyl chromate.

5-Methoxyhydrindanone, m.p. 106–107°, was obtained by the Bachman method, and 6-methoxytetralone, m.p. 77°, by oxidation of the corresponding alcohol with chromium trioxide–acetic acid. 3β-Acetoxy-Δ^5-pregnen-20-one, m.p. 142–144°, was obtained by catalytic hydrogenation (Pd–C) of Δ^5-pregnenolone acetate in ethyl acetate solution in acid medium. Other steroids were obtained as gifts from the Syntex Laboratories.

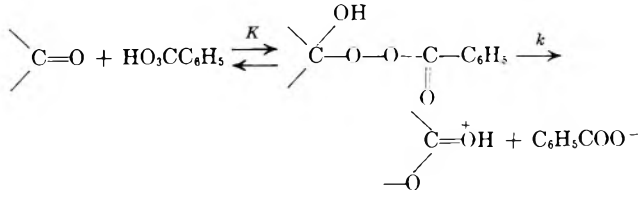
The perbenzoic acid was prepared by the method of Kergomar and Bigow[12] in almost quantitative yield. By difference of iodometric and base titration there was found to be 0.35% of benzoic acid present in the perbenzoic acid which was used in chloroformic solution for the kinetic experiments.

Results

The results obtained are given in Table I. In all cases a modified second-order rate equation was applied to take into consideration the amount of perbenzoic acid that autodecomposes slowly during the reaction.[11] Only the data for the first 30% of the reaction was considered since after this the per cent of reaction deviations from the modified second-order rate equation rises.

Discussion

Most of the results of Table I can be explained with the following mechanism.



In the first group of ketones (cyclopentanones), it is

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clear that the steric effects of the alkyl groups have a direct influence on the approach of the peracid to the carbonyl. This will affect mainly K and not k, and the over-all result is a lower rate. The rate constant of 3-methylcyclopentanone is lower than that for cyclopentanone, and the bicyclic ketones, camphor and fenchone, in which the keto group is surrounded by the methyl groups and the carbon skeleton, have much lower values.

Indanone has a lower rate constant than cyclopentanone as is expected due to the restriction in the polarization of the carbonyl which implies a lowering in resonance energy of this compound, going to the addition product (C). A methoxy group at C-5 increases the rate of oxidation in indanone and probably this is due to a higher migration capability of the aromatic group that increases k in comparison with the unsubstituted ketone.

In the cyclohexanones, 2-methyl-, 2,2-dimethyl-, and 3-methylcyclohexanones are less reactive than cyclohexanone owing to steric considerations; their rate constants can be easily explained on these grounds, since the oxidation slows as the groups get nearer and more bulky. In the 4-methyl- and 4-*t*-butylcyclohexanones it is at first sight surprising to find an increase in the rate, which is higher in the *t*-butylcyclohexanone.

We can consider the peracid oxidation as an addition reaction in which the anion attacks the tertiary carbonium ion of the polarized carbonyl group. Any factor stabilizing this ion in the transition state will favor the rate of oxidation.

There are several previous cases of 1:4 interactions in the cyclohexane. Owen[13] suggested the formation of a 1,4-oxygen bridge in the reaction of halohydrins with base. Bennett[14] suggested the presence of a cyclic halogenonium ion in the dehalogenation reactions of 1,4-dihalocyclohexanes and Goering[15] proposed a 1,4-bromonium ion bridge in the rearrangement of dibromocyclohexanes with ferric bromide. More conclusive was the solvolysis of *trans*-4-methoxycyclohexyl tosylate studied by Noyce.[16,17] This author and his co-workers suggested that anchimeric assistance is possible through an intermediate cyclic nonclassical ion in which the cyclohexane adopts the boat form, when the electrons on oxygen can stabilize the positive charge on the carbon. In the 4-methyl- and 4-*t*-butylcyclohexanones some type of 1,4-interaction must be operating which promotes reaction.[18]

Tetralone oxidation is 144 times slower than cyclohexanone and this result can be explained as being due to the decrease in resonance energy. A 6-methoxy group increases the migration capability of the aromatic ring and therefore k and the observed rate are higher.

In the halo ketones, it is of note that 2-chlorocyclohexanone and 2-bromocholestan-3-one are less reactive than cyclohexanone. In the chlorocyclohexanone the halogen is mainly equatorial[19] in the equilibrium mixture, and in the 2-bromocholestan-3-one it is known that bromine is α-equatorial. In both cases the dipole of the halogen and the carbonyl are in the same plane and this makes more difficult the polarization of the carbonyl with development of a positive charge on the carbonyl carbon. As a consequence these two halo ketones have a lower rate than cyclohexanone. A second bromine atom increases 26 times the rate in comparison with the monobromo ketone. This second bromine is axial and the increase in rate should be due to participation of the bromine atom and stabilization of the positive charge by formation of a bromonium ion.

Cholestan-3-one has a rate similar to that of cyclohexanone. The keto group at C-17 is oxidized at a rate that can be compared with the one of camphor and is in agreement for a 2,2,3-trisubstituted cyclopentanone. The C-20 keto group is still less reactive than the C-17 keto group.

The obtained results allow us to establish the following order of oxidation for keto steroids: 3-keto > 17-keto > 20-keto.[21]

Acknowledgment.—The authors thank Dr. A. Cross for improving the writing of the manuscript, and Dr. K. Kopecky for helpful comments.

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(21) A similar order has been found for the reduction of these ketones with sodium borohydride [J. L. Mateos, *J. Org. Chem.*, **24**, 2034 (1959)] and a similar trend is observed for the integrated absorption area of the carbonyl in their infrared spectra [R. Cetina and J. L. Mateos, *ibid.*, **25**, 704 (1960)].

Synthesis of α-(Ferrocenylmethyl) Ketones by the Enamine Method[1]

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Many aldehydes and ketones can be α-alkylated *via* C-alkylation of their enamines.[3-6] N-Alkylation of enamines, which occurs to a considerable extent when simple alkyl halides are used as alkylating agents, leads to ultimate recovery of starting carbonyl compounds and is, of course, undesirable. The desired C-alkylation occurs to the exclusion of N-alkylation when the alkylating agents are reactive halides like allyl halides, benzyl halides and α-halo esters, or conjugated olefins like acrylonitrile and acrylic esters. By analogy with benzyl halides, the ferrocenylmethyl

(1) (a) Supported in part by a grant from the Research Corporation; (b) abstracted from the M.S. thesis (University of Mississippi, Aug., 1963) of M. T. Dorsett; (c) a preliminary report was presented at the 14th Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov., 1962.
(2) To whom inquiries should be addressed at the Department of Chemistry, Florida Atlantic University, Boca Raton, Fla.
(3) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).
(4) G. Stork and H. Landesman, *ibid.*, **78**, 5128 (1956).
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(6) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

halides should bring about exclusive or at least predominant C-alkylation of enamines. The net result would be the introduction of the ferrocenylmethyl group into the α-position of carbonyl compounds. However, attempts at the synthesis and isolation of ferrocenylmethyl halides have so far failed, although the chloride has apparently been obtained in solution.[7] (Ferrocenylmethyl)trimethylammonium iodide has often served as ferrocenylmethylating agent in place of the missing ferrocenylmethyl halides.[8-15] We now report the successful use of this quaternary ammonium salt in the synthesis of 2-(ferrocenylmethyl)cyclopentanone and 2-(ferrocenylmethyl)cyclohexanone by the alkylation of the pyrrolidine enamines of cyclopentanone and cyclohexanone, respectively. To our knowledge this work represents the first instance of a quaternary ammonium salt being used in enamine alkylation. N-Ferrocenylmethylation of the enamines did not appear to take place, since no N-(ferrocenylmethyl)-pyrrolidine could be isolated after hydrolytic work-up. However, variable amounts of the latter substance were obtained along with reduced yields of the desired ketones, whenever the alkylation solvent used was not dry. The explanation lies in hydrolytic cleavage of a portion of the enamine in the wet solvent and subsequent reaction of the quaternary ammonium salt with pyrrolidine, a reaction which could be independently demonstrated. Other examples of the ferrocenylmethylation of secondary amines by the quaternary ammonium salt have been reported.[13]

The ultraviolet-visible spectra of the two α-(ferrocenylmethyl) ketones contained no evidence for intramolecular interaction between iron and the carbonyl group in the respective side chains. A broad band tending to eclipse the ferrocene spectrum in the 300–400-mμ region has been observed with ferrocene derivatives where interaction (charge transfer) between iron and a group in a side chain is very plausible.[14] The spectra of the ketones did not contain such a band.

Experimental[16]

2-(Ferrocenylmethyl)cyclohexanone.—A solution of N-cyclohexenylpyrrolidine[17,18] (3.10 g., 0.0226 mole) and (ferrocenylmethyl)trimethylammonium iodide[19] (4.50 g., 0.0117 mole) in 75 ml. of anhydrous acetonitrile (distilled over phosphorus pentoxide) was refluxed under a stream of nitrogen for 24 hr. By the end of the refluxing period trimethylamine evolution had practically ceased. New acetonitrile had to be added from time to time to compensate for losses caused by entrainment with nitrogen gas. For hydrolytic work-up the red-brown reaction mixture was treated with 75 ml. of water and 7.5 ml. of 6 *N* hydrochloric acid and refluxed for 3 hr. More water then was added. The brown oil which settled to the bottom solidified in the refrigerator. The crude product had m.p. 70–74° and weighed 3.04 g. (88%). After recrystallization from aqueous ethanol the substance consisted of yellow crystals, m.p. 73–75°. It is readily soluble in common organic solvents and insoluble in water. The ultraviolet-visible spectrum shows a shoulder at 328 mμ (log ϵ 2.13), a minimum at 368 (1.70), and a maximum at 436 (2.13). In comparison, the spectrum of simple ferrocene exhibits a minimum at 305 mμ (log ϵ 1.50), a maximum at 328 (1.84), a minimum at 364 (1.27), and a maximum at 432 (2.06). The ketone lacks the minimum at 305 mμ and has a shoulder rather than a peak at 328 mμ because the high wave-length side of the carbonyl absorption band falls in that region (the peak for the ketonic carbonyl group is generally somewhat below 300 mμ). The infrared spectrum (KBr pellet) of the ketone shows carbonyl absorption at 5.8 μ and possesses the various absorption bands of ferrocenes with an unsubstituted ring.

Anal. Calcd. for $C_{17}H_{20}FeO$: C, 68.93; H, 6.81; Fe, 18.86; O, 5.40. Found: C, 68.96, 68.95; H, 6.80, 6.86; Fe, 18.9; O, 5.50.

When the aqueous solution, after removal of the ketone, was made alkaline, a small quantity of brownish-black gummy solid precipitated. This material, other than being soluble in dilute mineral acid, did not resemble the N-(ferrocenylmethyl)pyrrolidine described below.

N-(Ferrocenylmethyl)pyrrolidine.—If the reaction of N-cyclohexenylpyrrolidine with (ferrocenylmethyl)trimethylammonium iodide was carried out in acetonitrile which had not been dried, the desired ketone was formed in reduced yield. Furthermore, when the aqueous solution after removal of the ketone was made alkaline, a quantity of N-(ferrocenylmethyl)pyrrolidine was obtained as yellow-brown precipitate. After recrystallization from aqueous ethanol, the crystals were glossy yellow and had m.p. 52–54°. The substance is soluble in common organic solvents and in dilute mineral acids and virtually insoluble in water. The ultraviolet-visible spectrum shows a minimum at 308 mμ (log ϵ 1.82), a maximum at 328 (1.95), a minimum at 364 (1.46), and a maximum at 440 (2.07), and thus closely resembles the spectrum of ferrocene. The infrared spectrum is in accord with the assigned structure.

Anal. Calcd. for $C_{15}H_{19}FeN$: C, 66.93; H, 7.10; Fe, 20.76; N, 5.21. Found: C, 67.29; H, 7.05; Fe, 21.3; N, 5.10.

Direct reaction of (ferrocenylmethyl)trimethylammonium iodide with pyrrolidine produced the identical compound.

2-(Ferrocenylmethyl)cyclopentanone.—This synthesis resembled that of the corresponding cyclohexanone except that N-cyclopentenylpyrrolidine[20] was used as the enamine. The crude ketone was first obtained as an oil which crystallized after standing for several days in the refrigerator. The melting point of the crude ketone was 39–42° and the yield was 54%. On attempted recrystallization, only oil was obtained. The substance is readily soluble in organic solvents and insoluble in water. The ketone in its oily form is subject to gradual self-condensation (probably of the aldol type) as evidenced by the fact that after prolonged standing the oil is no longer completely soluble in ether; the insoluble portion is an amorphous solid. The ultraviolet-visible spectrum of the crude ketone shows a minimum at 374 mμ (log ϵ 2.13) and a maximum at 436 mμ (log ϵ 2.26). The infrared spectrum (KBr pellet) shows a carbonyl peak at 5.8 μ as well as various absorption peaks associated with ferrocenes having an unsubstituted ring.

The ketone was converted into the oxime, m.p. 154–156° after three recrystallizations from aqueous ethanol, and into the semicarbazone, m.p. 218–228° dec. after two recrystallizations from aqueous ethanol. The semicarbazone is an especially advantageous derivative, since it is formed quantitatively and is recrystallizable with little loss.

Anal. Calcd. for $C_{17}H_{21}FeN_3O$: C, 60.14; H, 6.23; Fe, 16.46; N, 12.44. Found: C, 60.90; H, 6.32; Fe, 16.25; N, 11.87.

When the aqueous solution left after removal of 2-(ferrocenyl-

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(13) A. N. Nesmeyanov, E. G. Perevalova, L. S. Shilovtseva, and V. D. Tyurin, *ibid.*, 1997 (1962).

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(15) P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, 2990 (1963).

(16) Melting points are uncorrected. For determination of ultraviolet-visible spectra, the samples were dissolved in Spectro Grade acetonitrile. Microanalyses were carried out by K. W. Zimmermann, University of Melbourne, Australia.

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(18) S. Hünig, E. Benzing, and E. Lücke, *Chem. Ber.*, **90**, 2833 (1957).

(19) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957); modified synthesis by Osgerby and Pauson.[9] The synthesis was further modified by the use of metaphosphoric acid, in place of orthophosphoric acid, in the condensation of ferrocene with N,N,N′,N′-tetramethyldiaminomethane and by a longer reaction time (72 hr.). This led to improved conversions.

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methyl)cyclopentanone was made basic, a gummy solid was obtained from which no N-(ferrocenylmethyl)pyrrolidine was isolable. If undried solvent was used as solvent in the enamine alkylation, some N-(ferrocenylmethyl)pyrrolidine was obtained at this stage.

Biindolyls. III. Substituted 2,3′-Biindolyls from 3-Arylacetylindoles[1,2]

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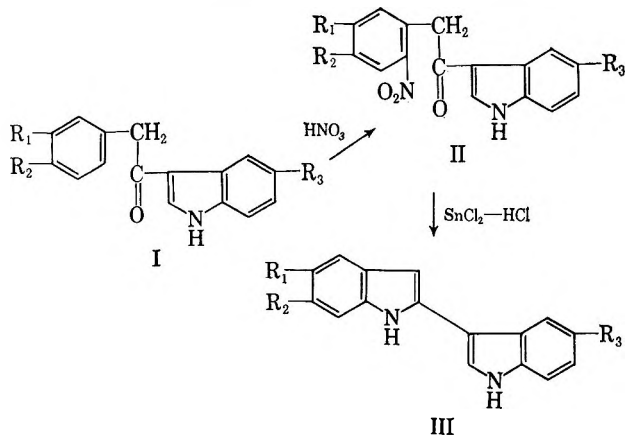
For reasons cited in an earlier paper[4] we have been seeking broadly applicable methods for the synthesis of substituted 2,3′-biindolyls. Although low yields of such compounds have been obtained on reduction of 2-(3-indolyl)-3H-pseudoindol-3-ones,[2] the more successful synthesis of 5,6-dimethoxy-2,3′-biindolyl (IIIa) by reductive cyclization of 3-(4,5-dimethoxy-2-nitrophenylacetyl)indole (IIa)[4] appeared to be more promising as a potentially general route to the desired class of compounds. It has now been found that the accessibility of the 3-(*o*-nitrophenylacetyl)indoles (II) required as starting materials is sharply limited, a deficiency which has confined the over-all method to a few special cases summarized by the sequence of formulas (I to III, a–d).

In this reaction sequence, the crucial introduction of the nitro group at the necessary *ortho* position of the phenyl ring is dependent on the relative reactivities of aryl and indolyl moieties. Although fortuitously favorable in the cases cited (60–95% yield of II), the balance is delicately controlled by all substituents as shown by unsuccessful attempts to nitrate 19 additional 3-arylacetylindoles,[5] most of which were expected to yield the required 3-(*o*-nitroarylacetyl)indoles For example, 3-methoxy-, 3,4-dichloro-, 3,4-dimethyl-, 2-chloro-3,4-dimethoxy-, 5-chloro-3,4-dimethoxy-, and 2-chloro-4,5-dimethoxyphenylacetylindoles, as well as their 5-bromoindole analogs, were all recovered unchanged from nitric–acetic acid media at room temperature. At higher temperatures, extensive decomposition occurred in all cases. The 2-methylindole analogs of Ia–d, although easily attacked by the same nitrating medium at room temperature, also gave no well-defined mononitration products.



	R_1	R_2	R_3
a	MeO	MeO	H
b	MeO	MeO	Br
c	O–CH_2–O		H
d	O–CH_2–O		Br

Reduction of the nitro ketones (IIb–d) with stannous chloride and hydrochloric acid in glacial acetic acid easily afforded the corresponding 2,3′-biindolyls (IIIb–d), albeit in yields of only 10–47%. All of these 2,3′-biindolyls showed ultraviolet absorption spectra similar to that of 2,3′-biindolyl, formed yellow solutions with dilute ethanolic hydrogen chloride, and gave stable blue "rosindoles" with Ehrlich's reagent, thus confirming their structural assignments, as well as those of the precursor nitro compounds (II). A more detailed structure proof for IIa has already been presented.[4]

Experimental[6]

Acylation of Indoles. General Procedure.—A solution of 0.11 mole of indole (or 5-bromoindole) in 50 ml. of anhydrous benzene was added dropwise during 10 min. to a vigorously stirred solution of 0.117 mole of phenylmagnesium bromide, prepared in the usual way, in 100 ml. of anhydrous ether. The resulting mixture was refluxed for 2 hr., then cooled to −10° in a Dry Ice–methanol bath. A solution of 0.100 mole of the arylacetyl chloride in 40 ml. of benzene was then added dropwise during 45 min. while the temperature was maintained at −8 to −10°. The cooling bath was removed; the mixture was stirred an additional 30 min., then hydrolyzed by addition of 50 ml. of 10% aqueous ammonium chloride. The resulting solid product was collected by filtration, washed several times with ether, then air-dried. The products so obtained are described individually in the following paragraphs.

3-(3,4-Dimethoxyphenylacetyl)-5-bromoindole (Ib).—The reaction of 5-bromoindolylmagnesium bromide and homoveratroyl chloride[4] gave this product directly on hydrolysis of the reaction mixture in 37% yield. Recrystallization from 95% ethanol afforded white needles, m.p. 228–230°, infrared (μ), 3.16 (N–H) and 6.06 (C=O).

Anal. Calcd. for $C_{18}H_{16}BrNO_3$: C, 57.76; H, 4.31; N, 3.74. Found: C, 57.89; H, 4.60; N, 3.67.

3-(3,4-Methylenedioxyphenylacetyl)indole (Ic).—Reaction of indolylmagnesium bromide and 3,4-methylenedioxyphenylacetyl chloride[7] yielded 21 g. (95%) of 1,3-di(3,4-methylenedioxyphenylacetyl)indole, which was recrystallized from *n*-propyl alcohol to give white needles, m.p. 145–146°, infrared (μ), 5.76 and 5.95 (C=O).

Anal. Calcd. for $C_{26}H_{19}NO_6$: C, 70.74; H, 4.34; N 3.17. Found: C, 70.95; H, 4.71; N, 3.14.

Two grams of this product was refluxed for 5 min. with a solution of 5 ml. of 10% sodium hydroxide in 20 ml. of 95% ethanol. The resulting hot solution was diluted with 10 ml. of water, filtered, and allowed to cool to room temperature. The resulting crop of crystals was collected, washed with water, then recrystallized from 95% ethanol to give 1.1 g. (88% yield) of Ic, m.p. 194–196°, infrared (μ), 3.01 (N–H) and 6.12 (C=O).

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.02. Found: C, 73.25; H, 4.80; N, 4.94.

3-(3,4-Methylenedioxyphenylacetyl)-5-bromoindole (Id).—Reaction of 5-bromoindolylmagnesium bromide and 3,4-methylenedioxyphenylacetyl chloride yielded 22.8 g. of a crude white solid

(1) This investigation was supported by Research Grant C-4425 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) Part II: T. E. Young and D. S. Auld, *J. Org. Chem.*, **28**, 418 (1963).

(3) Abstracted from the Ph.D. dissertation of M. F. M., Lehigh University, 1963.

(4) T. E. Young, *J. Org. Chem.*, **27**, 507 (1962).

(5) Syntheses and properties of these compounds will be reported elsewhere.

(6) Melting points are corrected. Infrared spectra were determined in potassium bromide on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were run on a Beckman DK-2A instrument. Indole and 5-bromoindole were obtained from Aldrich Chemical Co., Milwaukee, Wis.

(7) C. Mannich and O. Walther, *Arch. Pharm.*, **265**, 7 (1927); *cf. Chem. Zentr.*, 1, 1479 (1927).

which lacked a well-defined melting point and was probably a mixture of 3-acyl and 1,3-diacyl compounds. This mixture was hydrolyzed by brief refluxing with aqueous alcoholic sodium hydroxide as in the preceding example to yield 13.7 g. (38%) of 3-acyl compound (Id), which, after recrystallization from 95% ethanol, had m.p. 256–258°, infrared (μ), 3.13 (N–H) and 6.06 (C=O).

Anal. Calcd. for $C_{17}H_{12}BrNO_3$: C, 57.00; H, 3.38; N, 3.91. Found: C, 57.17; H, 3.59; N, 3.96.

3-(4,5-Dimethoxy-2-nitrophenylacetyl)-5-bromoindole (IIb).—A solution of 2.24 g. (0.006 mole) of Ib in 160 ml. of boiling glacial acetic acid was cooled to 80° and a solution of 0.54 g. (0.006 mole) of concentrated nitric acid (69.6%) in 10 ml. of glacial acetic acid was added. The yellow solution was allowed to cool, whereby the color deepened and a solid began to separate. The mixture was allowed to stand at room temperature for 3 hr., then the solid was collected on a filter, washed several times with glacial acetic acid, and air-dried. Recrystallization from 95% ethanol gave 2.08 g. (83%) of a pale yellow solid, m.p. 250° dec., infrared (μ), 3.05 (N–H) and 6.05 (C=O).

Anal. Calcd. for $C_{18}H_{15}BrN_2O_5$: C, 51.56; H, 3.61; N, 6.68. Found: C, 51.67; H, 3.79; N, 6.41.

3-(4,5-Methylenedioxy-2-nitrophenylacetyl)indole (IIc).—Four grams of Ic was nitrated as in the preceding example (4-hr. reaction time) to yield 2.80 g. (60%) of IIc, which recrystallized from glacial acetic acid as fine yellow needles, m.p. 239–240° dec., infrared (μ), 3.08 (N–H) and 6.20 (C=O).

Anal. Calcd. for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.72; N, 8.64. Found: C, 63.21; H, 3.93; N, 8.28.

3-(4,5-Methylenedioxy-2-nitrophenylacetyl)-5-bromoindole (IId).—Nitration of 0.40 g. of Id with 0.11 g. of concentrated nitric acid in 38 ml. of nitromethane for 1 hr. at 60° yielded 0.43 g. (95%) of IId, which crystallized from the reaction mixture. Recrystallization from nitromethane gave pale yellow needles, m.p. 266° dec., infrared (μ), 3.04 (N–H) and 6.18 (C=O).

Anal. Calcd. for $C_{17}H_{11}BrN_2O_5$: C, 50.63; H, 2.75; N, 6.94. Found: C, 50.77; H, 2.88; N, 6.65.

5,6-Dimethoxy-5′-bromo-2,3′-biindolyl (IIIb).—Two grams (0.0048 mole) of IIb was dissolved in 200 ml. of boiling glacial acetic acid, and a solution of 8.0 g. (0.035 mole) of stannous chloride dihydrate in 15 ml. of concentrated hydrochloric acid was added during 5 min. The solution was then boiled for 10 min. and allowed to stand at room temperature overnight. A yellow solid separated; it was collected on a filter, washed several times with acetic acid, followed by several washings with ether, and air-dried. The yield of orange-yellow powder was 2.2 g. This solid (presumably the hexachlorostannic acid complex) was mixed with 8 ml. of 95% ethanol and enough water to make a stirrable paste, and 5% sodium hydroxide solution was added dropwise until the pH of the mixture was about 7. The reaction mixture changed from red-orange to a pale yellow color at completion of the addition. The cream-colored solid was collected by filtration, washed several times with water, air-dried, then extracted with 50 ml. of boiling 95% ethanol divided roughly into three portions. The combined ethanol extracts were allowed to cool and a small amount of granular white solid which separated was removed by filtration and discarded. The ethanol filtrate was heated to boiling, diluted with 20 ml. of water, and allowed to cool. The slightly colored crystalline solid which separated was collected, then recrystallized twice from aqueous ethanol and twice from aqueous methanol to yield 0.40 g. (22%) of IIIb as off-white feathery needles, m.p. 220–221°; ultraviolet spectrum (95% ethanol): λ_{max} mμ (log ϵ), 247 (4.37), 293 shoulder (4.14), and 323 (4.40). An ethanolic solution of the compound gave a deep blue color with Ehrlich's reagent.

Anal. Calcd. for $C_{18}H_{15}BrN_2O_2$: C, 58.23; H, 4.07; N, 7.55. Found: C, 58.50; H, 4.35; N, 7.52.

5,6-Methylenedioxy-2,3′-biindolyl (IIIc).—A similar reduction of 2.40 g. (0.0074 mole) of IIc with 5.63 g. (0.025 mole) of stannous chloride dihydrate and 8 ml. of concentrated hydrochloric acid in 200 ml. of glacial acetic acid was effected as in the preceding example except that ethyl acetate was used for the extraction. Evaporation of the extracts followed by sublimation of the residue at 200° (0.4 mm.) afforded 0.20 g. (10% yield) of IIIc which, after one recrystallization from aqueous ethanol and a final sublimation, was obtained as fine white needles, m.p. 222–223° dec.; ultraviolet spectrum (95% ethanol): λ_{max} mμ (log ϵ), 240 (4.44), 279 (4.04), 289 shoulder (4.00), and 335 (4.40). An ethanolic solution of the compound gave a deep blue solution with Ehrlich's reagent.

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.89; H, 4.37; N, 10.14. Found: C, 74.09; H, 4.41; N, 10.25.

5,6-Methylenedioxy-5′-bromo-2,3′-biindolyl (IIId).—A similar reduction of 2.00 g. (0.0050 mole) of IId in 250 ml. of acetic acid with 4.00 g. (0.018 mole) of stannous chloride dihydrate in 6 ml. of concentrated hydrochloric acid, followed by a work-up analogous with that of the preceding example, gave 0.84 g. (47% crude yield) of product, m.p. 212–218° dec. Sublimation at 210–215° (0.08 mm.), accompanied by considerable decomposition of the unsublimed residue, yielded white crystals, m.p. 224–226° dec.; ultraviolet spectrum (95% ethanol): λ_{max} mμ (log ϵ), 248 (4.31), 281 shoulder (4.03), 291 shoulder (4.00), and 333 (4.37); deep blue color with Ehrlich's reagent.

Anal. Calcd. for $C_{17}H_{11}BrN_2O_2$: C, 57.48; H, 3.12; N, 7.89. Found: C, 57.39; H, 3.35; N, 7.91.

Acknowledgment.—The authors are indebted to Dr. V. B. Fish of this laboratory for the microanalyses.

The Photoaddition of Cyclic Ethers to 1-Octene

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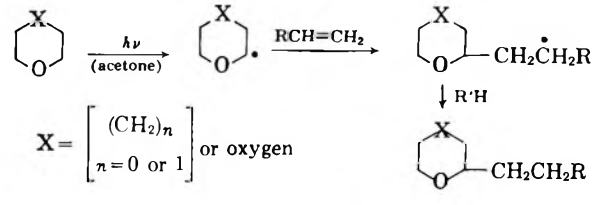
The peroxide-induced reactions of cyclic ethers with 1-octene and maleic anhydride have been reported to produce ketones[1] or α-substituted cyclic ethers[2,3] as the major products. Recent investigations on the light-induced reactions of maleic anhydride,[3] 7,7,8,8-tetracyanoquinodimethane, and tetracyanoethylene[4] with tetrahydrofuran have demonstrated that α-substituted tetrahydrofurans are the main reaction products, while the same reactions of maleic anhydride with tetrahydropyran and 1,4-dioxane have led to nondistillable mixtures.[3]

These studies prompted us to report the results of a similar investigation involving the photoaddition of cyclic ethers to 1-octene at room temperature which have mainly produced α-substituted alkyl ethers. The reaction can be induced directly by light or initiated photochemically by acetone, the latter conditions resulting in higher yields of the alkylated products.

Our results differ from those reported by Wallace and Gritter[1] in that the addition of tetrahydrofuran and tetrahydropyran to 1-octene occurs without ring opening. The formations of 1:1 adducts of tetrahydropyran and 1,4-dioxane with 1-octene are also in contrast to the results obtained by Jacobs and Ecke[3] who have not been able to isolate 1:1 adducts of the same ethers with maleic anhydride.

This addition of cyclic ethers to olefins presumably



(1) T. J. Wallace and R. J. Gritter, *Tetrahedron*, **19**, 657 (1963), and references cited therein.

(2) T. J. Wallace, R. J. Gritter, and H. G. Walsh, *Nature*, **198**, 284 (1963), and references cited therein.

(3) R. L. Jacobs and G. G. Ecke, *J. Org. Chem.*, **28**, 3036 (1963).

(4) J. Diekmann and C. J. Pedersen, *ibid.*, **28**, 2879 (1963).

involves a free-radical reaction, as previously suggested,[1,3] for which the preceding mechanism is represented.

Experimental[5]

Experiments with ultraviolet light were conducted in an apparatus similar to the one described by de Mayo[6] with slight modifications. The radiation sources for the acetone-initiated reactions and the direct light-induced reactions were accomplished by Hanau Q81 high pressure mercury vapor lamps fitted into Pyrex or quartz immersion tubes, respectively. The reaction mixtures were cooled externally by running water and were kept under oxygen-free nitrogen. Reactions in sunlight were performed in Pyrex tubes, and the system was flushed with nitrogen after each addition of the olefin.

Reagents were tetrahydrofuran, B.D.H., and tetrahydropyran and dioxane, Fluka. These cyclic ethers were freshly distilled over sodium before use: acetone, absolute, and 1-octene, Fluka. The olefin was shaken with aqueous ferrous sulfate solution and dried (Na_2SO_4); it was freshly distilled and filtered through a short column of Alcoa activated alumina F20 before use.

1-Octene and Tetrahydrofuran with Ultraviolet Light.—A mixture of 1-octene (0.5 g.), tetrahydrofuran (90 ml.), and acetone (5 ml.) was irradiated for 1 hr. A solution of 1-octene (5.1 g.) in acetone (5 ml.) then was added in ten equal portions in 1-hr. intervals and irradiation was continued for another 12 hr. Excess reagents were removed under reduced pressure and then the residue, whose infrared spectrum indicated only traces of carbonylic substances, was distilled. The fraction with b.p. 80–140° (1.5 mm.), 5.4 g., was chromatographed on alumina (270 g.). Elution with pentane gave 2-octyltetrahydrofuran (2.3 g., 25% based on olefin employed) which upon redistillation indicated b.p. 69–71° (0.4 mm.), $n^{26}D$ 1.4410; lit.[7] b.p. 85–87° (3 mm.), $n^{20}D$ 1.4412. This substance showed identical boiling point, infrared spectrum, refractive index, and gas chromatographic retention time with those of an authentic sample.[8] The n.m.r. spectrum of this compound exhibited multiplets at τ 6.15 and 8.1, a broad singlet at τ 8.65, and a triplet at τ 9.1 in the ratio 3:3.8:14:3.3.

Anal. Calcd. for $C_{12}H_{24}O$: C, 78.19; H, 13.13. Found: C, 77.90; H, 13.00.

1-Octene and Tetrahydrofuran in Sunlight.—A mixture of 1-octene (0.5 g.), tetrahydrofuran (90 ml.), and acetone (5 ml.) was left in direct sunlight for 1 day. A solution of 1-octene (5.1 g.) in acetone (5 ml.) was then added in ten equal portions in 1-day intervals, and the mixture was left in sunlight for another 7 days. After removal of the solvent, the residue, whose infrared spectrum indicated only traces of carbonylic substances, was filtered through alumina (450 g.) using a 1:1 benzene–ether mixture. The resulting oily residue (8 g.) was distilled *in vacuo*. The fraction with b.p. 70–130° (0.5 mm.), 5.5 g., was chromatographed on alumina (270 g.). Pentane eluted 2-octyltetrahydrofuran (2.7 g., 30%).

1-Octene and Tetrahydropyran with Ultraviolet Light.—The quantities and experimental conditions described above were followed. After removal of the reagents, the residue which contained only traces of carbonylic materials was distilled. The fraction with b.p. 75–150° (1.5 mm.), 4.3 g., was chromatographed on alumina (220 g.). Elution with pentane gave 2-octyltetrahydropyran (1.7 g., 17%), b.p. 84–86° (0.6 mm.), $n^{25}D$ 1.4458. This substance showed the same physical properties as an authentic sample prepared by the method of Paul.[9] Its n.m.r. spectrum indicated multiplets at τ 6.0 and 6.65, a broad singlet at τ 8.65, and a triplet at τ 9.15 in the ratio 1:2:19.8:3.1.

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.26; H, 13.12.

1-Octene and Tetrahydropyran in Sunlight.—The procedure described above with the same quantities were followed. After the usual work-up, the remaining residue (7.1 g.) was distilled and the fraction with b.p. 75–150° (1.5 mm.), 3.3 g., was chromatographed on alumina (170 g.). Elution with pentane led to 2-octyltetrahydropyran (2.1 g., 21%).

1-Octene and 1,4-Dioxane with Ultraviolet Light.—Similar procedure and quantities as described above were followed. The residue which contained only traces of carbonylic substances was distilled and the fraction with b.p. 80–180° (0.5 mm.), 5.2 g., was crystallized from petroleum ether (b.p. 60–80°). The precipitate which consisted of the dimers of dioxane[10] was filtered and the mother liquor was chromatographed on alumina (250 g.). The oily substance obtained on elution with pentane was crystallized from pentane to give octyl-1,4-dioxane[2] (2.7 g., 27%), m.p. 37–38°. This substance was further characterized by its n.m.r. spectrum which showed a multiplet at τ 6.2, a broad singlet at τ 8.65, and a triplet at τ 9.1 in the ratio 7:14:2.9, as well as by its mass spectral analysis which indicated a parent ion with m/e = 200 and a base peak with m/e = 87.

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.46; H, 11.82.

1-Octene and 1,4-Dioxane in Sunlight.—The procedure described above, using similar quantities, was followed. After removal of the reagents, the residue was distilled and the fraction with b.p. 80–180° (0.5 mm.), 7.3 g., was collected. Dimers of dioxane were isolated as explained above, and the remaining residue was chromatographed on alumina (350 g.). Elution with pentane led to octyl-1,4-dioxane (3.4 g., 34%).

1-Octene and 1,4-Dioxane with Ultraviolet Light (without Acetone).—A solution of 1-octene (1 g.) in 1,4-dioxane (100 ml.) was irradiated for 1 hr. 1-Octene (4.6 g.) then was added in eight equal portions in 1-hr. intervals and the mixture was irradiated for another 12 hr. After work-up, octyl-1,4-dioxane (0.5 g., 5%) was obtained.

Acknowledgment.—The authors are grateful to Professor Franz Sondheimer for his interest and encouragement. We are also indebted to Dr. Shvo for the n.m.r. determinations and to Drs. W. A. Ayer and S. Wolfe for the mass spectral analysis.

(10) K. Pfordte, *Ann.*, **625**, 30 (1959); G. Sosnovsky, *J. Org. Chem.*, **28**, 2934 (1963).

(5) Boiling points and melting points are uncorrected. Merck "acid-washed" alumina was used for chromatography. Gas–liquid chromatography was carried out with a "Pye" argon instrument on a 10% Apiezon M-Celite column at 125°. The n.m.r. spectra were determined on a Varian A-60 spectrometer in deuteriochloroform using tetramethylsilane as internal standard. Analyses were carried out in our microanalytical section directed by Mr. R. Heller.

(6) P. de Mayo, "Advances in Organic Chemistry," Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 370.

(7) G. I. Nikishin and V. D. Vorob'ev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 892 (1962); *Chem. Abstr.*, **57**, 12,300 (1962).

(8) 2-Octyltetrahydrofuran was prepared by treating 2-furfuraldehyde with heptylmagnesium bromide followed by catalytic hydrogenation, chrominum trioxide oxidation, and Wolff–Kishner reduction.

(9) R. Paul, *Bull. soc. chim. France*, [5]**2**, 311 (1935).

Reactions of Acetylenes. III. Cyclization of Urethanes

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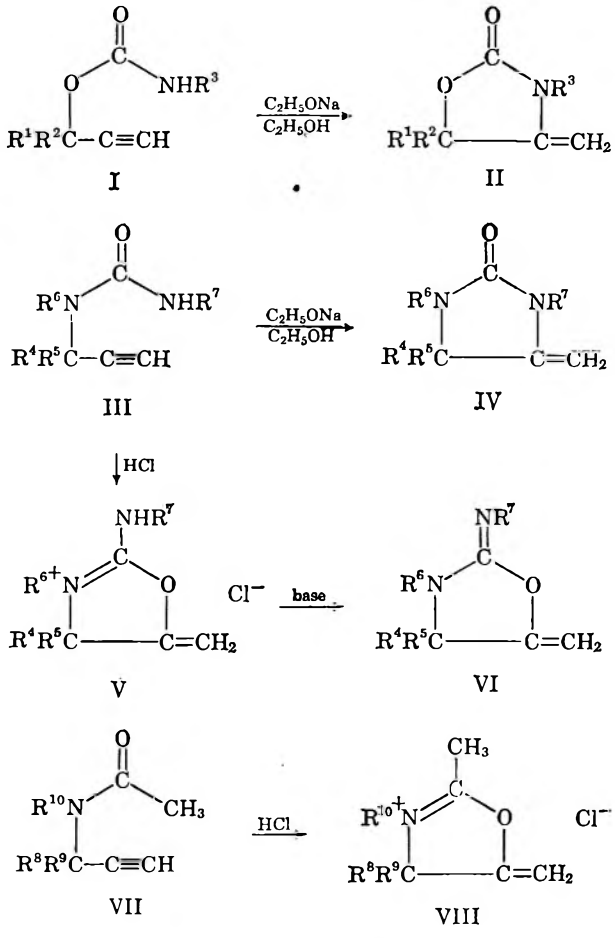
Earlier work[1] in this laboratory and elsewhere has shown that *t*-ethynylcarbinols react with isocyanates to form urethanes (I) which can be readily converted to oxazolidinones (II) by treatment with sodium ethoxide.

α,α-Disubstituted propargylureas (III) when treated with sodium ethoxide in ethanol also gave N-closure products, the imidazolidinones (IV)[1d,2]; treatment of

(1) (a) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **27**, 2927 (1962); (b) M. D. Cameron, U. S. Patent 2,844,590 (1958); (c) K. Sisido, K. Hukuoka, M. Tuda, and H. Nozaki, *J. Org. Chem.*, **27**, 2663 (1962); (d) N. Shachat and J. J. Bagnell, Jr., *ibid.*, **28**, 991 (1963).

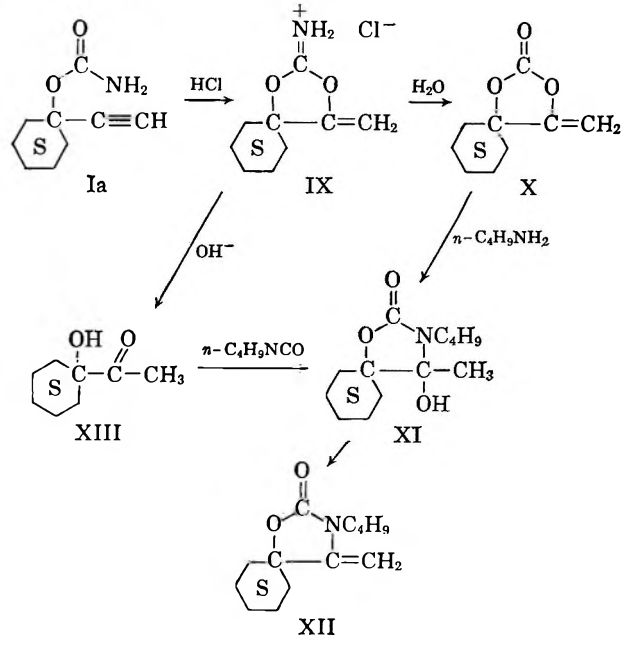
(2) N. R. Easton, D. R. Cassady, and R. D. Dillard, *ibid.*, **29**, 1851 (1964).

the ureas, however, with dry hydrogen chloride in ether precipitated the 2-aminooxazolinium chlorides (V). These salts, upon neutralization with base, gave the 2-iminooxazolidines.[2] This oxygen closure of the ureas was in agreement with the finding that N-acyl derivatives of α,α-disubstituted propargylamines (VII) gave five-membered ring products (VIII) upon treatment with dry hydrogen chloride.[3]



I II III IV V VI VII VIII

Since the base-induced cyclization of the ureas gave an N-closure, and the acid-catalyzed reaction produced an O-closure, an acid-catalyzed cyclization of the urethanes would be expected to give the O-closure. Treatment of an ether solution of a urethane, 1-ethynylcyclohexyl carbamate (Ia), with dry hydrogen chloride gave a hygroscopic precipitate. When this solid was dissolved in water, an oil was formed. Analyses of this oil showed it to be a nitrogen-free compound. The infrared spectrum ($CHCl_3$) had bands at 5.42, 5.49, 5.82, and 5.93 μ. The n.m.r.[4] spectrum showed, in addition to peaks for the cyclohexane ring, doublets centered at 258 and 284 c.p.s. (2H, J = 3 c.p.s.). These data fit the dioxolane structure (X). An examination of the ether-insoluble solid (isolated under anhydrous conditions) showed it to be the 2-iminodioxolane hydrochloride (IX). Treatment of this iminodioxolane hydrochloride with dilute base liberated the keto alcohol XIII.



Ia IX X XIII XI XII

Additional proof of structure was obtained by the facile formation of the oxazolidinone (XII) when the dioxolane (X) was treated with *n*-butylamine. This reaction proceeded through the intermediate hydroxy compound (XI). The methylene oxazolidinone was identical with that formed by the reaction of *n*-butyl isocyanate upon 1-acetylcyclohexanol (XIII).

In order to test the generality of this reaction, several other urethanes were subjected to this treatment and they formed similar products.

Since the completion of this work, compounds of this type have been reported.[5] They were prepared by the reaction of the *t*-ethynylcarbinols with carbon dioxide in the presence of a copper salt as catalyst.

Experimental

All melting points were taken in an open capillary using a Cu-latti electrically heated air bath melting point apparatus.

2-Imino-4,4-pentamethylene-5-methylenedioxolane.—A solution of 10 g. (0.06 mole) of 1-ethynylcyclohexyl carbamate in 200 ml. of ether was saturated with dry hydrogen chloride until precipitation was complete. The solid was removed by filtration under nitrogen. The n.m.r spectrum of the dried material was compatible with the proposed structure.

Anal. Calcd. for $C_9H_{14}ClNO_2$: N, 6.90. Found: N, 6.75. Owing to the hygroscopic nature of the solid, it was used immediately in the next reaction.

4,4-Pentamethylene-5-methylene-2-dioxolanone.—The crude product from the above reaction was added to 25 ml. of water and the resulting oil, extracted into ether and distilled, had b.p. 60° (2 mm.), yield 8 g. (79% based upon 1-ethynylcyclohexyl carbamate).

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.45; H, 7.28.

This compound was also prepared by the same route from 1-ethynylcyclohexyl-N-ethyl carbamate (yield 92%).

4,4-Dimethyl-5-methylene-2-dioxolanone.—By the above procedure N-ethyl-2-(2-methyl-3-butynyl) carbamate and N-(4-chlorophenyl)-2-(2-methyl-3-butynyl) carbamate were converted to 4,4-dimethyl-5-methylene-2-dioxolanone, b.p. 35° (10 mm.).

Anal. Calcd. for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.35; H, 6.38.

3-*n*-Butyl-4-methylene-5,5-pentamethylene-2-oxazolidinone. Method A.—Twenty-five millimoles (4.2 g.) of the dioxolane was dissolved in 50 ml. of *n*-butylamine. When the reaction had subsided and returned to room temperature, the excess amine was

(3) (a) N. R. Easton, R. D. Dillard, M. Livezey, D. E. Morrison, and G. F. Hennion, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1960, p. 44-O; (b) N. R. Easton and R. D. Dillard, *J. Org. Chem.*, **28**, 2465 (1963).

(4) The machine used was the Varian Associates Model HR60, 60 Mc. Deuteriochloroform was used as the solvent and tetramethylsilane as the internal standard.

(5) Badische Anilin, German Patents 1,098,953 (1961) and 1,145,632 (1963).

removed by vacuum distillation. The resulting solid, m.p. 105–106°, was identified as 3-*n*-butyl-4-hydroxy-4-methyl-5,5-pentamethylene-2-oxazolidinone.

The infrared spectrum showed characteristic peaks at 3.00 and 5.77 μ for the —OH and cyclic urethane carbonyl.

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.54; H, 9.48; N, 5.54.

The hydroxy compound was dehydrated by refluxing a benzene solution under a Dean–Stark trap. Vacuum removal of the solvent yielded an oil, b.p. 165° at 2 mm., yield 4.0 g. (72%).

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.85; H, 9.46; N, 6.25.

Method B.—Equal quantities (25 g.) of 1-acetylcyclohexanol and *n*-butyl isocyanate were dissolved in ether. The mixture was cooled in ice due to spontaneous exothermic reaction. Vacuum removal of the solvents yielded the hydroxymethyl oxazolidinone, m.p. 105–106°, identical with that obtained from the dioxolanone.

Treatment of 2-Imino-4,4-pentamethylene-5-methylenedioxolane with Aqueous Sodium Hydroxide.—A sample of the crude 2-iminodioxolane (IX) was dissolved in 10% sodium hydroxide solution. The resulting mixture was extracted with ether. The ether was removed at reduced pressure and the 1-acetyl-1-cyclohexanol distilled, b.p. 105–107° (26 mm.), $n^{25}D$ 1.4660.[6]

Acknowledgment.—The microanalyses were performed by Messrs. William Brown, Howard Hunter, George Maciak, David Cline, and Alfred Brown. Many of the starting materials were prepared in this laboratory by Mr. Lawrence White. The infrared and n.m.r. spectra were obtained by Mr. John Klemm, Mrs. Doris Stephens, and Miss Martha Hofmann. The authors wish to thank especially Dr. Harold Boaz and Messrs. Paul Landis and Donald Woolf, Jr., for their assistance in interpreting the infrared and n.m.r. data.

(6) G. F. Hennion and E. J. Watson, *J. Org. Chem.*, **23**, 656 (1958).

Cannizzaro Reactions Involving Aromatic Dialdehydes[1]

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An example of a Cannizzaro reaction of an aromatic dialdehyde is on record; Löw[2] found that the reaction of terephthalaldehyde with sodium hydroxide solution yields terephthalic acid, *p*-hydroxymethylbenzoic acid, and α,α'-*p*-xylenediol.

Bromoterephthalaldehyde has now been subjected to Cannizzaro reaction conditions and rather similar results have been observed. The products formed are: the diacid (15% yield), 3-bromo-4-hydroxymethylbenzoic acid (63% yield), and the diol (19% yield); total yield, 97%. The results indicate that the aldehyde function in bromoterephthalaldehyde which is *ortho* to halogen is more easily reduced and that the other aldehyde function is more easily oxidized.

The behavior of mixtures of terephthalaldehyde and formaldehyde and of bromoterephthalaldehyde and formaldehyde in strong sodium hydroxide solution has been studied also. It was found that the extent of reduction of the aromatic dialdehyde to diol increased as the relative amount of formaldehyde was increased. Two examples of these reactions are reported in the Experimental section: (1) a 1:8 terephthalaldehyde to formaldehyde mixture gave 68% yield of α,α'-*p*-xylenediol and 9% yield of *p*-hydroxymethylbenzoic acid; (2) a 1:12 bromoterephthalaldehyde to formaldehyde mixture gave 76% yield of bromo-α,α'-*p*-xylenediol and 22% yield of 3-bromo-4-hydroxymethylbenzoic acid.

Some of the compounds required for use or comparison were prepared by methods which have been described previously (terephthalaldehyde,[2] *p*-hydroxymethylbenzoic acid,[2] and α,α'-*p*-xylenediol[3]) or were available (terephthalic acid, Eastman White Label). Others have now been synthesized, and methods and related data are reported in the Experimental section; derivatives of a number of these compounds have been prepared by standard procedures.

Experimental

Bromoterephthalaldehyde.—Crude $\alpha,\alpha,\alpha',\alpha'$-tetrabromobromo-*p*-xylene (100 g., 0.2 mole, from *p*-xylene → bromo-*p*-xylene[4] → $\alpha,\alpha,\alpha',\alpha'$-tetrabromobromo-*p*-xylene[5]) and 200 ml. of concentrated sulfuric acid were placed in a flask fitted with a stirrer and attached to a glass aspirator to remove hydrogen bromide and bromine fumes; this was maintained at 140° until no more fumes were evolved (*ca.* 45 min.). The reaction mixture was poured onto crushed ice; after the ice had melted, the mixture was steam distilled. The product weighed 21 g. (49% yield), m.p. 67–68°; further purification by steam distillation or by crystallization from water increased the melting point to 75°.

Anal. Calcd. for $C_8H_5BrO_2$: C, 45.07; H, 2.35; Br, 37.56. Found: C, 44.97; H, 2.54; Br, 37.73.

From the aldehyde, the following compounds were prepared: (a) the **dioxime**, (b) the **tetraacetate**, and (c) **bromoterephthalic acid**.

The dioxime melted at 218° (from ethanol).

Anal. Calcd. for $C_8H_7BrN_2O_2$: Br, 32.92; N, 11.52. Found: Br, 33.25; N, 11.39.

The tetraacetate melted at 132° (from ethanol).

Anal. Calcd. for $C_{16}H_{17}BrO_8$: C, 46.04; H, 4.08; Br, 19.18. Found: C, 46.00; H, 4.27; Br, 18.99.

Bromoterephthalic acid melted at 299° (from water, sublimes), lit.[6] m.p. 299°, neut. equiv. 124.

α,α'-Dibromobromo-*p*-xylene.—To bromo-*p*-xylene[4] (92.5 g., 0.5 mole) bromine (160 g., 1 mole) was added slowly (quartz apparatus; ultraviolet irradiation; oil bath temperature, 130°; reaction time, 2 hr.). Cooling the reaction mixture caused the major portion of it to solidify; recrystallization from ligroin (b.p. 90–120°) gave colorless crystals, 60 g. (35% yield), m.p. 91–92°.

Anal. Calcd. for $C_8H_7Br_3$: Br, 69.97. Found: Br, 69.94.

Bromo-α,α'-*p*-xylenediol.—The above tribromo compound (25 g., 0.0729 mole) was refluxed with 10% potassium carbonate solution. The hot reaction mixture was filtered, and the cooled filtrate was saturated with potassium carbonate. The precipitated diol weighed 5.5 g. (35% yield), m.p. 110–111° (from water).

Anal. Calcd. for $C_8H_9BrO_2$: C, 44.24; H, 4.15; Br, 36.87. Found: C, 44.52; H, 4.43; Br, 36.80.

From the diol, the following compounds were prepared: (a) the **diacetate**, (b) the **dibenzoate**, and (c) the **di-*p*-nitrobenzoate**.

The diacetate melted at 66–67° (from ethanol).

Anal. Calcd. for $C_{12}H_{13}BrO_4$: Br, 26.58. Found: Br, 26.64.

The dibenzoate had a melting point of 98–99° (from ethanol).

Anal. Calcd. for $C_{22}H_{17}BrO_4$: Br, 18.82. Found: Br, 18.82.

The di-*p*-nitrobenzoate melted at 164.5–165.5° (from benzene).

Anal. Calcd. for $C_{22}H_{15}BrN_2O_8$: Br, 15.53; N, 5.44. Found: Br, 15.57; N, 5.24.

α-Bromo-2-bromo-*p*-tolunitrile.—2-Bromo-*p*-tolunitrile (42.5

(1) This investigation was supported in part by the Office of Naval Research.

(2) W. Löw, *Ann.*, **231**, 373 (1885).

(3) E. Grimaux, *ibid.*, **155**, 338 (1870).

(4) G. T. Morgan and E. A. Coulson, *J. Chem. Soc.*, 2211 (1929).

(5) By a method analogous to that used by J. M. Snell and A. Weissberger [*Org. Syn.*, **20**, 92 (1940)] for the preparation of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*p*-xylene.

(6) F. C. Whitmore and L. L. Isenhour, *J. Am. Chem. Soc.*, **51**, 2787 (1929).

g., 0.199 mole, from 2-bromo-*p*-toluidine[7] → 2-bromo-*p*-tolunitrile[8,9]) was brominated (34 g., 0.213 mole of bromine) under ultraviolet irradiation in a quartz flask; the system was heated in an oil bath (bath temperature, 175–180°). The reaction was continued until the gain in weight was *ca.* 17 g. When purification was attempted by warming the product with 200 ml. of ethanol, 4.5 g. of material did not dissolve, and it was discarded. The purified crystalline product weighed 24 g. (41% yield), m.p. 92° (from methanol).

Anal. Calcd. for $C_8H_5Br_2N$: Br, 58.18; N, 5.09. Found: Br, 58.31; N, 4.95.

2-Bromo-4-hydroxymethylbenzonitrile.—The α-bromo compound (10 g., 0.0341 mole) was refluxed with 1.5 l. of water in the presence of infusorial earth for 2.5 hr. The hot mixture was filtered, and the filtrate on cooling gave 6.2 g. (86% yield) of product, m.p. 101–102° (from water).

Anal. Calcd. for C_8H_6BrNO: Br, 37.74; N, 6.60. Found: Br, 37.56; N, 6.65.

2-Bromo-4-hydroxymethylbenzoic Acid.—The above nitrile (6.2 g., 0.0292 mole) was refluxed for 3 hr. with 80 ml. of 10% sodium hydroxide solution. Acidification of the reaction mixture with concentrated hydrochloric acid precipitated the product, 2.5 g. (37% yield), m.p. 147–148° (from water).

Anal. Calcd. for $C_8H_7BrO_3$: C, 41.56; H, 3.03; Br, 34.64; neut. equiv., 231. Found: C, 41.83; H, 3.12; Br, 34.74; neut. equiv., 232.2.

The **acetate** was prepared, m.p. 113–114° (from ethanol).

Anal. Calcd. for $C_{10}H_9BrO_4$: Br, 29.30; neut. equiv., 273. Found: Br, 29.18; neut. equiv., 272.9.

2-Bromoterephthalaldehydonitrile. A.—2-Bromo-4-hydroxymethylbenzonitrile (5 g., 0.0236 mole) was dissolved in concentrated nitric acid (25 ml.) at 15°. In a few minutes, evolution of oxides of nitrogen was observed; after *ca.* 5 min., when the reaction had subsided, the mixture was diluted with 125 ml. of water. The colorless product which separated was extracted with ether. Shaking the ether solution with saturated sodium bisulfite solution resulted in the formation of an addition compound; this was collected by filtration and washed with ethanol and with ether. In turn, the addition compound was dissolved in a minimum amount of water and decomposed by the addition of potassium carbonate solution and gentle warming. The yield of aldehyde was 4 g. (83%), m.p. 123° (from water).

Anal. Calcd. for C_8H_4BrNO: Br, 38.10; N, 6.67. Found: Br, 38.16; N, 6.64.

B.—2-Bromoterephthalaldehydonitrile, m.p. 123°, was obtained also in low yield by refluxing α-bromo-2-bromo-*p*-tolunitrile with cupric nitrate and nitric acid; the product was isolated first as the bisulfite addition compound, which was decomposed by warming it in potassium carbonate solution.

The melting point of a mixture of approximately equal parts of the isomeric 2- and 3-bromoterephthalaldehydonitriles (see below for the 3-bromo compound) was *ca.* 95°.

The **oxime** was prepared, m.p. 170° (from dilute ethanol).

Anal. Calcd. for $C_8H_5BrN_2O$: Br, 35.56; N, 12.44. Found: Br, 35.43; N, 12.53.

2-Bromoterephthalaldehydamide.—The aldehydonitrile (2 g., 0.00952 mole) was dissolved in 15 ml. of concentrated sulfuric acid, and the solution was warmed on a steam bath for 1 hr. The reaction mixture was cooled and diluted with 100 ml. of cold water; cooling the solution in a refrigerator for 12 hr. gave 1 g. of crystals (46% yield), m.p. 175° (from water).

Anal. Calcd. for $C_8H_6BrNO_2$: Br, 35.09; N, 6.14. Found: Br, 34.74; N, 6.38.

2-Bromoterephthalaldehydic Acid.—A 4-g. sample (0.0175 mole) of the amide was dissolved in 15 ml. of concentrated sulfuric acid, and a saturated solution of sodium nitrite (containing 1.2 g.) was added slowly below the surface of the liquid.[11] During the addition of the nitrite solution, the temperature of the reaction mixture was maintained at *ca.* 15°. After dilution with two volumes of water and cooling, the acid was collected by filtration. The product was dissolved in a slight excess of 10% potassium carbonate solution, and this was filtered to remove a trace of unchanged amide. The filtrate was acidified, and the product was recrystallized from a small volume of water; drying was accomplished in an atmosphere of nitrogen in a desiccator yielding 3 g. (75%), m.p. 172°.

Anal. Calcd. for $C_8H_5BrO_3$: C, 41.92; H, 2.18; Br, 34.93; neut. equiv., 229. Found: C, 41.96; H, 2.32; Br, 34.73; neut. equiv., 226.

From the aldehydic acid, the following compounds were prepared: (a) the **methyl ester** and (b) the **oxime**.

The methyl ester (with diazomethane) melted at 44° (from methanol).

Anal. Calcd. for $C_9H_7BrO_3$: C, 44.44; H, 2.88; Br, 32.92. Found: C, 44.51; H, 3.07; Br, 32.85.

The oxime melted at 120° (from dilute ethanol).

Anal. Calcd. for $C_9H_8BrNO_3$: Br, 31.01; N, 5.43. Found: Br, 30.92; N, 5.16.

α-Bromo-3-bromo-*p*-tolunitrile.—3-Bromo-*p*-tolunitrile (50 g., 0.255 mole, from *p*-nitrotoluene → 2-bromo-4-nitrotoluene → 3-bromo-*p*-toluidine → 3-bromo-*p*-tolunitrile[8,12]) was placed in a quartz flask fitted with a stirrer, a dropping funnel, and a reflux condenser. The system was heated in an oil bath (bath temperature, 175–180°) and irradiated with ultraviolet light. Bromine (40 g., 0.25 mole) was added slowly; the gain in weight was 17 g. The reaction mixture was poured into water, and the product which crystallized was collected by filtration and pressed free of oil. Crystallization from methanol gave 35 g. (50% yield) of product, m.p. 81°.

Anal. Calcd. for $C_8H_5Br_2N$: Br, 58.18; N, 5.09. Found: Br, 58.09; N, 5.14.

3-Bromo-4-hydroxymethylbenzonitrile.—α-Bromo-3-bromo-*p*-tolunitrile (25 g., 0.0909 mole) was refluxed with 2 l. of water until nearly complete solution was effected, and then the reaction mixture was subjected to steam distillation. The hot residue was filtered, the filtrate was allowed to cool, and crystals formed; the yield was 11 g. (57%), m.p. 134.5–135.5° (from water).

Anal. Calcd. for C_8H_6BrNO: Br, 37.74; N, 6.60. Found: Br, 37.61; N, 6.26.

3-Bromo-4-hydroxymethylbenzoic Acid. A. From 3-Bromo-4-hydroxymethylbenzonitrile.—The nitrile (10 g., 0.0472 mole) was warmed for 20 min. on a steam bath with 200 ml. of concentrated sulfuric acid; the reaction mixture was allowed to stand overnight at room temperature. It was then poured into 800 ml. of ice water, and the solution was evaporated to one-half volume. The crystals which formed when the aqueous solution was cooled were dissolved in potassium carbonate solution, and the acid was precipitated by acidifying the solution with dilute hydrochloric acid, giving 6.2 g. (57% yield), m.p. 174.5–176.5° (from water).

B. From α-Bromo-3-bromo-*p*-tolunitrile.—This nitrile (10 g., 0.0364 mole) was refluxed for 10 hr. with 125 ml. of 10% sodium hydroxide solution. The reaction mixture was cooled and acidified with concentrated hydrochloric acid, and the product which precipitated was recrystallized from water, giving 3.2 g. (38% yield), m.p. 175–176°.

Anal. Calcd. for $C_8H_7BrO_3$: C, 41.56; H, 3.03; neut. equiv., 231. Found: C, 41.47; H, 3.08; neut. equiv., 230.2.

From the alcohol acid, the following compounds were prepared: (a) the **acetate** and (b) the **methyl ester**.

The acetate melted at 145–146° (from 50% ethanol).

Anal. Calcd. for $C_{10}H_9BrO_4$: Br, 29.30; neut. equiv., 273. Found: Br, 29.36; neut. equiv., 274.5.

The methyl ester (with diazomethane) melted at 88–89° (from 50% methanol).

Anal. Calcd. for $C_9H_9BrO_3$: Br, 32.61. Found: Br, 32.59.

3-Bromoterephthalaldehydonitrile.—To a solution containing 20 g. of cupric nitrate, 30 ml. of concentrated nitric acid, and 250 ml. of water, 10 g. (0.0364 mole) of α-bromo-3-bromo-*p*-tolunitrile was added, and the mixture was refluxed for 12 hr. The reaction mixture was cooled and extracted with ether. The ether solution was concentrated to *ca.* 30 ml. and shaken with saturated sodium bisulfite solution. The bisulfite addition compound was collected and dissolved in a minimum amount of water, and the aldehyde was regenerated by saturating the aqueous solution with potassium carbonate and warming it. The aldehyde was recrystallized from 50% ethanol, yielding 3.1 g. (41%), m.p. 120.5°.

(7) J. R. Johnson and T. L. Sandborn, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 111.

(8) A. Claus and H. Kunath, *J. prakt. Chem.*, [2]**39**, 485 (1889).

(9) This nitrile was converted to 2-bromo-*p*-toluamide by the action of concentrated sulfuric acid at 100° for 1 hr., m.p. 175° (from water), lit. m.p. 137°[8] and 175–176°.[10] A mixture of approximately equal amounts of this amide and the 3-bromo isomer (see ref. 12) melted at 142°.

(10) M. S. Gibson, *J. Chem. Soc.*, 776 (1956).

(11) J. J. Sudborough, *ibid.*, **67**, 602 (1895).

(12) This nitrile was converted to 3-bromo-*p*-toluamide by the method used for the 2-bromo isomer (see ref. 9), m.p. 174–175° (from water). *Anal.* Calcd. for C_8H_8BrNO: N, 6.54. Found: N, 6.38.

Anal. Calcd. for C_8H_4BrNO: Br, 38.10; N, 6.67. Found: Br, 38.20; N, 6.63.

The **oxime of 3-bromoterephthalaldehydonitrile** was prepared, m.p. 151° (from 50% ethanol).

Anal. Calcd. for $C_8H_5BrN_2O$: Br, 35.56; N, 12.44. Found: Br, 35.20; N, 12.53.

3-Bromoterephthalaldehydamide.—The nitrile (2 g., 0.00952 mole) was hydrolyzed by warming it with 20 ml. of concentrated sulfuric acid on a steam bath for 1 hr. The resulting solution was poured into 100 ml. of water, and the amide was purified by crystallization from water, yielding 2.1 g. (97%), m.p. 173°.

Anal. Calcd. for $C_8H_6BrNO_2$: Br, 35.09; N, 6.14. Found: Br, 34.99; N, 6.22.

3-Bromoterephthalaldehydic Acid.—The amide (2 g., 0.00877 mole) was dissolved in 20 ml. of concentrated sulfuric acid, and saturated sodium nitrite solution (containing 2.6 g.) was added slowly below the surface of the liquid.[11] The mixture was cooled and stirred; then it was warmed on a steam bath for a short time; finally it was poured into 100 ml. of water, yielding 1.93 g. (96%), m.p. 236° (from water).

Anal. Calcd. for $C_8H_5BrO_3$: C, 41.92; H, 2.18; neut. equiv., 229. Found: C, 41.83; H, 2.32; neut. equiv., 228.

The **methyl ester of 3-bromoterephthalaldehydic acid** was prepared (with diazomethane), m.p. 77° (from 25% ethanol).

Anal. Calcd. for $C_9H_7BrO_3$: C, 44.44; H, 2.88; Br, 32.92. Found: C, 44.85; H, 3.14; Br, 32.79.

The **oxime** of the methyl ester (above) was prepared, m.p. 131° (from 50% ethanol).

Anal. Calcd. for $C_9H_8BrNO_3$: Br, 31.01; N, 5.43. Found: Br, 30.78; N, 5.43.

Analysis of 3-Bromo-4-hydroxymethylbenzoic Acid–Bromoterephthalic Acid Mixtures.—By experiment it was shown that the volume of standard alkali solution required to neutralize mixtures of these acids was a linear function of weight–percentage composition. A graph[13] representing these data was constructed. Samples of the acid mixtures from the Cannizzaro reaction of bromoterephthalaldehyde (below) were titrated; from the graph, the compositions were determined.

Cannizzaro Reactions. A. Terephthalaldehyde and Formaldehyde.—A mixture of 45 g. (0.6 mole) of 40% formaldehyde solution and 10 g. (0.0746 mole) of terephthalaldehyde was placed in a flask fitted with a stirrer, a dropping funnel, and a thermometer. Methanol (50 ml.) was added, and the mixture was stirred until solution was effected. Sodium hydroxide solution (30 g. in 30 ml. of water) was added in small portions at such a rate that the temperature of the reaction mixture did not exceed 60°. In turn, the mixture was cooled to room temperature and poured into four volumes of water.

Crystals of α,α'-*p*-xylenediol formed and were collected by filtration. The filtrate was extracted with two 150-ml. portions of ether. From the ether solution, additional diol was obtained. The total yield was 7 g. (68%), m.p. 119° (from water).

The aqueous alkaline solution from which the diol had been extracted was acidified with 50% sulfuric acid, and two extractions with 150-ml. portions of ether were made. From the ether solution, *p*-hydroxymethylbenzoic acid was recovered. The yield was 1 g. (9%), m.p. 181° (from water).

B. Bromoterephthalaldehyde and Formaldehyde.—Bromoterephthalaldehyde (10.6 g., 0.05 mole) and formaldehyde (45 g. of 40% solution, 0.6 mole) were dissolved in methanol and treated with sodium hydroxide solution as in A immediately above.

Bromo-α,α'-*p*-xylenediol was isolated in a total yield of 8.25 g. (76%), m.p. 113° (from water).

The acidic product, which was recovered as in A above, was 3-bromo-4-hydroxymethylbenzoic acid, 2.5 g. (22% yield), m.p. 176° (from water).

C. Bromoterephthalaldehyde.—Bromoterephthalaldehyde (10.6 g., 0.05 mole) was dissolved in 100 ml. of methanol. This solution was cooled in an ice bath, and sodium hydroxide solution (40 g. in 60 ml. of water) was added in small portions at such a rate that the reaction temperature did not exceed 60°. After the alkali had been added, the ice bath was removed, and the reaction mixture was maintained at 60° for 1 hr.; then it was poured into three volumes of water, and this solution was warmed on a steam bath to remove methanol.

The aqueous alkaline solution was extracted with two 150-ml. portions of ether, and from the ether solution, 2 g. (19% yield) of bromo-α,α'-*p*-xylenediol was recovered, m.p. 113° (from water).

The aqueous alkaline solution was acidified with hydrochloric acid, and the acidic organic material (7 g.) which precipitated was collected by filtration. The filtrate was extracted with two 150-ml. portions of ether. From the ether solution, more acidic organic material (2 g.) was obtained. The total weight of acidic material was 9 g. Fractional crystallization of a portion of the acid mixture[14] from water resulted in the isolation of two components, bromoterephthalic acid which sublimes at 299° and 3-bromo-4-hydroxymethylbenzoic acid, m.p. 176°. Analysis of the acid mixture by the procedure described above gave bromoterephthalic acid (20%) and 3-bromo-4-hydroxymethylbenzoic acid (80%). This corresponds to 1.8 g. (15% yield) of the dibasic acid and 7.2 g. (63% yield) of the alcohol acid.

The total yield of products—diol and acids—corresponded to 97% of the aldehyde used in the reaction.

(13) S. E. Hazlet and R. B. Callison, *J. Am. Chem. Soc.*, **66**, 1248 (1944).

(14) The melting behavior of this mixture was studied carefully. Melting started at 169°, and the major portion of the sample was converted to a clear liquid at *ca.* 175°; suspended in the liquid was a solid phase which persisted until the temperature was 235–240°; between 240 and 255° this last solid portion melted. Because melting was not observed below 169°, it was concluded that 2-bromo-4-hydroxymethylbenzoic acid (m.p. 147–148°) was not present in the mixture.

Mixtures were prepared [(a) 10:1, (b) 10:3, and (c) 10:10, respectively] from 3-bromo-4-hydroxymethylbenzoic and bromoterephthalic acids. Melting points were (a) major portion, 165–170°, suspended solid persisted to *ca.* 230°; (b) major portion, 161–170°, suspended solid remained to *ca.* 235°; (c) partial melting, 173°, second component melted at *ca.* 275°.

The Preparation of Organic Phosphorus Compounds by Ivanov Reactions. II

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It has been found, contrary to a statement in the literature,[1] that the Ivanov-like reagent diethyl α-chloromagnesiobenzylphosphonate (I), prepared by the action of isopropylmagnesium chloride on diethyl benzylphosphonate, does behave like a Grignard reagent.

Interaction of I with carbon dioxide yielded an oily acid, diethyl α-carboxybenzylphosphonate (II) which could not be purified; by the use of diazomethane the pure ester, diethyl α-carbomethoxybenzylphosphonate (III), was obtained.

Reagent I reacted with ethylene oxide and with diphenylchlorophosphine oxide to produce diethyl α-(β-hydroxyethyl)benzylphosphonate (IV) and diethyl α-(diphenylphosphinyl)benzylphosphonate (V), respectively.

It was shown that after reaction of I with formaldehyde, acidification of the reaction mixture, and distillation of the crude product (an oil), diethyl α-methylenebenzylphosphonate (VI) was formed; this product may have been formed by spontaneous loss of water from the α-hydroxymethyl derivative which had been produced after acidification of the reaction mixture or possibly during distillation.

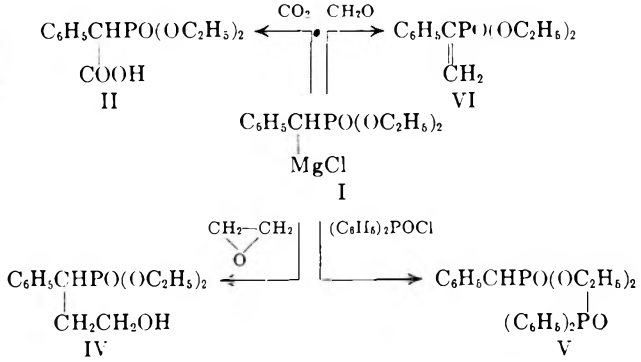
The product isolated after the reaction of I with benzophenone was also an unsaturated phosphorus compound, diethyl α-(diphenylmethylene)benzylphosphonate (VIII), which may have been produced by

(1) D. Ivanov and G. Borissoff, *Naturwissenschaften*, **46**, 171 (1959).

TABLE I

Compound no.	M.p. or b.p. (mm.), °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% P Calcd.	% P Found
III	125–130 (1)	75	$C_{13}H_{19}O_3P$	54.54	54.36	6.69	6.77	10.81	10.70
IV	135 (0.5)	13	$C_{13}H_{21}O_4P$	57.33	56.94	7.77	7.39	11.37	11.44
V[d]	161–162[a]	15	$C_{23}H_{26}O_4P_2$	64.49	64.17	6.12	6.24	14.46	14.66
VI	127 (0.3)	21	$C_{12}H_{17}O_3P$	59.99	59.72	7.13	7.31	12.89	12.77
VIII[d]	183–185[a]	10	$C_{24}H_{25}O_3P$	73.45	73.17	6.42	6.10	7.89	8.02
X	181–183[a,b]	95	$C_{24}H_{27}O_3P$	73.08	73.04	6.90	6.79	7.85	7.82
XI[d]	186–188[a,c]	23	$C_{20}H_{19}O_3P$	71.00	71.22	5.66	5.91	9.16	8.87
XII	130 (0.3)	28	$C_{13}H_{19}O_3P$	61.42	61.17	7.53	7.62	12.18	12.06
XIV	150–155 (0.5)		$C_{15}H_{21}O_5P$	57.69	57.74	6.78	7.18	9.92	9.65

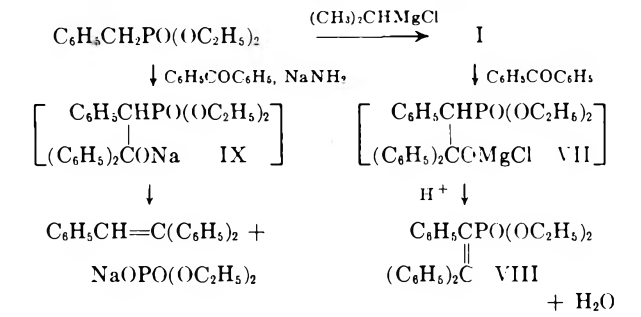
[a] Melting point. [b] The mixture melting point with VIII was 167–175°. [c] The mixture melting point with X was 175–182°. [d] Compound VIII was recrystallized from nitromethane; XI, from absolute ethanol; V, from ethyl acetate.



loss of water from the diphenylhydroxymethyl derivative after the reaction mixture, which contained VII, had been acidified.

An intermediate IX, analogous to VII, was postulated by Horner, *et al.*,[2] as the initial product formed when a mixture of diethyl benzylphosphonate, benzophenone, and sodamide was heated. Cleavage of the intermediate took place with the formation of triphenylethylene in 88% yield.[3]

In view of the fact that VIII was isolated in only 10% yield, it is possible that some triphenylethylene may have been present in the reaction mixture.



Compound VIII was hydrogenated to form diethyl α-(benzohydryl)benzylphosphonate (X), and this ester was hydrolyzed to yield α-(benzohydryl)benzylphosphonic acid (XI).

An Ivanov-like reagent, $C_6H_5CH{=}CHCH(MgCl)PO(OC_2H_5)_2$, was prepared from diethyl cinnamylphosphonate (XII), a substance which was synthesized from the sodium derivative of diethyl phosphite and cinnamyl chloride. The reagent was allowed to react with carbon dioxide whereby diethyl α-carboxycinnamylphosphonate (XIII) was formed. Since this acid could not be purified, it was converted by the use of diazomethane into diethyl α-carbomethoxycinnamylphosphonate (XIV) which was obtained in pure form.

An allylic rearrangement might have taken place during the preparation of XII and the Ivanov-like reagent.[4] However, based on statements in the literature[5] and on the following data, obtained from XII and XIV, it seems that this was not the case: the ultraviolet spectra showed the presence of a double bond conjugated with a benzene ring (styrene group), and the infrared spectrum of XII indicated a *trans* configuration about an internal double bond.

Experimental

The yields and physical properties of the products obtained are listed in Table I.

Preparation of Diethyl α-Chloromagnesiobenzylphosphonate (I).—Diethyl benzylphosphonate[6] (22.8 g., 0.1 mole), dissolved in 25 ml. of sodium-dried benzene, was added dropwise to a stirred solution of isopropylmagnesium chloride which had been prepared from 8.4 g. (0.11 mole) of isopropyl chloride, 2.7 g. (0.11 g.-atom) of magnesium, 1 ml. of ethyl bromide, and 100 ml. of ether. The mixture was stirred and refluxed for 12 hr.

Diethyl α-Carboxybenzylphosphonate (II) and Diethyl α-Carbomethoxybenzylphosphonate (III).—Dry Ice (about 25 g.) was added to a stirred suspension of I. After 1 hr. the mixture was stirred and hydrolyzed by the dropwise addition of a mixture of 10 ml. of concentrated hydrochloric acid and 200 ml. of water. The organic layer was extracted with aqueous sodium bicarbonate; the alkaline layer was acidified and extracted with benzene. After removal of the solvent from the dried benzene layer, the oily residue weighed 9.4 g. (35%). This product (II) could not be purified. The pure ester (III) was obtained by the use of diazomethane.

Diethyl α-(β-Hydroxyethyl)benzylphosphonate (IV).—Ethylene oxide (44.0 g., 1 mole) was added, dropwise, to a stirred suspension of I; the mixture was stirred for 10 hr. and hydrolyzed in the manner mentioned above. The organic layer was separated and dried, the solvent was removed, and the product was distilled.

Diethyl α-(Diphenylphosphinyl)benzylphosphonate (V).—Diphenylchlorophosphine oxide (23.7 g., 0.1 mole) was added dropwise to a stirred suspension of I. The mixture was stirred and refluxed for 4 hr., stirred for 12 hr., and then hydrolyzed. The mixture was filtered to remove diphenylphosphinic acid. The organic layer in the filtrate was separated and dried, and the solvent was removed. The residue, a mixture of an oil and a solid, was filtered with the use of a sintered-glass funnel. The solid material was washed with a small amount of ether and then triturated with hot petroleum ether (b.p. 90–100°).

Diethyl α-Methylenebenzylphosphonate (VI).—After 150 ml. of ether had been added to a suspension of I, the mixture was stirred and formaldehyde, obtained from 45 g. of paraformalde-

(2) L. Horner, H. Hoffmann, and H. G. Wippel, *Chem. Ber.*, **91**, 64 (1958); see also W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

(3) Cleavage of complex compounds analogous to IX, with the formation of phosphorus-free olefins, has been reported by H. Pommer [*Angew. Chem.*, **72**, 811 (1960)].

(4) See F. F. Blicke and H. Zinnes, *J. Am. Chem. Soc.*, **77**, 5399 (1955).

(5) G. W. Wheland, "Advanced Organic Chemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., p. 536; see also A. G. Catchpole and E. D. Hughes, *J. Chem. Soc.*, 4 (1948).

(6) B. C. Saunders, G. J. Stacey, F. Wild, and I. G. E. Wilding, *ibid.*, 699 (1948).

hyde, was introduced in a manner described previously.[7] The material was stirred for 10 hr. and then hydrolyzed. The organic layer was washed with water and dried, the solvent was removed, and the residue was distilled. The product decolorized permanganate rapidly.

Diethyl α-(Diphenylmethylene)benzylphosphonate (VIII).—Benzophenone (18.2 g., 0.1 mole), dissolved in 250 ml. of ether, was added dropwise to a stirred suspension of I. The mixture was stirred and refluxed for 1 hr., stirred for 12 hr., and hydrolyzed. The solvent was removed from the dried organic layer. The oily residue solidified when it was triturated with petroleum ether (b.p. 30–40°). It was triturated again with petroleum ether (b.p. 90–100°).

Diethyl α-(Benzohydryl)benzylphosphonate (X).—A mixture of 2.0 g. of VIII, dissolved in 100 ml. of warm absolute ethanol, and 0.2 g. of 5% palladium on carbon was hydrogenated for 18 hr. under an initial pressure of 40 lb. After filtration, with the use of Celite, water was added to the hot filtrate until it became turbid. The product separated from the cold mixture.

α-(Benzohydryl)benzylphosphonic Acid (XI).—A mixture of 1.0 g. of X and 20 ml. of concentrated hydrochloric acid was refluxed for 24 hr., and the inorganic acid was then removed in a stream of air. The residue was treated with aqueous sodium bicarbonate, and the mixture was extracted with benzene. The alkaline layer was acidified and extracted with benzene. After removal of the solvent from the dried benzene layer, the residue was recrystallized.

Diethyl Cinnamylphosphonate (XII).—To a stirred, refluxing suspension of 11.5 g. (0.5 g.-atom) of sodium and 500 ml. of xylene there was added dropwise 72.5 g. (0.52 mole) of diethyl phosphite.[8] The mixture was refluxed for 5 hr. and 76.0 g. (0.5 mole) of cinnamyl chloride[9] was added dropwise to the stirred refluxing mixture. After the material had been refluxed for 8 hr., it was cooled, the liquid was decanted from the sodium chloride, and the salt was washed with xylene. The solvent was removed and the residue was distilled. The product decolorized permanganate.

Diethyl α-Carboxycinnamylphosphonate (XIII) and Diethyl α-Carbomethoxycinnamylphosphonate (XIV).—The Ivanov-like reagent was prepared, in the usual manner, from 12.7 g. (0.05 mole) of diethyl cinnamylphosphonate dissolved in 25 ml. of benzene. After the addition of about 25 g. of Dry Ice, the mixture was stirred for 3 hr. and then hydrolyzed with dilute hydrochloric acid. The organic layer was shaken with aqueous sodium bicarbonate whereupon three layers were obtained. The alkaline layer and the oil were separated and the mixture was acidified with dilute hydrochloric acid. After extraction with benzene, the solvent was removed from the dried extract and the oily product XIII (6 g., 40%), which decolorized permanganate instantly, was treated with diazomethane to yield XIV.

Acknowledgment.—This investigation was supported by grants from The Wm. S. Merrell Company and from the American Foundation or Pharmaceutical Education.

(7) F. F. Blicke, H. Raffelson, and B. Barna, *J. Am. Chem. Soc.*, **74**, 253 (1952).

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Preparation of Acyl Halides and Esters from Salts of Perfluoroalkanoic Acids[1]

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It is quite well known that perfluoroacyl chlorides,[2] fluorides,[3] and esters[4] may be prepared from the corresponding free perfluoroalkanoic acids. While acyl chlorides have been prepared from salts by means of inorganic chlorides,[5] the use of organic acyl chlorides[5c] normally produces mixed anhydrides; in certain cases, partially fluorinated acyl chlorides have been obtained by the latter procedure,[6] albeit only in fair yield.

The use of benzenesulfonyl fluoride to convert sodium benzoate to benzoyl fluoride (plus benzoic anhydride) has been reported,[7] though the reaction was not offered as a useful synthetic procedure.

The purpose of this Note is to call attention to several synthetic advantages which may be gained by the use of the salts, rather than the free perfluoroalkanoic acids, in exchange reactions with certain acyl halides and esters. These are (1) high yields, (2) simplicity of procedure, (3) applicability to small scale, (4) freedom from evolution of hydrogen chloride or other volatile species, (5) as a corollary, fractional distillation of the product in good purity directly from the reaction mixture. For large-scale preparations the procedure is somewhat inconvenient owing to the formation of a caked solid phase, and to the relatively high reaction temperatures usually required to achieve a suitable rate of production. In certain cases, as for example perfluorocyclohexanecarboxylic acid,[8] the salt is too unstable to permit such procedures, but this is not the usual case.[9]

It is probable that the greatest value of the salt reactions lies in small-scale analytical applications, as for example in the characterization of fluorocarbon materials by alkaline cleavage or by permanganate oxidation. Normally the sodium or potassium salts are separated from inorganic contaminants by virtue of the relative insolubility of the latter in warm absolute ethanol. Acyl halides and methyl esters are especially desired for nuclear magnetic resonance spectroscopy and for retention time measurement by gas–liquid chromatography, as well as for molecular weight and saponification number determinations. Analytical purity of product is often obtained on a 1- to 5-g. scale without recourse to refractionation.

Experimental

The reactions were conveniently carried out by treating the powdered well-dried salt (usually the sodium salt) with a two- to threefold excess (*i.e.*, about an equal weight) of the organic exchange agent, in a flask of such size as to be about half filled therewith, and which was fitted with a short fractionating column of perhaps five to ten theoretical plates. An intermittent take-off head was desirable for boiling point determination, as well as

(1) Abstracts, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., 1955, p. 27M.

(2) (a) CF_3COCl *via* PCl_5: R. G. Jones, *J. Am. Chem. Soc.*, **70**, 143 (1948); and A. L. Henne, R. M. Alm, and M. Smook, *ibid.*, **70**, 1968 (1948). (b) C_3F_7COCl and higher homologs *via* PCl_5: M. Hauptschein, J. F. O'Brien, C. S. Stokes, and R. Filler, *ibid.*, **75**, 87 (1953); J. H. Simons, W. T. Black, and R. F. Clark, *ibid.*, **75**, 5621 (1953); and R. Filler, J. F. O'Brien, J. V. Fenner, and M. Hauptschein, *ibid.*, **75**, 966 (1953); (c) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 549.

(3) G. Olah, I. Kuhn, and I. Beke, *Chem. Ber.*, **89**, 862 (1956).

(4) (a) F. Swarts, *Bull. classe sci. acad. roy. Belg.*, **6**, 300 (1920); (b) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 480.

(5) (a) J. H. Simons and E. O. Ramler, *J. Am. Chem. Soc.*, **65**, 389 (1943); (b) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 547; (c) p. 559.

(6) (a) M. Prober, *J. Am. Chem. Soc.*, **75**, 968 (1953); (b) **77**, 910 (1955).

(7) W. Steinkopf and P. Jaeger, *J. prakt. Chem.*, [2]**128**, 65 (1930).

(8) T. J. Brice and J. H. Simons, *J. Am. Chem. Soc.*, **73**, 4017 (1951).

(9) L. J. Hals, T. S. Reid, and G. H. Smith, *ibid.*, **75**, 4595 (1953).

to prevent contamination of the product by the organic exchange agent when the reaction proceeds slowly despite high pot temperatures. While the reactions begin around 150° (much lower in the case of dimethyl sulfate), it is sometimes necessary to heat the mixture as high as 250° to collect the last of the product. Yields and physical properties are given in Table I.

TABLE I

REACTIONS OF SALTS OF PERFLUOROALKANOIC ACIDS

Product[a]	Exchange agent	Yield, %	B.p., °C.	$n^{25}D$[b]
n-C_3F_7COCl	C_6H_5COCl	88	39	1.2852
n-C_3F_7COCl	$C_6H_5CCl_3$	92	39	1.2854
n-C_3F_7COCl	p-$CH_3C_6H_4SO_2Cl$	80	39	1.2851
n-C_3F_7COCl[c]	$C_6H_5CCl_3$	87	39	1.2851
n-$C_7F_{15}COCl$	o-$C_6H_4(COCl)_2$	76	136	1.3035
(n-$C_9F_{19}COCl$)[d]	C_6H_5COCl	(−)[d]	(153)[d]	(1.3150)[d]
n-$C_9F_{19}COCl$	o-$C_6H_4(COCl)_2$	88	173	1.3087
n-$C_5F_{11}COF$	p-$CH_3C_6H_4SO_2F$	68	59	1.2625
n-$C_7F_{15}COF$	p-$C_2H_5C_6H_4SO_2F$	80	104	1.2764
n-$C_3F_7CO_2CH_3$	p-$CH_3C_6H_4SO_3CH_3$	98	81	1.2901
n-$C_3F_7CO_2CH_3$	$(CH_3)_2SO_4$	98	81	1.2922

[a] The sodium salt was used in all cases but one. Amounts used varied from 5 to 50 g. The structure of the salt used corresponds to the structure of the product. [b] This is the refractive index of the "crude" product; it agrees closely with the reported value. [c] The calcium salt was used. [d] The product was contaminated with benzoyl chloride, which codistilled.

The organic exchange agent should be chosen to boil far above the desired product, as otherwise it may become a serious contaminant owing to codistillation; this results from partial immiscibility with the fluorinated product and *cannot* be overcome by increasing the efficiency of the fractionating column. Benzoyl chloride, or benzotrichloride (which forms benzoyl chloride during the reaction), may be used for synthesis of up to six-carbon perfluoroacyl chlorides, but higher ones require phthalyl chloride. In special cases, dimethyl sulfate may be used for the synthesis of close-boiling esters by the expedient of using slightly *less than equimolar* amounts; it is thereby completely converted to the salt of methylsulfuric acid, and thus does not contaminate the product.

The identity and purity of the products was well established by comparison of physical properties with literature values, and also by infrared spectroscopy; in addition, the following analytical data were secured on the "crude" products of Table I in order to lend further support to the claims of purity. The n-C_3F_7COCl,[2b,10] from the sodium salt *via* $C_6H_5CCl_3$, had a strong infrared band due to C=O at 5.52 μ.

Anal. Calcd. for C_4ClF_7O: Cl, 15.25. Found: Cl (hydr.), 15.2.

For n-$C_7F_{15}COCl$[2b] also, the C=O band was at 5.52 μ.

Anal. Calcd. for $C_8ClF_{15}O$: C, 22.2; Cl, 8.25; F, 65.9. Found: C, 22.3; Cl (hydr.), 8.3; F, 65.1.

Similarly, n-$C_9F_{19}COCl$[2b] had its C=O band at 5.53 μ.

Anal. Calcd. for $C_{10}ClF_{19}O$: C, 22.6; Cl, 6.66; F, 67.9. Found: C, 22.7; Cl (hydr.), 6.7; F, 67.2.

The sample of n-$C_5F_{11}COF$ had its C=O band at 5.32 μ.

Anal. Calcd. for $C_6F_{12}O$: C, 22.8; F(hydr.), 6.02. Found: C, 23.0; F (hydr.), 6.0.

The n-$C_7F_{15}COF$ showed its C=O band at 5.31 μ, and was, therefore, not further analyzed. There was no question as to the identity of the $C_3F_7CO_2CH_3$,[11] which is a well-known compound.

Acknowledgment.—The author thanks Dr. W. E. Keiser and Dr. J. J. McBrady for the infrared spectral analysis.

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(11) W. H. Pearlson, "Fluorine Chemistry," Vol. 1, J. H. Simons, Ed., Academic Press, New York, N. Y., 1950, p. 503.

Alkaline Hydrolysis of Ethyl Benzoate in Aqueous Dimethyl Sulfoxide

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The data presented in the recent review article of Parker[1] very clearly demonstrate the marked rate-enhancing ability of dipolar aprotic solvents such as dimethyl sulfoxide upon bimolecular displacement reactions effected with anions. Thus Friedman and Shechter[2] reported the greatly accelerated displacement of halide by cyanide, azide, thiocyanate, and halide ions; Smiley and Arnold[3] observed the facile interconversion of primary and secondary halides to nitriles by the action of cyanide ion in dimethyl sulfoxide; and Cram and co-workers[4] found that use of dimethyl sulfoxide as a solvent allows both the Wolff–Kishner reduction and the Cope elimination reaction to be run at room temperature.

In accordance with these findings and his own excellent work with SNAr-type reactions, Parker[5a] postulated that any bimolecular reaction of a small anion passing through a large polarizable transition state will be considerably accelerated in the change from protic to dipolar aprotic solvents.

Such a reaction that has yet to be investigated kinetically in dipolar aprotic solvents is the alkaline hydrolysis of esters.[5b] In consideration of the large amount of work that has been carried out towards elucidating the mechanism of ester saponification (BAc^2),[6,7] a quantitative study of the effect of an aprotic solvent upon this reaction should be of interest. To this end, the present paper deals with the alkaline hydrolysis of ethyl benzoate in aqueous dimethyl sulfoxide. This ester was selected for study because a similar investigation carried out with ethyl benzoate in aqueous ethanol permits a comparison with a typical protic solvent system.

Table I presents the kinetic findings of this work. It is readily apparent from this table that alkaline hydrolysis of ethyl benzoate in aqueous dimethyl sulfoxide is accelerated relative to aqueous ethanol. Since the mechanism of the base-catalyzed hydrolysis of a normal ester[6,7] involves the production of a large polarizable transition state *via* the rate-determining addition of hydroxide ion to the carbonyl carbon atom of the ester, the data reported in Table I are in accord with Parker's postulate. Change from aqueous ethanol to aqueous dimethyl sulfoxide leads to a diminishment in hydroxide ion solvation[1,8] and an increase in transition state

(1) A. J. Parker, *Quart. Rev.*, (London) **16**, 163 (1962).

(2) L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960).

(3) R. A. Smiley and C. Arnold, *ibid.*, **25**, 257 (1960).

(4) D. J. Cram, M. Sohyum, and G. R. Knox, *J. Am. Chem. Soc.*, **84**, 1734 (1962).

(5) (a) A. J. Parker, *J. Chem. Soc.*, 1328 (1961). (b) NOTE ADDED IN PROOF.—E. Tommila and co-workers [*Acta Chim. Scand.*, **17**, 1957, 1980 (1963)] have recently reported a similar rate-enhancing influence of dimethyl sulfoxide in the saponification of ethyl acetate.

(6) M. Polanyi and A. L. Szabo, *Trans. Faraday Soc.*, **30**, 508 (1934).

(7) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).

(8) J. E. Prue and P. J. Sherrington, *Trans. Faraday Soc.*, **57**, 1796 (1961).

TABLE I

RATES OF ALKALINE HYDROLYSIS OF ETHYL BENZOATE IN AQUEOUS DIMETHYL SULFOXIDE

Solvent, % by vol.	Temp., °C.	$k_2 \times 10^4$ l./mole/sec.	Rel. rate
85% aq. EtOH	25.0	7.0[a]	1
85% aq. DMSO[b]	25.0	2240 ± 80[c]	320
	20.0	1550 ± 50	
	15.0	1050 ± 15	
	10.0	735 ± 20	
80% aq. DMSO	25.0	1140 ± 34	160
	20.0	810 ± 20	
	15.0	550 ± 20	
	10.0	385 ± 30	
75% aq. DMSO	25.0	660 ± 27	94
	20.0	480 ± 8	
	15.0	350 ± 35	
	10.0	250 ± 15	
70% aq. DMSO	30.0	700 ± 28	
	25.0	500 ± 14	71
	20.0	350 ± 9	
	15.0	250 ± 6	
65% aq. DMSO	35.0	770 ± 10	
	30.0	535 ± 15	
	25.0	380 ± 26	54
	20.0	270 ± 7	
	15.0	180 ± 16	

[a] R. A. Fairclough and C. N. Hinshelwood, *J. Chem. Soc.*, 538 (1937). [b] Dimethyl sulfoxide. [c] One standard deviation unit.

TABLE II

THERMODYNAMIC ACTIVATION PARAMETERS FOR ALKALINE HYDROLYSIS OF ETHYL BENZOATE IN AQUEOUS DIMETHYL SULFOXIDE

Solvent	Mole fraction of organic component	ΔH^*, cal./mole	ΔS^*, e.u.
Aq. EtOH[a]	0.334	15,490	−19.2
	0.444	16,020	−19.0
	0.493	16,400	−17.0
	0.690[b]	17,320	−15.8
	0.850	18,420	−12.4
Aq. DMSO	0.320	11,700 ± 240[c]	−26 ± 3
	0.372	11,500 ± 120	−26 ± 1
	0.433	10,200 ± 300	−30 ± 3
	0.504	11,200 ± 400	−25 ± 4
	0.591	12,200 ± 250	−21 ± 3

[a] Obtained from data of ref. 10. [b] C. A. Burkhard and R. E. Burnett, *J. Am. Chem. Soc.*, 80, 341 (1958). [c] One standard deviation unit from the mean.

solvation[5] with concomittant decrease in free energy of activation.

The data in Table II reveal that substitution of aqueous dimethyl sulfoxide for aqueous ethanol leads to both a reduced entropy and enthalpy of activation with the enthalpic change controlling the free energy of activation in agreement with the Hughes–Ingold theory of solvent effects on reaction kinetics.[9] Although the small differences in activation parameters provide only a slight basis for an anomalous dependency of activation enthalpy upon the mole fraction of dimethyl sulfoxide, such speculation is tempting. Further work is planned in this area to describe more adequately the solvation mechanism.

Experimental

Preparation of Materials.—Ethyl benzoate (n^{20}D 1.5048) was purified by fractional distillation and analysis by g.l.p.c. gave only a single sharp peak. Dimethyl sulfoxide was dried over 4A Molecular Sieves and analysis by g.l.p.c. did not reveal the presence of any significant amount of impurity. The dimethyl sulfoxide–water—sodium hydroxide mixtures were prepared according to the following scheme: a weighed quantity of sodium hydroxide was dissolved in a measured volume of water which in turn was diluted with measured volumes of dimethyl sulfoxide to give, respectively, 65, 70, 75, 80, and 85% (by volume) aqueous dimethyl sulfoxide solutions approximately 0.05 *N* in sodium hydroxide. In all cases, mixing dimethyl sulfoxide with water produced a shrinkage of the total volume.

Rate Measurements.—The kinetic experiments were carried out using both ester and sodium hydroxide in equal concentrations (about 0.05 *M*). The ester was weighed out in a volumetric flask, placed in a constant temperature bath (accurate to ±0.1°), and rapidly brought up to volume with the appropriate solvent mixture (pre-equilibrated to the reaction temperature, zero time was recorded as the time when one-half the solvent had been added). Aliquots were removed periodically; the reaction was quenched by addition to an excess of aqueous hydrochloric acid of known normality, and finally back-titrated with standardized aqueous sodium hydroxide to a bromthymol blue end point. The values of k_2 were calculated from the second-order reaction rate equation

$$k_2 = x/at\,(a - x)$$

where a is the initial concentration of each reactant and $a - x$ is the concentration of each reactant at time t. All of the measured reactions followed strictly second-order kinetic law, and consumed, within experimental error, 100% of the base present.

Treatment of the Kinetic Data.—The thermodynamic activation functions were obtained by IBM 1620 computer regression analysis of $\ln k/T$ *vs.* $1/T$.

(9) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 345-350.

Preparation of Tetracyclopropyllead and a Study of Some of Its Cleavage Reactions

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Research in organometallic chemistry hasl ead to the discovery of many well-known aliphatic and aromatic lead compounds. Organometallic compounds containing small groups such as the vinyl and cyclopropyl have aroused much interest in the past few years. Tetravinyllead has been prepared[1]; moreover, vinyl metal compounds have been extensively studied with examples having been prepared for common metals in all the A families of the periodic table. Although larger cycloalkyllead compounds have been reported,[2,3] the preparation of tetracyclopropyllead could not be found in the literature. Only a few cyclopropylmetal compounds have been reported, among which are cyclopropyllithium,[4] cyclopropylmagnesium bromide,[5] and dicyclopropylmercury.[6] Recently, some cyclopropyl compounds of the group IV elements—silicon, germanium, and tin—have been prepared.[7]

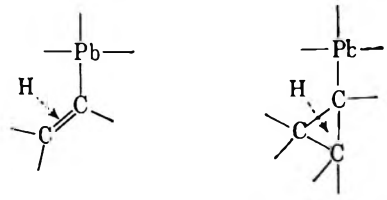
We have prepared the last cyclopropyl organometallic compound of the group IV-A family, tetracyclopro-

(1) E. C. Juenge and S. E. Cook, *J. Am. Chem. Soc.*, **81**, 3578 (1959).
(2) E. Krause and O. Schlottig, *Ber.*, **58**, 427 (1925).
(3) G. Gruttner, *ibid.*, **47**, 3257 (1914).
(4) H. Hart and J. M. Sandri, *Chem. Ind.* (London), 1014 (1956).
(5) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 3176 (1951).
(6) G. F. Reynolds, R. E. Dessy, and H. H. Jaffe, *J. Org. Chem.*, **23**, 1217 (1958).
(7) D. Seyferth and H. M. Cohen, *Inorg. Chem.*, **1**, 913 (1962).

pyllead, from lead dichloride and cyclopropylmagnesium bromide. Tetracyclopropyllead, like tetraethyllead and tetravinyllead, was found to explode upon heating to elevated temperatures but could be distilled at reduced pressure without decomposition.

We have also found that cyclopropyllead salts can be prepared by reactions analogous to those used for the preparation of alkyl, aryl,[8] and vinyl[1] lead salts. Thus, tricyclopropyllead chloride and dicyclopropyllead dichloride were prepared from the reaction of tetracyclopropyllead with hydrogen chloride and chlorine, respectively.

The cyclopropyl group like the vinyl group was found to be more readily cleaved from lead than the ethyl group. Tetravinyllead has been reported to react more readily with acetic acid than tetraethyllead.[1] A mixture of equivalent amounts of tetracyclopropyllead and acetic acid with silica gel as catalyst gave, at room temperature, immediate but slow evolution of gas and formation of a solid within 24 hr. An equivalent mixture of tetracyclopropyllead and acetic acid when heated to 90° gave immediate formation of a white solid. It was shown that equivalent amounts of tetraethyllead and acetic acid with silica gel as catalyst showed, at room temperature, no sign of reaction or formation of solid after 24 hr.[1] Browne and Reid[9] have also shown that an equivalent mixture of tetraethyllead and acetic acid with silica gel as catalyst gave, when refluxed at 100°, slow evolution of gas and required about 30 min. to produce a good yield of triethyllead acetate. Similar cleavage tendencies were observed from more dilute solutions of tetraethyl, tetravinyl, and tetracyclopropyllead in acetic acid. At one dilution, precipitation occurred in 2 hr. with tetravinyllead, 10 hr. with tetracyclopropyllead, and not within 24 hr. with tetraethyllead. The ease of cleavage of vinyl and cyclopropyl groups may be associated with the π- and the partial π-character, respectively, of these groups permitting protonation at π-centers followed by rupture of the neighboring lead-to-carbon bond.



Similar effects of the vinyl and cyclopropyl groups have been reported,[10] such as the high *ortho*-to-*para* ratios of nitration products of styrene and phenylcyclopropane. Comparison of ease of cleavage of tetravinyl- and tetracyclopropyllead is complicated by production of different products by reaction with carboxylic acids.

Products obtained in reactions of carboxylic acids with tetracyclopropyllead were generally not pure. Reaction of tetracyclopropyllead with equivalent amounts of acetic acid, monochloroacetic acid, and dichloroacetic acid yielded essentially dicyclopropyllead salts (I), while trichloroacetic acid yielded primarily tricyclopropyllead salts (II) with some dicyclopropyllead salts. It is reported[11] that the reaction of a plumbane with a carboxylic acid often yields a trialkyllead salt but that sometimes a dialkyllead salt or a mixture of these compounds is obtained. Thus, pure products are sometimes difficult to obtain,[9] and our work presents some further examples of the formation of dialkyllead salts by the reaction of plumbanes with carboxylic acids. Moreover, it is illustrated that the plumbane may be an important factor governing which salt is produced. Dithizone technique[12] was employed to determine the approximate content of di- and tricyclopropyllead salts produced. Carbon and hydrogen analyses obtained on the impure products seemed consistent with the dithizone results. In those reactions producing essentially pure products, a total lead per cent was also determined by dithizone technique (Table I).

TABLE I

DITHIZONE ANALYSES[12]

For reaction $Cp_4Pb \xrightarrow{RCOOH} \cdot Cp_2Pb(OCOR)_2$ (I) $+ Cp_3PbOCOR$ (II)[a]

Acid reactant	Dialkyllead salt (I), %	Trialkyllead salt (II), %	Total Pb, % calcd.	Total Pb, % found
CH_3COOH	95+[b]	Trace	50.9 (I)	49.2
$ClCH_2COOH$	95+[b]	Trace	43.5 (I)	42.6
Cl_2CHCO_2H	95+[c]	Trace	38.0 (I)	36.9
Cl_3CCO_2H	25	75		

[a] Cp = cyclopropyl. [b] C–H analysis was slightly high when calculated for dialkyllead salt. [c] C–H analysis was consistent for the dialkyllead salt.

The reactions between equivalent amounts of tetracyclopropyllead and mono-, di-, and trichloroacetic acids gave a white solid almost immediately at room temperature. Precipitation from ether solutions was slower with the rate of precipitation increasing with increased acidity of the chloro acid.

Seyferth and Cohen[7] reported that the most noticeable feature of the infrared spectra of many cyclopropylmetal compounds is the strong absorption near 900 cm.$^{-1}$. Moreover, this peak seems to be characteristic of the atom to which the cyclopropyl group is attached. Thus, in the IV-A family it has been shown that increased wave lengths for cyclopropylmetal compounds occur with increased atomic weights in the progression silicon, germinium, and tin. We have found that tetracyclopropyllead is consistent with this progression, absorbing at the highest wave length of the series (see Table II).

TABLE II

INFRARED ABSORPTION PEAKS OF CYCLOPROPYLMETAL COMPOUNDS

Compounds	Infrared absorption, cm^{-1}
Cyclopropyltrimethylsilane	902
Cyclopropyltrimethylgermane	888
Cyclopropyltrimethyltin	875
Tetracyclopropyllead	865

Further work is planned to investigate the relative cleavage rates of cyclopropyllead and vinyllead compounds and to examine the products obtained in these reactions.

(8) G. Gruttner, *Ber.*, **51**, 1298 (1918).
(9) O. H. Browne and E. E. Reid, *J. Am. Chem. Soc.*, **49**, 830 (1927).
(10) R. Ketcham, R. Cavestri, and D. Jambotkar, *J. Org. Chem.*, **28**, 2139 (1963).
(11) R. Heap, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 658 (1951).
(12) M. E. Griffing, A. Rozek, L. J. Snyder, and S. R. Henderson, *Anal. Chem.*, **29**, 190 (1957).

Experimental[13]

Cyclopropyl bromide was prepared according to the excellent procedure described by Professor J. S. Meek, University of Colorado.[14]

Tetracyclopropyllead.—The cyclopropylmagnesium bromide was prepared from 5.08 g. of magnesium, 25 g. of cyclopropyl bromide, and 175 ml. of tetrahydrofuran as solvent.[5] The reaction was allowed to cool to room temperature and 42 g. of lead dichloride was added with constant stirring over a period of 25 min. The reaction mixture appeared green-brown in color, turning deep black from lead deposition near the end of the reaction. The system was then refluxed in an oil bath at 70–80° for 90 min. The tetrahydrofuran was then removed under slightly reduced pressures at an oil bath temperature of 40–45°. After the tetrahydrofuran had been removed, the system was connected to a cold trap (−80°), the pressure was reduced to about 0.1 mm., and the oil bath temperature was raised to 90°. After 30 hr., 10.4 g. of crude product had collected. The crude product (mol. wt. calcd., 371.5; found, 398) was redistilled, yielding 7.54 g. (29.8% yield) of colorless liquid boiling at 57–58.5° (0.1 mm.). A middle cut boiling at 58° (0.1 mm.), $n^{24}D$ 1.5505, was taken for analysis.

Anal. Calcd. for $C_{12}H_{20}Pb$: C, 38.79; H, 5.44. Found: C, 38.70, 38.48; H, 5.73, 5.62.

Tricyclopropyllead Chloride.—To a clean, dry test tube was added 215 mg. of tetracyclopropyllead and an equivalent amount of concentrated hydrochloric acid. A white precipitate formed immediately. The reaction was allowed to stand for 1 hr. with frequent stirring. The crystals were then washed with *n*-hexane and filtered. The yield was 186 mg. (84% yield) of colorless crystals, m.p. 173–174°.

Anal. Calcd. for $C_9H_{15}ClPb$: C, 29.55; H, 4.13. Found: C, 29.57; H, 4.21.

Dicyclopropyllead Dichloride.—A solution of 57.5 mg. of tetracyclopropyllead in 5 ml. of *n*-hexane was saturated with chlorine gas during which time precipitation occurred. The mixture was allowed to sit for 1 hr. with occasional addition of chlorine. The precipitate was collected, washed with *n*-hexane several times, and dried under vacuum at room temperature leaving 44.8 mg. (81%) of dicyclopropyllead dichloride, m.p. 250° dec.

Anal. Calcd. for $C_6H_{10}Cl_2Pb$: C, 20.00; H, 3.00. Found: C, 20.34; H, 2.82.

Dicyclopropyllead Bisdichloroacetate.—Tetracyclopropyllead (200 mg., 0.54 mmole) and 70 mg. of dichloroacetic acid (0.54 mmole) were mixed in 5 ml. of ether. After about 3 hr., precipitation began. After 20 hr., the white needles were collected, washed several times with 5-ml. portions of ether, and dried under vacuum at room temperature. The yield was 130 mg., m.p. 179–180° dec.

Anal. Calcd. for $C_{10}H_{12}Cl_4O_4Pb$: C, 22.03; H, 2.22. Found: C, 21.89; H, 2.48.

Other lead salts reported in Table I were obtained by similar reactions. Products in these cases were impure or mixtures, and dithizone analyses for them are reported in Table I also.

Acknowledgment.—The authors gratefully acknowledge Mr. S. R. Henderson of Ethyl Corporation for analyses and to the Ethyl Corporation for samples of tetraethyllead used in these studies.

(13) Analyses were by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(14) We are indebted to Mr. Dean Sinclair, Kansas State University, for bringing this excellent procedure to our attention.

Michael Addition of Hydroxylamines to Activated Double Bonds. A Convenient Synthesis of N,N-Dialkyl Hydroxylamines

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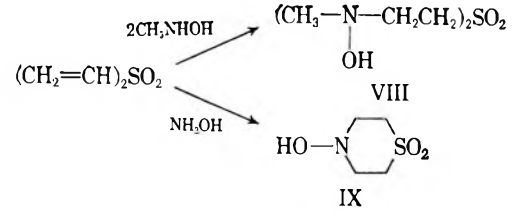
N,N-Dialkyl hydroxylamines have not been readily available, because attempts to synthesize them by dialkylation of hydroxylamine and by oxidation of secondary amines have given low yields, and the thermal decomposition of N-oxides have been restricted to the lower aliphatic members. We have found that a satisfactory route to these compounds lies in the addition of N-alkyl hydroxylamines to activated double bonds, a reaction not previously reported, although hydroxylamine itself has been used in addition reactions with methyl acrylate,[3] cinnamates,[4] mesityl oxide,[5] chalcones,[6] nitro olefins,[7,8] acrylonitrile,[9] 2-vinylpyridines,[10] diphenylmethylene carbamate,[11] and vinyl ketones.[12] In these cases, the products were generally the 1:1 adducts, which, on consideration of the difunctional character of the hydroxylamine, might not have been expected.

From the reaction of N-methylhydroxylamine with a number of vinyl compounds we obtained high yields of N-methyl-N-alkyl hydroxylamines (Table I). N,N-Dialkyl hydroxylamines were also produced by the reaction of hydroxylamine with vinyl sulfones and vinylpyridines (Table II), and in no case could the monosubstituted hydroxylamine, the 1:1 adduct, be isolated.

The expected product, bis(2-N-methylhydroxylaminoethyl) sulfone (VIII), was obtained when divinyl sulfone was allowed to react with N-methylhydroxylamine. However, in the reaction of divinyl sulfone with hydroxylamine, cyclization occurred and 4-hydroxytetrahydro-1,4-thiazine 1,1-dioxide (IX) was produced almost quantitatively. That IX is indeed the product, having arisen by intramolecular rather than intermolecular condensation, is indicated by the fact that it was also obtained, as the only product, from a high dilution experiment. Cyclic addition products have been isolated from the reaction of divinyl sulfones and primary amines.[13]



Experimental[14]

Vinyl Compounds.—The acrylamide, 2-vinylpyridine, 4-vinylpyridine, and divinyl sulfone used were the commercially available materials. Vinyl ethyl sulfone, b.p. 69–70° (0.7 mm.), was synthesized from 2-chloroethyl ethyl sulfone and triethylamine,[15] rather than by the dehydration of 2-hydroxyethyl ethyl sulfone[16] which was unsatisfactory.

(1) To whom inquiries should be directed.

(2) Polaroid Corp., Cambridge, Mass.

(3) C. Harris and W. Harrmann, *Ber.*, **37**, 252 (1904).

(4) T. Posner, *et al.*, *ibid.*, **57**, 1128, 1133 (1924), and prior publications.

(5) C. Harris, *et al.*, *ibid.*, **36**, 656 (1903), and preceeding publications.

(6) R. P. Barnes, *et al.*, *J. Am. Chem. Soc.*, **76**, 276 (1954).

(7) T. Posner, *Ann.*, **389**, 32 (1913).

(8) C. D. Hurd and T. Patterson, *J. Am. Chem. Soc.*, **75**, 285 (1953).

(9) U. Hoffmann and B. Jacobi, U. S. Patent 1,992,615 (1935).

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(13) A. C. Bellaart, *Rec. trav. chim.*, **81**, 156 (1962).

(14) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

TABLE I

N-METHYL-N-ALKYL HYDROXYLAMINES

$$RCH{=}CH_2 + CH_3NHOH \longrightarrow RCH_2CH_2N(CH_3)OH$$

Compound No.	R	Yield, %	Solvent	M.p., °C.	Empirical formula		Calcd., %	Found, %
I	$-CONH_2$	60.5	Methanol	94–95[a]	$C_4H_{10}N_2O_2$	N	23.71	23.41
II	$-SO_2C_2H_5$	49	Water	106[b]	$C_5H_{13}NO_2S$	C	35.91	36.50
						H	7.38	8.31
						N	8.37	8.30
III		79	*c*	108–109[d]	$C_9H_{16}IN_2O^e$	C	36.73	36.88
						H	5.13	5.41
						N	9.52	9.82
IV		83.5	*c*	78[f]	$C_8H_{12}N_2O$	C	63.13	63.24
						H	7.95	8.05
						N	18.41	18.10

[a] Recrystallized from methanol. [b] Recrystallized from benzene. [c] No solvent was employed. [d] Boiling point at 1.8 mm.; $n^{25}D$ 1.5275. [e] Analyzed as the methiodide, m.p. 113–114°. [f] Recrystallized from ligroin.

TABLE II

N,N-DIALKYL HYDROXYLAMINES

$$2RCH{=}CH_2 + NH_2OH \longrightarrow RCH_2CH_2N(OH)CH_2CH_2R$$

Compound No.	R	Yield, %	Solvent	M.p., °C.	Empirical formula	Calcd., %	Found, %
V	$-SO_2C_2H_2$	88.5	Water	134–135[a]	$C_8H_{19}NO_6S$	N 5.11	4.78
VI		61.5	*b*	110–111[c,d]	$C_{14}H_{17}N_3O$	N 17.27	16.88
VII		62	Methanol	148–149[c,e]	$C_{14}H_{17}N_3O$	N 17.27	17.26

[a] Recrystallized from methanol. [b] No solvent was employed. [c] Recrystallized from benzene. [d] Lit.[10] m.p. 105–106.5°. [e] Lit.[10] m.p. 143–144°.

N,N-Dialkyl Hydroxylamines (General Procedure).—To 0.2 mole of N-methylhydroxylamine hydrochloride or hydroxylamine hydrochloride in 100 ml. of methanol or water, as indicated (Tables I and II), was added 0.1 mole of anhydrous sodium carbonate, followed by 0.15 mole of the vinyl compound. The reaction proceeded quite rapidly and, in the case of I, the sodium chloride was removed by filtration after stirring for 30 min. Evaporation of the methanol gave the product. The water-insoluble sulfones II and V separated during the course of the reaction and were filtered off. To prepare compounds III, IV, VI, and VII, the hydroxylamine hydrochlorides were added either directly or to a methanolic solution of the vinylpyridines and the products were extracted with chloroform from the reaction mixture after it had been neutralized by the addition of aqueous sodium bicarbonate.

Reaction of Divinyl Sulfone and Methylhydroxylamine.—To 20 g. (0.24 mole) of N-methylhydroxylamine hydrochloride in 100 ml. of water was added 13 g. (0.12 mole) of anhydrous sodium carbonate with ice cooling. Then 11.8 g. (0.1 mole) of divinyl sulfone was added dropwise and the mixture was stirred for 30 min. The crude product which had separated was filtered off and recrystallized from ethanol, yielding 15.7 g. (74%) of bis-(2-N-methylhydroxylaminoethyl) sulfone (VIII), m.p. 166–167°; λ_{max} (KBr) 3.18 (OH), 7.83 and 8.7 (SO_2) μ.

Anal. Calcd. for $C_6H_{16}N_4OS$: N, 13.19. Found: N, 12.93.

Reaction of Divinyl Sulfone and Hydroxylamine.—Six grams (0.05 mole) of anhydrous sodium carbonate was added to a solution of 6.9 g. (0.1 mole) of hydroxylamine hydrochloride in 200 ml. of water. Then 11.8 g. (0.1 mole) of divinyl sulfone was added dropwise with vigorous stirring. The stirring was continued for 30 min. and the separated solid was then collected. This consisted of 12.9 g. (85.5%) of 4-hydroxytetrahydro-1,4-thiazine 1,1-dioxide (IX), m.p. 192–193° dec.; λ_{max} (KBr) 2.98 (OH), 7.85 and 8.88 (SO_2) μ.

Anal. Calcd. for $C_4H_9NO_3S$: C, 31.77; H, 5.99; N, 9.26. Found: C, 31.74; H, 6.19; N, 9.35.

In a high-dilution experiment using 1500 ml. of water, the same compound was obtained as the only product.

(15) A. H. Ford Moore, *J. Chem. Soc.*, 2433 (1949).

(16) M. F. Schostakovskii, E. N. Prilezhaeva, V. A. Azovskaya, and G. V. Dmitrieva, *Zh. Obshch. Khim.*, **30**, 1123 (1960); *Chem. Abstr.*, **55**, 414 (1961).

The Rate of Reaction of Piperidine with Piperonal in Methanol

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Although secondary amines cannot react with aromatic carbonyl compounds to form uncharged aldimines or ketimines, cations of the type $ArCH{=}\overset{+}{N}R_2$ (I) exist and may be intermediates in reactions catalyzed by piperidine or other secondary amines.[2] Having already studied the kinetics of ammonia[3] and primary amines[4] with aromatic aldehydes, we attempted to detect a reaction between piperidine and piperonal in methanol to form I or its tetrahedral precursor, $ArCH(OH)NR_2$ (Ia).

The ultraviolet absorption at the λ_{max} of piperonal (312 mμ) did indeed decrease in the presence of piperidine. Since no peak appeared at the higher wave length expected for I (in analogy with a protonated Schiff base[5]), this species was not present in appreciable quantity, though it might be formed in more acidic solutions. Moreover, the reaction was readily reversed by water. These observations suggested that

(1) National Science Foundation Research Participant, 1962.

(2) M. L. Bender and R. Breslow, in "Comprehensive Biochemistry," M. Florkin and E. H. Stotz, Ed., Elsevier Publishing Co., New York, N. Y., 1962; N. J. Leonard and J. V. Pankstelis, *J. Org. Chem.*, **28**, 3021 (1963).

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(4) R. L. Hill and T. I. Crowell, *J. Am. Chem. Soc.*, **78**, 2284 (1956); G. M. Santerre, C. J. Hansrote, Jr., and T. I. Crowell, *ibid.*, **80**, 1254 (1958).

(5) T. I. Crowell and D. W. Peck, *ibid.*, **75**, 1075 (1953).

the methoxyamine II, the known product in similar systems in the presence of potassium carbonate,[6] was being produced.

$$ArCHO + R_2NH + CH_3OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\underset{OCH_3}{|}}{ArCHNR_2} + H_2O$$

II

$$K_1 = \frac{k_1}{k_{-1}} = \frac{[II][H_2O]}{[ArCHO][R_2NH]} \quad (1)$$

Equilibrium Constant.—The equilibrium constant K_1 was calculated from both ultraviolet and infrared spectrophotometric determination of piperonal. The values obtained at 25.0° were $K_1 = 2.4 \pm 0.1$ for eight runs over a range of 0.045–0.45 *M* piperidine and 0.50–1.21 *M* water (ultraviolet); $K_1 = 1.9 \pm 0.5$ for seventeen runs, 0.12–1.2 *M* piperidine, 0.14–0.36 *M* piperonal, and no added water (infrared). The data are consistent with the net reaction (1). Increasing the already high pH by adding sodium methoxide did not change the equilibrium constant. This seems to eliminate the concentration of the conjugate base of Ia as an important variable. Typical results are shown in Table I.

TABLE I

EQUILIBRIUM CONCENTRATIONS[a] IN METHANOL AT 25°

[ArCHO][b]	[R_2NH]	[H_2O]	[II][c]	K
9.2×10^{-5}	0.0232	0.05	9.2×10^{-5}	2.2
10.0×10^{-5}	0.091	0.50	4.4×10^{-5}	2.4
12.3×10^{-5}	0.091	1.21	2.1×10^{-5}	2.3
4.9×10^{-5}	0.453	0.51	9.5×10^{-5}	2.2
0.0132	1.067[c]	0.139[c]	0.139	1.4
0.0336	0.134[c]	0.104[c]	0.104	2.4
0.0280	0.276[c]	0.124[c]	0.124	2.0
0.0689	0.468[c]	0.276[c]	0.276	2.4

[a] Moles per liter. [b] Measured by ultraviolet (first four runs) or infrared (last four runs). [c] Calculated assuming reaction as in eq. 1.

Rate Constants.—From four kinetic runs at room temperature and 0.03–0.8 *M* piperidine, $k_1 = 0.049 \pm 0.006$ l. mole^{-1} min.$^{-1}$. The piperonal concentration was 10^{-4} *M* so that the forward reaction was pseudo first order. Equilibrium was established in these experiments due to a small but significant amount of water in the methanol; the first-order rate constants were calculated from the initial rates and divided by the piperonal concentrations to give the second-order constant k_1. Since the twenty-sevenfold variation in piperidine concentration would lead to a change of 0.7 pH unit, it appears that the rate is insensitive to pH in the alkaline solutions studied.

The calculated value of k_{-1} referred to below, is then 0.049 2.2 or 0.022 l. mole^{-1} min.$^{-1}$ for the hydrolysis of II by dilute solutions of water in methanol.

We prepared the diamine (III) from piperonal and piperidine in benzene, according to Stewart and Hauser.[6] The rate of hydrolysis of III to piperonal was proportional to the water concentration. The second-order rate constant is 0.025 ± 0.02 l. mole^{-1} min.$^{-1}$ (nine runs, 0.025–0.25 *M* water). This value is so close to the calculated k_{-1} (eq. 1) as to suggest that the reaction of III with methanol to form II is rapid, followed by rate-controlling hydrolysis of II. We confirmed this by treating III with methanol. The n.m.r. spectrum of the solution showed piperonal to be absent at this stage. After one minute, methanol and piperidine were removed by evaporation. Hydrolysis and titration of the residue showed that III had lost 1 equiv. of piperidine as in eq. 2.

$$\underset{III}{ArCH(NR_2)_2} + CH_3OH \xrightarrow{fast} \underset{\underset{OCH_3}{|}}{ArCHNR_2} + R_2NH \quad (2)$$

II

Thus methanolysis appears to be the first step in the mechanism of hydrolysis of the diamine III when the water concentration is low.

Experimental

Rate and Equilibrium Studies.—Solutions of piperonal and piperidine (freshly treated to remove pyridine[7]) were prepared in reagent-grade methanol. The water content of each component was determined by Karl Fisher titration. Ultraviolet spectra were determined on a Perkin-Elmer Spectracord. Infrared measurements of the 5.9- and 6.2-μ carbonyl peaks were made on a Perkin-Elmer Model 21, using silver chloride cells.

N,N′-(3,4-Methylenedioxybenzylidene)bispiperidine (III).—This compound, prepared by the method of Stewart and Hauser,[6] was recrystallized from isooctane, to yield white crystals, m.p. 74–78°. Hydrolysis gave 97–100% of the theoretical quantity of piperonal (ultraviolet spectrum) and of piperidine (titration). Neither the infrared nor the n.m.r. spectrum showed characteristic aldehyde absorption.

Anal. Calcd. for $C_{18}H_{26}N_2O_2$: N, 9.27. Found: N, 9.08.

Acknowledgment.—We are grateful to the National Science Foundation for a research grant and to Mrs. Winnie Faye Coyne and Mr. Robert A. Pages for n.m.r. spectra.

(6) A. T. Stewart and C. R. Hauser, *J. Am. Chem. Soc.*, **77**, 1099 (1955). See also E. P. Burrows, R. F. Hutton, and W. D. Burrows, *J. Org. Chem.*, **27**, 316 (1962).

(7) T. E. Young and E. D. Amstutz, *J. Am. Chem. Soc.*, **73**, 4773 (1951)

Direct Formylation of Sydnones[1a,b]

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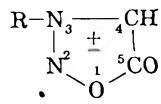
The ease with which the sydnone ring undergoes a variety of electrophilic substitution reactions led us to suggest that its reactivity was comparable to that of thiophene.[1a] We now wish to report that the direct formylation of 3-phenylsydnone (Ia) and of 3-benzylsydnone (Ib) by the Vilsmeier procedure[2] introduces the aldehyde group into the 4-position under conditions remarkably similar to those used in formylating thiophene.[3]

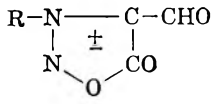
(1) (a) Sydnones. IV. Part III: J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.*, **83**, 178 (1961). (b) Part of this work was performed at Fordham University. Supported, in part, by grants (CY-2962 and CA-5478) from the National Cancer Institute of the Public Health Service. (c) To whom all inquiries should be sent.

(2) A. Vilsmeier and A. Haack, *Ber.*, **60B**, 119 (1927); A. W. Weston and R. J. Michaels, *Org. Syn.*, **31**, 108 (1951).

(3) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 635 (1948).

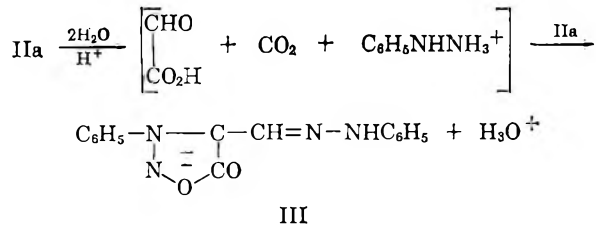


Ia, R = C_6H_5
Ib, R = $C_6H_5CH_2$



IIa, R = C_6H_5
IIb, R = $C_6H_5CH_2$

The ultraviolet and infrared spectra of the sydnonecarboxaldehydes were consistent with the structure (II) proposed. Furthermore, oxidation of IIa with potassium permanganate in acetone produced a small quantity of 3-phenyl-4-sydnonecarboxylic acid, which proved to be identical with an authentic sample.[4] On standing, the acidic filtrate from IIa deposited red crystals of the phenylhydrazone (III) of IIa, which presumably formed by reaction of unhydrolyzed IIa with the phenylhydrazine generated *in situ* by acid hydrolysis of IIa. Attempts to isolate the phenylhydrazone of glyoxylic acid were unsuccessful.



III

Both III and the 6-purinylhydrazone of IIa were prepared by conventional methods. They have been submitted to the Cancer Chemotherapy National Service Center (CCNSC) for screening for anticancer activity.

Experimental[5]

3-Phenyl-4-sydnonecarboxaldehyde (IIa).—N-Methylformanilide (28.4 g., 0.210 mole) and phosphoryl chloride (31.7 g., 0.205 mole) were mixed, and, after 0.5 hr., 30.0 g. (0.186 mole) of Ia was added portionwise with swirling and cooling as needed to keep the temperature below 45°. Hydrogen chloride was evolved vigorously. After standing overnight, the viscous, dark-brown mixture was dissolved in 150 ml. of acetone and poured (stirring) into 750 ml. of ice water. The yellow-orange precipitate was filtered, washed (cold water), and dried to yield 18.4 g. (52.1%) of 3-phenyl-4-sydnonecarboxaldehyde (IIa), m.p. 143–146°. Three recrystallizations from the minimum amount of boiling absolute ethanol afforded irregular, pale yellow plates, m.p. 147–150° dec. (with sublimation from 125°), λ_{max}^{EtOH} 240 and 321 mμ (ε 11,500 and 9780), λ_{max}^{KBr} 5.64 (sydnone C=O) and 6.10 μ (aldehyde C=O).

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 57.05; H, 3.35; N, 14.55.

After several days at room temperature, the aqueous filtrate from the crude IIa deposited clusters of red needles, shown to be identical (mixture melting point and infrared spectra) with authentic III (see below). The yield was 1.7 g. (equivalent to 2.5 g. of IIa).

3-Phenyl-4-sydnonecarboxaldehyde Phenylhydrazone (III).—Addition of aqueous phenylhydrazine hydrochloride to IIa in ethanol produced III, red needles, m.p. 173–174° (ethyl acetate–hexane); λ_{max}^{EtOH} 245, 297, and 424 mμ (ε 8790, 12,800, and 12,100); λ_{max}^{KBr} 5.78 (sydnone C=O), 6.28, 6.40, and 6.52 μ (probably C=N).

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: N, 19.99. Found: N, 19.43.

3-Phenyl-4-sydnonecarboxaldehyde 6-Purinylhydrazone.—6-Hydrazinopurine[6] (0.16 g., 1.1 mmoles) in 9 ml. of boiling water containing 1 drop of acetic acid was added to IIa (0.20 g., 1.1 mmoles) in 15 ml. of hot ethanol and the mixture was heated 15 sec. over steam and cooled 4 hr. in ice; the yellow solid was washed and dried to yield 0.27 g. (80%) of purinylhydrazone. This highly insoluble material was recrystallized three times from the minimum amount of hot (100°) dimethyl sulfoxide (to which water was added up to turbidity) to yield the analytical sample, m.p. 290–293° dec. (softening at 281°); $\lambda_{max}^{dioxane}$ 274 and 385 mμ (ε 44,800 and 13,000); λ_{max}^{KBr} 5.85 (sydnone C=O), 6.20, and 6.32 μ (probably C=N).

Anal. Calcd. for $C_{14}H_{10}N_8O_2$: C, 52.17; H, 3.13; N, 34.77. Found: C, 52.12; H, 2.98; N, 34.80.

3-Phenyl-4-sydnonecarboxylic Acid.—To a solution of IIa (*ca.* 0.1 g.) in 7 ml. of acetone was added solid potassium permanganate (*ca.* 0.2 g.) in small portions with stirring. After 5 min., excess permanganate was removed by addition of solid sodium sulfite. The filtered solution was poured into 14 ml. of cold water and the unchanged aldehyde was removed by filtration. The acidified filtrate was extracted with four 15-ml. portions of ether, and the combined extracts were dried and evaporated to yield 20 mg. of white solid, m.p. 190–193° dec., λ_{max}^{EtOH} 220 and 309 mμ (ε 14,500 and 8960), λ_{max}^{KBr} 5.52 (sydnone C=O) and 5.97 μ (acid C=O) This sample was identical (mixture melting point and infrared spectrum) with an authentic sample.[4]

3-Benzyl-4-sydnonecarboxaldehyde (IIb).—N-Methylformanilide (5.0 g., 0.037 mole) and 5.6 g. (0.036 mole) of phosphoryl chloride were allowed to stand 0.5 hr., cooled in an ice bath, and treated (stirring) with 5.6 g. (0.032 mole) of Ib. Next day the brown gum was dissolved in 15 ml. of dioxane and poured into ice, giving IIb as a waxy orange solid (1.0 g., 15%). Chromatography from benzene on a silica column (elution with 10% chloroform or ethyl acetate in benzene) yielded orange prisms, m.p. 79–80°; λ_{max}^{MeOH} 240.5 and 318.5 mμ (ε 9060 and 8560); λ_{max}^{KBr} 3.24, 3.41, 5.64 (sydnone C=O), and 6.09 μ (aldehyde C=O).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.81; H, 3.95; N, 13.72; mol. wt., 204.2. Found: C, 58.89; H, 3.82; N, 13.91; mol. wt. (Rast), 204.

(4) Kindly supplied by Dr. Hiroshi Kato; H. Kato and M. Ohta, *Bull. Chem. Soc. Japan*, **32**, 282 (1959).

(5) All melting points are uncorrected. The ultraviolet spectra were obtained with a Cary recording spectrophotometer, and the infrared spectra with a Beckman IR-5 double-beam instrument by use of the potassium bromide pellet procedure. Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

(6) A liberal sample was kindly supplied to us through the courtesy of Ronald B. Ross of CCNSC.

A Convenient Preparation of Chloroform-*d*[1]

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Chloroform-*d* of purity sufficient for most n.m.r. spectroscopy can be prepared conveniently and economically by a modification of the original synthesis of this compound by Breuer.[2] Breuer prepared chloroform-*d* by the following reactions.

$$2Na + 2D_2O \longrightarrow 2NaOD + 2D_2\uparrow$$

$$NaOD + Cl_3CCHO \longrightarrow CDCl_3 + NaCHO_2$$

The first reaction involves the loss of deuterium from the reaction and the danger of explosion of the liberated deuterium. To avoid these difficulties, an alternative preparation of sodium deuterioxide by the reaction of sodium peroxide and deuterium oxide was used. Sodium peroxide is a common chemical which is obtainable in the anhydrous state. It reacts with deuterium oxide.

(1) Other preparations of chloroform-*d* are listed in A. Murray and D. Williams, "Organic Syntheses with Isotopes," Interscience Publishers, Inc., New York, N. Y., 1958, p. 1477. See also M. T. Forel, *et al.*, *Bull. soc. chim. France*, 1922 (1959); P. J. Paulsen and W. D. Cooke, *Anal. Chem.*, **35**, 1560 (1963).

(2) F. W. Breuer, *J. Am. Chem. Soc.*, **57**, 2236 (1935).

$$2Na_2O_2 + 2D_2O \longrightarrow 4NaOD + O_2\uparrow$$

The reaction utilizes all deuterium to form the sodium deuterioxide and avoids the danger of explosion since oxygen, instead of deuterium, is evolved. Deuterium oxide, used as solvent, is recoverable without significant loss of purity.

Experimental

To 60 ml. of deuterium oxide in a 500-ml. three-necked flask equipped with reflux condenser, dropping funnel, and well-sealed stirrer, under dry nitrogen, contained in an ice–salt bath, was added cautiously with stirring 40 g. of sodium peroxide, followed by 98 g. of anhydrous chloral[3] (prepared by passing vapors of redistilled chloral over Drierite kept at 100°[2]) during 40 min. The ice was allowed to melt and the two layers that formed were separated. The chloroform was washed with water at pH 6 and dried over magnesium sulfate. The product was filtered and distilled (b.p. 62°) to give chloroform-*d* in yields averaging 90%, with 95% isotopic purity (isotopic purity determined by the nuclear magnetic resonance spectrum). The product was stored under nitrogen in sealed vials.[4]

(3) Trichloroacetophenone and hexachloroacetone are possible substitutes for chloral [W. Boyer, *et al.*, *J. Am. Chem. Soc.*, **73**, 770 (1951); P. J. Paulsen and W. D. Cooke, (ref. 1)].

(4) Deuterioethanol can be added as a stabilizer [P. J. Paulsen and W. D. Cooke, (ref. 1)].

The Reaction of Piperidine with Commercial Chloroform and Other Halomethanes

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In a recent note[1] the authors reported that from the reaction of piperidine with chloroform they isolated piperidine hydrochloride and detected the presence of N-formylpiperidine. Observations made in these laboratories, where the above reaction forms part of a wider investigation involving many bases, including alkaloids and organic halides, indicate that such a conclusion must be reassessed in terms of the purity of the chloroform.

It has been shown that commercial chloroform B.P. currently manufactured mainly by direct chlorination methods contains chlorobromomethane (0.2–0.5% v./v.) and methylene chloride (up to 0.1% v./v.) which cannot be removed by the usual fractionation methods of purification.[2,3] Such impurities were not present in chloroform obtained from earlier bleach processes.[4] Of these impurities, it is chiefly the chlorobromomethane which reacts with bases, "purified" chloroform (freed from these impurities) being almost unreactive.[2–5] The extent of reaction depends on the steric requirements of the base.[3,6] A study[3] of the rates of reaction of piperidine with chloroform B.P. and "purified" chloroform indicated that the base did not react to any appreciable extent with the latter, even at 60°.

The purpose of this communication is to show that impurities found in chloroform B.P. can react with piperidine to produce a number of products including piperidine hydrochloride, piperidine hydrobromide, and 1,1′-dipiperidylmethane. Equimolecular quantities of piperidine and chloroform B.P. interact to produce a mixture of piperidine hydrochloride and hydrobromide. The extent to which this reaction occurs after standing for 24 hr. (1% yield) is in agreement with that recorded by Pierce and Joullie[1] but the melting point found for the solid does not agree with their value. Infrared evidence is not helpful in elucidating the nature of the product as it does not distinguish between piperidine hydrochloride and hydrobromide. Its identity was established, however, by obtaining the same product from the interaction of piperidine and authentic chlorobromomethane. A second product of this reaction was shown to be 1,1′-dipiperidylmethane. The latter is also formed, together with the hydrobromide and hydrochloride, respectively, of the base, when piperidine reacts with either methylene bromide or methylene chloride.

Whereas piperidine reacts readily at room temperature with both chlorobromomethane and methylene bromide, boiling under reflux is required for the base to react with methylene chloride. This is not unexpected since the case with which halogens are replaced by nucleophillic groups (I > Br > Cl) is related to the bond energies (C–Cl > C–Br > C–I).

The products from the reaction of piperidine with excess chlorobromomethane are obtained in yields which are almost quantitatively related to this equation.

$$4C_5H_{10}NH + CH_2X_2 \longrightarrow 2C_5H_{10}NH\cdot HX + C_5H_{10}N\cdot CH_2\cdot NC_5H_{10}$$
(X = halogen)

When excess piperidine is used in the reaction with methylene bromide, the products again are formed in proportions approximating to the above equation.

On treating piperidine with "purified" chloroform, only a very small amount (0.025%) of piperidine hydrochloride is formed after 24 hr. Heating the reactants for several days, however, increases the yield (6%) and also facilitates the detection of a second product, N-formylpiperidine.

Experimental

Materials.—The three samples of chloroform used were I, b.p. 60–61.5°, $n^{20}D$ 1.4460, B.P. quality; II, b.p. 61.0–61.5°, $n^{20}D$ 1.4460, B.P. quality purified by successive washings with concentrated sulfuric acid and distilled water and drying overnight over calcium chloride which was removed by filtration, the filtrate being distilled through a 30-cm. Dufton column; III, b.p. 60.5–61.0°, $n^{20}D$ 1.4455, B.P. quality "purified" by boiling under reflux for several days with strychnine when recovery of the solvent yielded a sample of chloroform free from chlorobromomethane and methylene chloride.[3,4]

Chlorobromomethane was dried over calcium chloride and distilled through a 30-cm. Dufton column. The fraction boiling at 68–69°, $n^{20}D$ 1.4818, was collected.

Methylene bromide was dried over calcium chloride and distilled from a Claisen flask with a fractionating side arm, b.p. 96–97°, $n^{20}D$ 1.5420.

Methylene chloride was dried over calcium chloride and distilled from a Claisen flask with a fractionating side arm, b.p. 40–41°, $n^{20}D$ 1.4250.

(1) A. Pierce and M. M. Joullie, *J. Org. Chem.*, **27**, 2220 (1962).
(2) A. C. Caws and G. E. Foster, *J. Pharm. Pharmacol.*, **9**, 824 (1957).
(3) H. Williams, *ibid.*, **11**, 400 (1959).
(4) D. I. Coomber and B. A. Rose, *ibid.*, **11**, 703 (1959).
(5) H. Williams, *Chem. Ind.* (London), 900 (1960).
(6) H. Williams, to be published.

Piperidine was purified by standing over potassium hydroxide pellets for 1 week. The pellets were removed by filtration and the filtrate was distilled through a 30-cm. Dufton column, b.p. 105–106°, $n^{20}D$ 1.4527.

Commercial anhydrous ether and benzene were allowed to stand over sodium for 1 week and redistilled.

Reaction of Piperidine and Chloroform.—Piperidine (8.5 g., 0.1 mole) was mixed separately with (1) chloroform I (11.9 g., 0.1 mole), (2) chloroform II (11.9 g., 0.1 mole), and (3) chloroform III (11.9 g., 0.1 mole). After 24 hr., excess anhydrous ether was added to each solution. A white solid (0.11 g.) precipitated immediately from reactions 1 and 2, whereas reaction 3 yielded only a slight precipitate (0.003 g.), m.p. 245°, corresponding to piperidine hydrochloride, after standing for a short time. The product of reactions 1 and 2 had a melting point of 236° and a mixture of both produced no depression in the melting point. (Pierce and Joullie[1] record 244° as the melting point of this product.)

The same product was produced next by interaction of piperidine (0.1 mole) with "purified" chloroform III (0.1 mole) containing authentic chlorobromomethane (0.5% v./v.), and by mixing piperidine (0.1 mole) with authentic chlorobromomethane (0.1 mole), when a vigorous exothermic reaction occurred and a white solid separated almost immediately. In Table I the melting points and mixture melting points of the products prepared by the various methods A, B, and C are listed.

TABLE I

Sample[a]	M.p., °C.
A	235
B	234
C	234
A + B	235
A + C	234
B + C	235

[a] A = piperidine + chloroform B.P. (I), B = piperidine + chlorobromomethane, C = piperidine + chlorobromomethane in "purified" chloroform (III).

The following considerations contribute towards the elucidation of the structure of this product. The substance gives qualitative reactions for bromide.[7] After controlled oxidation with nitric acid,[8] the aqueous solution gave a precipitate with silver nitrate. The volumes of 0.1 *N* silver nitrate required before and after treating the solid with sodium and alcohol (Stepanov method) were identical. Hence, both the chlorine and bromine are ionized and the product appears to be an equimolecular mixture of piperidine hydrochloride and piperidine hydrobromide.

Anal. Calcd. for $C_5H_{11}N \cdot HCl \cdot C_5H_{11}N \cdot HBr$: C, 41.74; H, 8.35; N, 9.74; ionic Br, 27.83, ionic Cl. 12.34. Found, for the products formed from reaction of piperidine with (a) chlorobromomethane (b) chloroform B.P. (I), (c) chloroform II, and (d) "purified" chloroform (III) containing chlorobromomethane: (a) C, 41.46; H, 8.59; N, 9.56; ionic Br, 28.06; ionic Cl, 12.51. (b) ionic Br, 25.33; ionic Cl, 15.08; (c) ionic Br, 24.42; ionic Cl, 14.50; and (d) ionic Br, 27.65; ionic Cl, 13.06.

A higher proportion of chloride in (b) and (c) may be due to reaction of the base with the methylene chloride impurity.[3] Finally, the products formed by methods A, B, and C (see Table I) did not depress the melting point of a mixture of authentic piperidine hydrochloride and hydrobromide (234°).

Reaction of Piperidine with Chlorobromomethane.—Piperidine (25.5 g., 0.3 mole) was added to chlorobromomethane (64.8 g., 0.5 mole) in dry benzene (100 ml.) contained in a flask fitted to a condenser carrying a tube containing calcium chloride and soda lime. The reaction was markedly exothermic and a turbidity formed within 3–5 min. After 24 hr., the white crystalline solid was removed by filtration, washed with dry benzene, and dried, yielding 20.96 g., m.p. 236°. It did not depress the melting point of a mixture of authentic piperidine hydrochloride and hydrobromide.

Anal. Calcd. for $C_5H_{11}N \cdot HBr \cdot C_5H_{11}N \cdot HCl$: Br, 27.83; Cl, 12.34. Found: Br, 28.53; Cl, 11.98.

The filtrate was concentrated and then fractionated under reduced pressure to give a colorless liquid (X) in 12.30-g. yield, b.p. 55–58° (0.8 mm.), 238° (760 mm.), $n^{20}D$ 1.4825.

(7) F. Fiegel, "Spot Tests," Vol. 1, 4th Ed., Elsevier Publishing Co., London, 1954, p. 246.

(8) "British Pharmacopoeia," Pharmaceutical Press, London, 1958, p. 509.

Reaction of Piperidine with Methylene Bromide.—Piperidine (51 g., 0.6 mole) was added to methylene bromide (17.4 g., 0.1 mole) in dry benzene (50 ml.) in a flask fitted as before. The reaction was again exothermic and a white solid commenced separating within 0.25 hr. After 48 hr., the white crystalline solid was recovered and dried, yielding 29.73 g., m.p. 235°. It did not depress the melting point of authentic piperidine hydrobromide.

Anal. Calcd. for $C_5H_{11}N \cdot HBr$: Br, 48.19. Found: Br, 48.00.

The filtrate on fractionation under reduced pressure gave a colorless liquid (Y) in 15.03 g. yield, b.p. 58° (0.7 mm.), 238° (760 mm.), $n^{20}D$ 1.4820.

Reaction of Piperidine with Methylene Chloride.—Piperidine (17 g., 0.2 mole) was added to methylene chloride (25.5 g., 0.3 mole) in dry benzene (50 ml.) in a flask fitted as before. The reaction was exothermic, but no solid separated on standing for 2 hr. After boiling under reflux for 24 hr., the white crystalline solid which had formed was removed by filtration, washed with dry benzene, and dried, yielding 14.71 g., m.p. 243°. It did not depress the melting point of authentic piperidine hydrochloride.

Anal. Calcd. for $C_5H_{11}N \cdot HCl$: Cl, 29.16. Found: Cl, 28.71.

The filtrate on fractionation under reduced pressure gave a colorless liquid (Z) in 3.61-g. yield, b.p. 60° (1.0 mm.), 236° (760 mm.), $n^{30}D$ 1.4825.

Authentic 1,1′-dipiperidylmethane was prepared from piperidine and aqueous formaldehyde.[9] It was a colorless liquid, b.p. 58–60° (1.0 mm.), 238° (760 mm.), $n^{20}D$ 1.4825; lit. b.p. 235°, $n^{25}D$ 1.4810.[10]

Anal. Calcd. for $C_{11}H_{22}N_2$: C, 72.52; H, 12.09. Found: C, 72.95; H, 12.01.

Identification of Liquids X, Y, and Z.—The identity of liquids X, Y, and Z was established by the following considerations. Their boiling points and refractive indices were identical with those of authentic 1,1′-dipiperidylmethane; the infrared spectra of X, Y, Z, and authentic 1,1′-dipiperidylmethane were identical.

Anal. Calcd. for $C_{11}H_{22}N_2$: C, 72.52; H, 12.09; N, 15.38. Found for X: C, 72.98; H, 12.02; N, 15.99. Found for Y: C, 71.75; H, 12.06. Found for Z: C, 71.81; H, 12.13.

In the preparation according to the directions of Erhenberg[11] of derivatives with carbon disulfide, X, Y, and Z gave products, which after recrystallization from petroleum ether (b.p. 60–80°) had identical melting points (60°). Mixtures of these derivatives, in turn, with an authentic sample of the carbon disulfide derivative of 1,1′-dipiperidylmethane showed no depression in melting point (lit.[11] m.p. 58°).

Reaction of Piperidine with "Purified" Chloroform III.—Piperidine (17 g., 0.2 mole) was added to "purified" chloroform (35.7 g., 0.3 mole) in dry benzene (50 ml.) in a flask fitted as before. After boiling under reflux for 120 hr., a small quantity of white crystals had separated. These were removed by filtration, washed with "purified" chloroform, and dried, yielding 1.53 g., m.p. 245°. It did not depress the melting point of authentic piperidine hydrochloride.

Anal. Calcd. for $C_5H_{11}N \cdot HCl$: Cl, 29.16. Found: Cl, 29.22.

The filtrate on fractionation under reduced pressure gave a colorless liquid in 0.13-g. yield, b.p. 48–50° (1.0 mm.), whose properties (infrared spectrum, mercuric chloride derivative) were identical with those of authentic N-formylpiperidine.[1]

(9) Knoevenagel, *Ber.*, **31**, 2585 (1898).

(10) T. C. Simmons and F. W. Hoffmann, *et al.*, *J. Am. Chem. Soc.*, **79**, 3429 (1957).

(11) Erhenberg, *J. prakt. Chem.*, [2]**36**, 117 (1877).

1,12-Dioxa[5.5]paracyclophane

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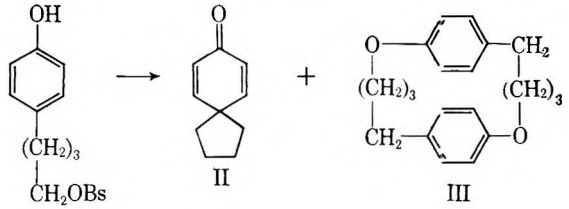
We wish to report the isolation and characterization of 1,12-dioxa[5.5]paracyclophane[2] (III), a by-product of the solvolysis of 4-(*p*-hydroxyphenyl)butyl brosylate

(I). The solvolysis of I and the isolation and characterization of the principal product (II) has been previously described.[3]

The neutral products from the solvolysis of I were chromatographed on a column of grade I basic alumina rather than distilled as previously described. Elution with benzene–pentane (1:9) gave a solid (III). Continued elution with benzene–pentane (2:3) gave II. The minor product (III) is clearly a dimer (osmometric molecular weight 294, calculated for III 296.4).[4] The infrared spectrum of III shows no hydroxyl absorption. The ultraviolet spectrum (λ_{max} 223, 277, and 285 mμ) is comparable with that of 4-methylanisole (223, 279, and 286 mμ).[5] The nuclear magnetic resonance spectrum of III shows eight aromatic protons as a pair of superimposed A_2B_2 patterns centered at τ 3.48, four protons as an unsymmetric triplet at 6.08 ($-CH_2-O-$), four protons as a similar triplet at 7.58 (benzylic methylene protons), and eight protons as a broad multiplet at 8.52 (remaining methylene protons).

Structure III is confirmed by the following chemical evidence. Refluxing constant boiling hydriodic acid converts III to 4-(4-iodobutyl)phenol (IV) Immediate



reduction of IV using 5% palladium on sodium carbonate as catalyst gives 4-*n*-butylphenol (V) identified by its spectral properties[6] and the crystalline phenylcarbamate, m.p. 114–115°.

The preparation of III by dimerization of I points to a useful synthetic method for heteroatom substituted paracyclophanes. Although the solvolysis reaction was run in this study at twice the original[3] concentration, the results imply that solvolysis of I in still more concentrated solutions should favor higher yields of 1,12-dioxa[5.5]paracyclophane.

Experimental

General Procedure.—A solution containing 14.5 g. of 4-(*p*-hydroxyphenyl)butyl brosylate (I) in 950 ml. of 0.025 *N* potassium *t*-butoxide in *t*-butyl alcohol was heated in a constant temperature bath at 54.8 ± 0.1° for 7 hr. The work-up of the reaction mixture was identical with that of Baird and Winstein[3] except the crude residue (usually 4–4.5 g.) was not distilled, but carefullly chromatographed on Woelm grade I basic alumina using increasing concentrations of benzene in pentane.

Elution with benzene in pentane (1:9) gave III (5–7% yield, m.p. 123–126°). One recrystallization from cyclohexane gave pure III, m.p. 132–132.5°. The infrared spectrum (KBr) of III showed bands at 3.30, 3.42, 3.51, 6.22, 6.33, 6.65, 6.92, 7.72, 8.15, 12.05, 12.20, 12.50, and 12.91 μ. In the ultraviolet, III showed $\lambda_{max}^{95\%\ EtOH}$ 223 mμ (ε 14,000), 277 (2320), and 285 (1710).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 80.97; H, 8.16; mol. wt., 296.4. Found: C, 80.90; H, 7.93; mol. wt., 294 (osmometric).

Elution (2:3 benzene–pentane) provided nearly pure II as determined by ultraviolet analysis, $\lambda_{max}^{95\%\ EtOH}$ 242 mμ (ε 14,500).[3] For complete purity, the liquid was distilled[7] giving a product that was solid at room temperature.

Degradation of 1,12-Dioxa[5.5]paracyclophane (III) to 4-*n*-Butylphenol (V).—A solution containing 400 mg. of III in 7 ml. of constant boiling hydriodic acid was heated under reflux for 5 hr., at which time all but a very small amount of III had gone into solution. The cooled reaction mixture was diluted with 25 ml. of water and extracted with three 15-ml. portions of ether. The combined ether fractions were dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, a semisolid, reddish residue was obtained that showed hydroxyl absorption in the infrared. The residue was immediately dissolved in 10 ml. of 5% ethanolic potassium hydroxide. A small quantity of solid would not dissolve and was filtered off. After the addition of 5% palladium on sodium carbonate (400 mg.), the ethanolic solution was hydrogenated at atmospheric pressure. The solution absorbed 23.5 ml. (60.5 ml. theory) of hydrogen. After removal of the catalyst by filtration, the solution was diluted with 50 ml. of water and extracted with four 15-ml. portions of ether. The ether extracts were combined and dried over anhydrous sodium sulfate. Removal of the ether under reduced pressure left 310 mg. of a yellow oil. The oil was chromatographed on a silicic acid column (15 × 300 mm.) providing 153 mg. of 4-*n*-butylphenol (V). The infrared spectrum (CCl_4) of V showed bands at 3.00, 3.32, 3.43, 3.50, 6.21, 6.62, 8.08, 12.12, and 12.42 μ. A concentrated solution of V in CCl_4 showed absorption at 5.33 and 5.70 μ.[6]

The reaction of V with phenyl isocyanate gave 4-*n*-butylphenyl phenylcarbamate, m.p. 114–115°, lit.[8] m.p. 115°.

(1) (a) National Institutes of Health Predoctoral Fellow, 1961–1963. Portions of this manuscript were abstracted from a thesis submitted by A. A. Griswold to the faculty of Iowa State University of Science and Technology, 1963. (b) Research Department, Chemicals Co., Union Carbide Corp., South Charleston, W. Va.

(2) The nomenclature used is that proposed by D. J. Cram and J. Abell, *J. Am. Chem. Soc.*, **77**, 1179 (1955).

(3) R. Baird and S. Winstein, *ibid.*, **84**, 788 (1962).

(4) This determination was made by Mr. T. A. Rettig.

(5) "Organic Electronic Spectral Data," Vol. I, M. J. Kamlet, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 210.

(6) D. D. Shrewsbury, *Spectrochim. Acta*, **16**, 1294 (1960); P. Montigny and G. Bichet, *Compt. rend.*, **237**, 820 (1954).

(7) Decomposition of II during distillation can be reduced by pretreating the glassware with dilute base.

(8) J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.*, **117**, 103 (1920).

Cyclopropanes from an Easily Prepared, Highly Active Zinc–Copper Couple, Dibromomethane, and Olefins

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The general reaction developed by Simmons and Smith for the preparation of cyclopropanes[1] from olefins, diiodomethane, and zinc–copper couple has proven to be exceedingly useful. The single drawback of their procedure, the inconvenience of preparing an active zinc–copper couple, was alleviated somewhat by the findings of Shank and Shechter[2] that a more conveniently prepared zinc–copper couple described by Hennion and Sheehan[3] will take part in the Simmons–Smith reaction. The couples described by these various groups may require several hours of tedious manipulations to prepare, may vary in activity from batch to batch, frequently requiring activation by iodine, and will react only with the expensive diiodomethane and chloroiodomethane. Reported here is a vastly simplified preparation of a *highly active* zinc–copper couple which, in the presence of olefins and without the use of

(1) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **81**, 4256 (1959).

(2) R. S. Shank and H. Shechter, *J. Org. Chem.*, **24**, 1825 (1959).

(3) G. F. Hennion and J. C. Sheehan, *J. Am. Chem. Soc.*, **71**, 1964 (1949).

TABLE I

Olefin (mole)	Polyhalomethane (mole)	Granular Zn–Cu, mole	Reaction time, hr.	Product	% yield[b]
Cyclooctene (0.26)	CH_2I_2 (0.31)	0.47	20	Bicyclo[6.1.0]nonane	82
Cyclooctene (0.26)	CH_2Br_2 (0.35)	0.47	30	Bicyclo[6.1.0]nonane	56
Cyclooctene (0.26)	CH_2Br_2 (0.35)	0.47	40	Bicyclo[6.1.0]nonane	43[c]
Cyclooctene (0.26)	$CHBr_3$ (0.35)	0.47	25	...	0
Cyclooctene (0.26)	$CHBrCl_2$ (0.40)	0.5[a]	20	...	0
Cyclooctene (0.26)	$PhCHCl_2$ (0.40)	0.54	20	...	0
Cyclohexane (0.29)	CH_2Br_2 (0.44)	0.47	25	Norcarane	61[d,e]

[a] Zinc–copper couple prepared from zinc dust. The granular couple proved unreactive. [b] Yields were obtained from gas chromatographic analysis. Only a limited amount of effort was made to maximize these yields. [c] Preparative gas chromatographic isolation afforded a 28% yield of a colorless liquid, $n^{25}D$ 1.4671; A. C. Cope and C. L. Woo [*J. Am. Chem. Soc.*, **85**, 3601 (1963)] give $n^{25.5}D$ 1.4668. [d] Distillation through a spinning band column gave a 38% yield of a colorless liquid, b.p. 115–116°, $n^{25}D$ 1.4542; lit.[2] b.p. 116°, $n^{25}D$ 1.4542. [e] This 61% yield, which is somewhat better than the 50% yield obtained by Shank and Shechter,[2] fell to 40% in the case of diiodomethane and 2% in the case of dibromomethane when zinc–copper dust was used in place of the granular couple.

iodine activation, forms cyclopropanes, not only with diiodomethane, but also with dibromomethane.

The new zinc–copper couple is readily prepared by treating either zinc granules or zinc dust with a hot acetic acid solution of cupric acetate monohydrate, then washing with acetic acid and ether.[4] The couple prepared from zinc dust is more reactive[5] than granular zinc couple and can be used in reactions involving unreactive polyhalomethanes. The granular zinc–copper couple has the advantage of giving a smoother, more easily controlled reaction. The couple reacts spontaneously with both diiodomethane and dibromomethane. When an olefin is present both dihalomethanes give cyclopropanes. Compared to diiodomethane only a small sacrifice in yield was encountered when dibromomethane is used as a source of the elements of methylene.

A convenient procedure for carrying out the Simmons–Smith reaction involves slow addition of a mixture of the olefin and dihalomethane to a warm, rapidly stirred suspension of the couple in ether. The reaction will start faster if a small portion of the dihalomethane is added first to the ether–couple suspension to initiate the reaction before addition of the olefin–dihalomethane mixture. An attempt to improve on this procedure by adding dibromomethane to a mixture of cyclooctene and couple in ether gave a lower yield.

Bromoform, carbon tetrabromide, 2,2-dibromopropane, and benzal chloride also react readily with this zinc–copper couple. However, no cyclopropane derivatives have yet been detected when the reactions are carried out in the presence of an olefin. Instead, gas chromatographic analysis indicates that the olefin is essentially unchanged, while the polyhalomethanes have been consumed to give a number of high boiling products, probably as a result of intermolecular condensation. Iodoform also reacts readily with this couple, but chloroform, dichloromethane, and 2,2-dichloropropane have proven unreactive.

Other zinc couples of somewhat less reactivity have been formed by variations in solvents as well as metal salts. Thus, a moderately reactive zinc–copper couple can be prepared by treating zinc with a hot solution of anhydrous cupric chloride in tetrahydrofuran. Couples derived from zinc and other metals are easily prepared by treating zinc with an appropriate metal salt in acetic acid. In this way zinc–silver, zinc–platinum, and zinc–palladium couples were obtained from acetic acid solutions of silver acetate, chloroplatinic acid, and hydrated palladium chloride. Although these four couples spontaneously reacted with diiodomethane, they were relatively sluggish compared to the cupric acetate derived couple. Thus, their use in the preparation of cyclopropanes was not investigated. All of these couples will no doubt prove useful in other dehalogenation reactions.

Experimental

Materials.—The granular zinc was Baker's 30-mesh reagent grade, while Fisher's zinc dust, both the 97% reagent grade and the technical grade, was used. The cupric acetate monohydrate was Fisher's reagent grade. The organic compounds were the best grade obtainable, usually Eastman's White Label grade. The cyclooctene was part of a generous sample supplied by Cities Service Research and Development Co.

Preparation of Granular Zinc–Copper Couple.—To a hot (nearly refluxing) solution of 0.5 g. of cupric acetate monohydrate in 50 ml. of glacial acetic acid was added 30–35 g. (*ca.* 0.5 mole) of granular zinc (30 mesh). The mixture was shaken for 1 to 3 min., keeping it hot during this period to prevent precipitation of zinc acetate. The acetic acid was decanted and the zinc–copper couple was washed with a 50-ml. portion of glacial acetic acid, then with three 50-ml. portions of ether.[6] The couple was shaken with each washing for 0.5–1 min. At this point the ether-moistened couple is ready for use as is or it can be freed of ether by passing a stream of nitrogen through it.

Preparation of Zinc–Copper Dust.—To a hot, rapidly stirred solution of 2.0 g. of cupric acetate monohydrate in 50 ml. of glacial acetic acid was added 35 g. of zinc dust. After about 0.5 min. all of the copper had deposited on the zinc. The couple was allowed to settle for 0.5–1 min., then as much of the acetic acid as possible was decanted taking care not to lose the silt-like couple. The dark reddish gray couple was then washed with one 50-ml. portion of acetic acid followed by three 100-ml. portions of ether.[6] The moist couple was ready for use.

Synthesis of Cyclopropanes.—The general procedure used for the synthesis of norcarane and bicyclo[6.1.0]nonane (Table I) was as follows. The erlenmeyer flask used for the preparation of the zinc–copper couple and containing *ca.* 0.5 mole of the couple was fitted with a condenser, dropping funnel, and magnetic stirrer. The solvent, 100 ml. of ether, was added followed by a few milliliters of the dihalomethane.[7] If the reaction does not start immediately (as indicated by bubbles rising from the couple) brief warming will initiate it. While the stirred suspension was kept at gentle reflux (either by the heat of reaction in the case of diiodo-

(4) In early preparations a few absolute ethanol washings were made before the ether washings. These ethanol washings were found to be unnecessary. They also decreased the reactivity of the couple.

(5) Caution should be exercised in handling the zinc dust couple. The unchanged zinc residue from one preparation charred some paper which was in contact with it. Careful addition of cold water to the used couple seems to deactivate it.

(6) To prevent violent boiling of the ether it may be necessary to cool the couple in ice–water.

(7) Adding all of the dihalomethane to the couple as is usually done[1,2] may cause the reaction mixture to erupt violently from the flask. This is especially true when zinc–copper dust and diiodomethane are used.

methane or by slight warming in the case of dibromomethane), a mixture of *ca.* 0.25 mole of olefin and the remainder of the dihalomethane (0.35 mole total) was added dropwise over a period ranging from 0.5 to 2 hr. The reaction mixture was stirred at reflux for 20–30 hr. At the end of this time the reactions involving CH_2I_2 were a dark brown-purple while those run with CH_2Br_2 were a milky purple. The ether solution was then slowly decanted from the unchanged couple into a separatory funnel containing a mixture of ice and 1 *N* hydrochloric acid. (In the case of CH_2Br_2 reactions a moderate amount of gas evolution takes place upon hydrolysis.) The ethereal solution was separated, washed with a second portion of ice–hydrochloric acid, washed three times with water, and finally dried over potassium carbonate. The product was separated by the usual techniques.

Hydroboration of 1,4-Dihalo-2-alkenes

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Hawthorne[2] observed that diborane added electrophilically to vinyl chloride in ethereal solvents at −80° to form β-chloroethylboranes that were thermally unstable and decomposed at room temperature to form ethylene. With vacuum line technique and in

$$B_2H_6 + H_2C{=}CHCl \xrightarrow[-80°]{\text{ether}} B{-}CH_2CH_2{-}Cl \xrightarrow[\text{temp.}]{\text{room}} B{-}Cl + CH_2{=}CH_2$$

dimethyl ether as solvent, a low yield of crystalline β-chloroethylboron dichloride dimethyl etherate was isolated and found to hydrolyze and produce ethylene quantitatively.

$$Cl_2B{-}CH_2CH_2{-}Cl + 3H_2O \longrightarrow B(OH)_3 + 3HCl + CH_2{=}CH_2$$

In contrast, the reaction of allyl chloride with diborane in ethyl ether was not hazardous and went smoothly at room temperature to give moderate yields of thermally stable γ-chloropropylboranes which were hydrolyzed to cyclopropanes by excess sodium hydroxide. The almost quantitative cleavage to cyclopropane differed markedly from the rapid attack of water on β-chloroethyl derivatives and attempts to dehydrohalogenate with pyridine were unsuccessful. The reaction was also applied by Hawthorne[3] to β-alkylallyl and β-arylallyl chlorides to produce the corresponding substituted cyclopropanes. It was presumed that the base coordinated with boron to increase the carbanionic character of the boron–carbon bond and this novel basic hydrolysis was related to

$$C_2H_6 + CH_2{=}CH{-}CH_2Cl \xrightarrow{\text{ether}} B{-}CH_2CH_2CH_2Cl \xrightarrow{NaOH} B{-}OH + Cl^- + \underset{\displaystyle CH_2}{\overset{\displaystyle CH_2}{\diagup\!\diagdown}}$$

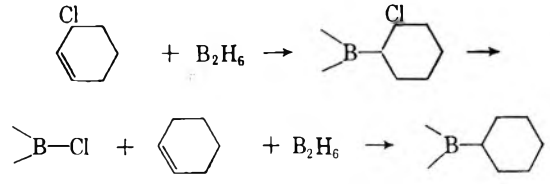
the similar cleavage of γ-chloropropyl groups from γ-chloropropyltrichlorosilane observed by Sommer.[4] The

$$HO^- + B{-}CH_2CH_2CH_2Cl \rightleftharpoons \underset{\displaystyle CH_2CH_2}{\overset{\displaystyle OH}{B}}{-}CH_2Cl \longrightarrow HO{-}B + \underset{\displaystyle CH_2{-}CH_2}{\overset{\displaystyle CH_2}{\diagup\!\diagdown}} + Cl^-$$

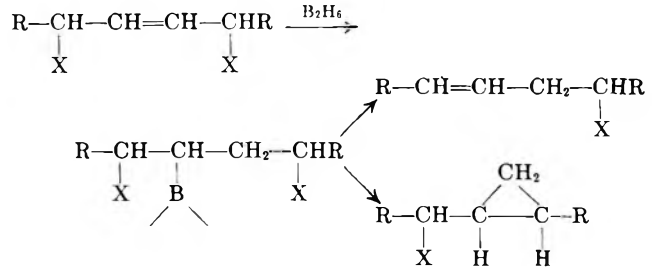
less than quantitative yields of cyclopropanes were attributed to side reactions such as hydroboration at the secondary carbon which was more important with β-alkyl and β-aryl substituents and may have led to β-elimination and olefin formation. Binger and

$$H_2C{=}\underset{\displaystyle R}{C}{-}CH_2Cl + B_2H_6 \longrightarrow B{-}CH_2{-}\underset{\displaystyle H}{\overset{\displaystyle R}{C}}{-}CH_2Cl + CH_3{-}\underset{\displaystyle B}{\overset{\displaystyle R}{C}}{-}CH_2Cl \xrightarrow{HCl} \underset{\displaystyle CH_2{-}CH_2}{\overset{\displaystyle CHR}{\diagup\!\diagdown}} + CH_3{-}\underset{\displaystyle CH_2}{\overset{\displaystyle R}{C}}{=}CH_2$$

Köster[5] similarly observed that 3-chlorocyclohexene underwent elimination to form cyclohexene which reacted with diborane to form cyclohexylborane.



In this study, olefin and cyclopropane formation were compared by hydroboration of 1,4-dihalo-2-alkenes which could then undergo β- or γ-elimination to form a 4-halo-2-alkene or α-halocyclopropane, respectively.



Olefin formation by elimination is both kinetically and stereochemically favored and occurs spontaneously on warming to room temperature with water whereas cyclopropane formation requires treatment with aqueous sodium hydroxide.

The three 1,4-dihalo-2-alkenes studied underwent the expected β-elimination to form 4-halo-1-alkenes. Hydroboration of 1,4-dichloro-2-butene at room temperature produced a mixture of products which were

(1) From a thesis submitted by S. H. Pohl in partial fulfillment of the requirements for the M.A. degree, Sept., 1963; Cities Service University Fellow, 1961–1962.

(2) M. F. Hawthorne and J. A. Dupont, *J. Am. Chem. Soc.*, **80**, 5830 (1958).

(3) M. F. Hawthorne, *ibid.*, **82**, 1886 (1960).

(4) L. H. Sommer, R. E. von Strien, and F. C. Whitmore, *ibid.*, **71**, 3056 (1949).

(5) P. Binger and R. Köster, *Tetrahedron Letters*, **No. 4**, 156 (1961).

presumed to be formed from further hydroboration of 4-chloro-1-butene. This was prevented by hydroborating at −25 to −30° over 12 hr. and hydrolysis of the reaction mixture before warming to room temperature. Under identical conditions, 2,5-dichloro-2,5-dimethyl-3-hexene gave 5-chloro-2,5-dimethyl-2-hexene while 3,6-dibromocyclohexene was transformed to 4-bromocyclohexene. The relatively lower yield (12%) of the latter olefin may be attributed to the fact that bromine is a better leaving group than chlorine and may undergo more elimination during hydroboration.

Experimental

4-Chloro-1-butene.—Diborane was generated by adding over 5 hr. 3.1 g. (0.076 mole) of sodium borohydride (Callery Chemical) in 50 ml. of diglyme (purified by distillation over sodium) to 27.0 g. (0.20 mole) of redistilled Eastman boron trifluoride in 25 ml. of diglyme. It was fed through a delivery tube to a reaction flask, previously flushed with nitrogen, which was kept at −30° and contained 18.6 g (0.15 mole) of the 55–55° (20 mm.) fraction of Eastman 1,4-dichloro-2-butene dissolved in 50 ml. of diglyme. After borohydride addition was complete, the generator was warmed for 10 min. at 70° and the reaction mixture kept at −25 to −30° for 7 hr. and then hydrolyzed with 25 ml. of water followed by 25 ml. of 1.0 *M* aqueous sodium bicarbonate. After the mixture had come to room temperature, the upper layer was separated, dried over anhydrous sodium sulfate, and distilled at 74–75° (761 mm.) through a Vigreux column to give 4.5 g. of a liquid that was identified by its b.p. of 74–75°, d^{20}_4 0.918, $n^{20}D$ 1.4192° (lit.[6] b.p. 75°, d^{20}_4 0.9211, $n^{20}D$ 1.4205°), mol. wt. by Dumas 93.0 (calcd. 90.5), and infrared spectrum with peaks at 6.1 (C=C stretching), 7.1 (terminal C=C), and 15.5 μ (C—Cl stretching). Hydroboration followed by oxidation gave 4-chloro-1-butanol which formed a phenylurethane, m.p. 56°, lit.[7] 54°.

5-Chloro-2,5-dimethyl-2-hexene—2,5-Dimethyl-2,4-hexadiene (Tennessee Eastman) was purified by distillation and then treated with an equimolar amount of chlorine by the method of Skvarchenko[8] to form 2,5-dichloro-2,5-dimethyl-3-hexene. An 18.5-g. (0.10 mole) sample of the latter was hydroborated by the procedure described above and the product distilled to give 4.1 g. of a liquid, b.p. 67–68° (25 mm.) which was identified as 5-chloro-2,5-dimethyl-2-hexene by the 0.5 min. required for reaction with alcoholic silver nitrate as compared with immediate precipitation with 2,5-dichloro-2,5-dimethyl-2-hexene, infrared peaks at 6.1 (C=C stretching) and medium intensity at 14 μ (C—Cl stretching), and its formation of a Grignard reagent which was hydrolyzed to 2,5-dimethyl-2-hexene, b.p. 110–111°, d^{20}_4 0.7244, $n^{20}D$ 1.4133 (lit.[8] b.p. 112.2°, d^{20}_4 0.720, $n^{20}D$ 1.4140).

Anal. Calcd. for $C_8H_{15}Cl$: C, 65.6; H, 10.2; Cl, 24.2. Found: C, 65.2; H, 9.93; Cl, 24.4.

4-Bromocyclohexene.—Wohl-Zeigler[9] bromination of cyclohexene gave 3-bromocyclohexene which was dehydrohalogenated with quinoline to 1,3-cyclohexadiene. Addition of an equimolar amount of bromine to this diolefin by the method of Crossley and Haas[10] gave 3,6-dibromocyclohexene; 25.0 g. (0.10 mole) of this product was hydroborated by the procedure above. Hydrolysis and separation of the reaction product gave 1.9 g. of 4-bromocyclohexene, b.p. 53–55° (15 mm.), d^{20}_4 1.3772, $n^{21}D$ 1.5188 (lit.[11] b.p. 48° (12 mm.), d^{20}_4 1.3779, $n^{20}D$ 1.5168).

Anal. Calcd. for C_6H_9Br: Br, 49.5. Found: Br, 49.9.

Acknowledgment.—The authors wish to express their thanks to the Cities Service Research and Development Corporation for their support of this work with a University Fellowship Grant to S. H. P.

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An Improved Laboratory Method for the Preparation of Diacetylene

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Diacetylene is a highly reactive bifunctional building block for the synthesis of a variety of polyacetylenic derivatives.[1,2] However, due to its instability, it has never been deliberately prepared on a commercial scale, and is consequently not readily available as a synthesis intermediate. It polymerizes rapidly above 0°, and in the presence of air can be readily detonated in vapor concentrations of 20–25% by a suitable ignition source.

The presently accepted method of preparing free diacetylene at the bench-scale level is the dehydrohalogenation of 1,4-dichlorobut-2-yne with either sodium hydroxide[3,4] or with sodamide in liquid ammonia. The latter method utilizes 3 moles of sodamide/mole of dichloride and forms the disodium diacetylide *in situ*, while the former method yields free diacetylene in 60% conversion

Although the base-catalyzed cleavage of 1,4-acetylenic diols[5] to acetylene is well known, the analogous cleavage of 1,3-diyne-1,6-diols to diacetylene and ketone has been studied only by Zalkind and Aizikovich.[6] In their cursory investigation, they employed large amounts of base (alkali metal carbonates and alkaline earth hydroxides) and obtained from 2,7-dimethylocta-3,5-diyne-2,7-diol low conversions to diacetylene, besides the semicleavage product, 2-methylhexa-3,5-diyn-2-ol.

$$(CH_3)_2\text{—}\underset{\displaystyle OH}{\overset{\displaystyle |}{C}}\text{—}C\equiv C\text{—}C\equiv CH$$

During the course of work at this laboratory it was necessary conveniently to prepare free diacetylene as a starting material. Consequently, the above diynediol (B), readily available from acetone and acetylene *via* the following catalytic reactions,[1,2,7] was considered an excellent starting material for diacetylene preparation. Under optimum conditions the conversions to A and B, respectively, average 95–100%.

$$(CH_3)_2C{=}O + CH{\equiv}CH \xrightarrow[\text{liq. } NH_3]{KOH} (CH_3)_2\text{—}\underset{\displaystyle OH}{\overset{\displaystyle |}{C}}\text{—}C\equiv CH \quad (1)$$

A

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(2) R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Academic Press, Inc., New York, N. Y., 1955, pp. 38, 83, 127, 129, 205, and references cited therein.
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(7) R. J. Tedeschi, *et al.*, *J. Org. Chem.*, **28**, 1740 (1963); U. S. Patent 3,082,260 (March 19, 1963).

$$A \xrightarrow[O_2]{CuCl-NH_4Cl} (CH_3)_2-\underset{OH}{C}-C\equiv C-C\equiv C-\underset{OH}{C}-(CH_3)_2 \quad (2)$$

B

$$B \xrightarrow[xylene]{KOH \text{ or } NaOH} HC\equiv C-C\equiv CH + (CH_3)_2C=O + KOH \quad (3)$$

We have found that the successful base-catalyzed cleavage of B is highly dependent upon the concentration of sodium or potassium hydroxide used as catalyst as shown in Table I.

TABLE I

DIACETYLENE FROM DIMETHYLOCTADIYNEDIOL[a]

Base, g.	% conversion to Diacetylene	% conversion to Acetone
KOH, 0.02	0	0
KOH, 0.07	74	88
KOH, 0.10	71	80
NaOH, 0.13	80	83
KOH, 0.23	61	83

[a] 0.10 mole of diynediol in 100 ml. of xylene.

Amounts of potassium hydroxide larger than 0.23 g. result in increased amounts of dark, polymeric residues and lower diacetylene conversions. Sodium hydroxide, however, yields less polymer and higher diacetylene conversions at equivalent concentrations. The above diacetylene conversions are minimum values since a presently undetermined amount of diacetylene complexes with or dissolves in the acetone as it is condensed. Similar complex formation of diacetylene with N-methylpyrrolidone has been reported by Shachat.[8] Diacetylene, however, can be separated from acetone solutions by water scrubbing,[9] if higher conversions are required.

Other solvents such as mineral oil, pyridine, dioxane, or water gave inferior results due to either foaming, sublimation, polymerization, or difficulty of separation. Xylene functioned efficiently, since it was a good solvent for the diynediol at 80–100°, and while refluxing on the sides of the flask minimized its sublimation. It also does not complex strongly with diacetylene, thereby allowing the latter to have a short residence time in the cleavage medium which in turn minimizes polymerization. Alkali metal carbonates and alkaline earth hydroxides were found to be inferior cleavage catalysts, yielding negligible amounts of diacetylene at the above catalyst concentrations.

When the above cleavage is carried out in an atmosphere of nitrogen and the diacetylene rapidly is condensed and stored below −30°, no danger of detonation or exothermic polymerization is incurred. An advantage of the present method is that small amounts of diacetylene can be generated and used as needed, using the stable dimethyloctadiynediol as starting material. In this way the hazardous storage of diacetylene for prolonged periods of time can be avoided. In fact, it is preferable to lead the evolved gas directly into the desired reaction medium.

The cleavage is always performed under nitrogen, and the diacetylene is used within several hours after preparation. Overnight storage at Dry Ice temperature under a nitrogen atmosphere can be employed but is not recommended as common practice. The operator should at all times be protected with a face shield and the apparatus used in an efficient hood equipped with a Plexiglas (or similar type) shield or window.

If diacetylene, either as the pure liquid (b.p. 10.3°) or in organic solutions, is allowed to stand at 0° or above for more than 1 hr., pronounced darkening followed by the rapid precipitation of polymer is observed. At 10° the discoloration is rapid and solutions containing 10% diacetylene in acetone or xylene will set to a porous gel on standing overnight. However, no discoloration or polymer formation was noted for diacetylene stored at −20 to −35° under nitrogen during 4 hr. Polymer derived from diacetylene has been found to be stable to impact, friction, and slow heating, and when thrown on a hot plate at 200° disappears quietly in a puff of smoke. Attempts to stabilize solutions of diacetylene with pyridine, hydroquinone, phenyl-β-naphthylamine, or diphenylpicrylhydrazyl were ineffective. The best inhibitor system was refrigeration below −30° and the careful exclusion of air. A sample of diacetylene which had been stored, in one instance, over the weekend at Dry Ice temperature in the absence of a nitrogen blanket on redistillation decomposed in the distillation vessel with a mild explosion and the formation of much finely divided carbon. It is believed that unstable peroxides were the cause.

Using the conditions described for this cleavage, no significant amounts of the partial cleavage product 2-methylhexa-3,5-diyn-2-ol are obtained. However, this diynol derivative can be obtained in an impure condition in 52–56% conversions, together with 30–38% diacetylene, by cleavage in the presence of sodium or potassium carbonates (0.20 g. of carbonate/0.10 mole of diynediol) using mineral oil (Nujol) as solvent. This high boiling product (137° at 70 mm.) is relatively unstable and polymerizes both during and after distillation. It was noted that a sample in a vial expanded on polymerizing to a hard dark red-brown glossy mass and cracked the vial. The instability of this compound agrees with earlier observations.[6,10]

Experimental

3-Methyl-1-butyn-3-ol.—This material (b.p. 104°) is available commercially[11] or it can be prepared catalytically in liquid ammonia[7] or stoichiometrically at atmospheric pressure using powdered potassium hydroxide in ether or acetal solvents.[5]

2,7-Dimethylocta-3,5-diyne-2,7-diol.—This product is conveniently prepared[1,2] by the oxidative coupling of 3-methyl-1-butyn-3-ol in aqueous solution using a catalytic amount of cuprous chloride solubilized by excess ammonium chloride. Oxygen is considerably more effective than air as oxidant, although the latter can be employed. The resulting diynediol is sparingly soluble in water, and is readily freed of cuprous chloride by washing with concentrated ammonium chloride solution, then water, followed by recrystallization from xylene, and air drying the product (m.p. 132–133°).

Base-Catalyzed Cleavage of 2,7-Dimethylocta-3,5-diyne-2,7-diol to Diacetylene.—The diynediol, if not recrystallized, should be clarified (Nu-char) and filtered in hot xylene solution (commercial *ortho–para* mixture) from residual copper salts to avoid the later possibility of forming copper diacetylene complexes or acetylides which may initiate the exothermic decomposition or polymerization of diacetylene.

(8) N. Shachat, *J. Org. Chem.*, **27**, 2928 (1962).

(9) British Patent 800,206 (Aug. 20, 1958); U. S. Patent 2,941,020 (June 14, 1960).

(10) W. Chodkiewicz, *et al.*, *Compt. rend.*, **239**, 885 (1954); *Chem. Abstr.*, **49**, 6081 (1954).

(11) Air Reduction Chemical and Carbide Co., 150 East 42nd St., New York 17, N. Y.

The apparatus for base-cleavage and separation of diacetylene from xylene and acetone consists principally of a decomposition flask (A), an acetone–xylene condensation receiver (B), a graduated diacetylene trap (C), and a reactor flask (D).

Flask A is a 500-ml., 29/42 standard taper, three-necked flask equipped with a thermometer well or joint. One neck is equipped with a gas inlet tube for introduction of nitrogen while the furthest neck is equipped with a 10-in. Vigreux column (29/42 joints, 1-in. o.d.). The middle neck is equipped with a Tru-bore stirrer and mineral oil seal to minimize possible loss of diacetylene. The top of the Vigreux column is equipped with a standard distillation head, which condenses acetone (water cooling below 25°) yet allows the major part of the evolved diacetylene to be swept (nitrogen) into C or D. The condensed acetone can be allowed to reflux or led directly to B.

Collection flask B is a 250-ml., three-necked flask equipped with a 0.5-in. (o.d.) delivery tube leading from the distillation head of A into receiver B. A stopcock (0.25-in. bore) located 2 in. above the neck of B serves to isolate B from A and collect acetone. The furthest neck of B is fitted with a 10-in. packed (stainless steel 0.25-in. Podbielniak) column, the top of which is equipped with a total return condenser for acetone, but allows diacetylene gas to be collected in C or D. The receiver is kept at a temperature 55–60° to minimize diacetylene solubility in acetone.

Diacetylene–nitrogen sweep gas lines (0.25-in. i.d., Pyrex) leading from distillation head (A) and total return condenser (B) meet at a T-connection prior to leading into the diacetylene trap (C). Trap C (1-in. i.d.) is graduated to 0.20-ml. accuracy and has a capacity of about 50 ml. It is equipped with an entrance tube ending approximately at the 20-ml. mark, and an exit tube used to vaporize the diacetylene slowly under a slow nitrogen current into the cooled reactor (D) containing an appropriate solvent. Trap C is cooled to approximately −50 to −70° by the use of Dry Ice and alcohol, and by immersing the trap up to the 20-ml. mark. However, care must be exercised to avoid freezing (−36°) the diacetylene in the entrance line and causing a plug. The bath is lowered somewhat if crystallization is noted, otherwise a bath temperature of −30 to −35° can be used safely for several hours if the diacetylene is to be used in a reaction.

The generation of diacetylene is started by first adding to flask A, 100 ml. of xylene, 0.10 mole (16.6 g.) of 2,7-dimethylocta-3,5-diyne-2,7-diol, and 0.10 g. of powdered 90–98% potassium or sodium hydroxide (latter preferred). The reaction system previously well purged with nitrogen is now purged again with nitrogen for 10 min. using a moderate flow through a mineral oil bubble counter. The reaction slurry is stirred at a speed sufficient to maintain good mixing, but to prevent splashing, as the reaction slurry is heated.

As the reaction temperature approaches 90° some gradual volatilization of possibly acetone and diacetylene is noted. With the use of constant heat input, the reaction temperature rises to 92–94° and then falls to 87–88° whereupon active distillation of both acetone and diacetylene is observed. When approximately 50% (by volume) of the expected amounts of products have been collected in B and C, the rate of distillation decreases as the reaction temperature increases. By the time the boiling point of xylene (139°) is reached, distillation of acetone and condensation of diacetylene have essentially ceased. Slowing the rate of heating after distillation starts has been observed to be detrimental to the conversion to diacetylene. The acetone collection chamber is kept at 60° to minimize solubility of diacetylene in acetone. Both flasks A and B are swept with slow currents of nitrogen during the cleavage and for 15 min. after heating was halted. The nitrogen sweep for both A and B can be operated independently of each other. The conversion to diacetylene is measured directly by noting the volume of liquefied gas (d^0_4 0.7364) or by weighing the cold tared trap. If stored overnight, it should be cooled to −70 to −80° under a nitrogen atmosphere. Exposure to air and alkali must be avoided at all times, and a safety face shield should be worn when handling this material. A well-ventilated hood with a sliding glass or Plexiglas window should be used. It is preferable to lead the diacetylene directly into reaction vessel (D) or shortly after (within several hours) it is collected in C to vaporize it slowly into D using a current of nitrogen and a water bath at 5–10°. Recommended solvents for dissolving diacetylene and for carrying out the reactions are methylal, dioxane, liquid ammonia, N-methylpyrolidone, and dimethyl sulfoxide. The diacetylene collected on redistillation leaves no residue and boils at 9–10°.

The physical constants are diacetylene,[12] b.p. 10.3° (760 mm.); m.p. −36 to −35°; d^0_4 0.7364; vapor pressure 1.6 mm. (−78°), 93.5 (−35.5°), 519 (0°).

(12) F. Straus and L. Kollek, *Ber.*, **59B**, 1664 (1926).

α-Methyldopa. Resolution and Configuration

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The hypotensive activity of 3-(3,4-dihydroxyphenyl)-2-methylalanine (α-methyldopa) resides in the optical isomer with a negative rotation,[1] $[\alpha]^{25}D$ −4° (*c* 2, 0.1 *N* hydrochloric acid).

The same isomer inhibits the decarboxylation of L-3,4-dihydroxyphenylalanine (L-dopa) by mammalian decarboxylase while the other isomer is totally inactive.[2] This suggests that the biologically active isomer has the L configuration. The rotatory dispersion curve for (−)-α-methyldopa (Fig. 1) supports this sug-

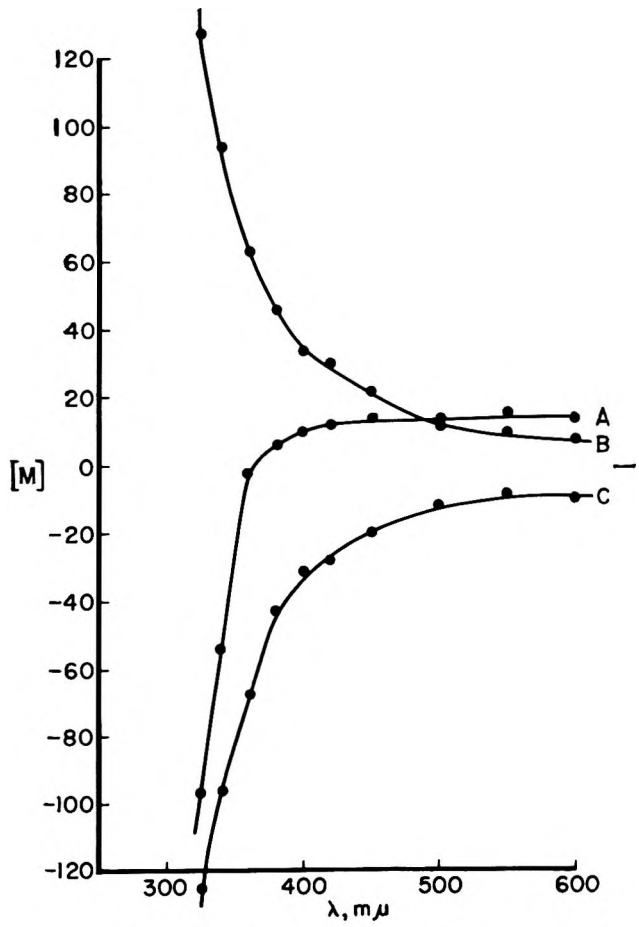


Fig. 1.—Rotatory dispersion curves: A, D-dopa; B, L-α-methyldopa; C, D-α-methyldopa. Measurements were made at 25° on 1% solutions of the amino acids in 6 *N* hydrochloric acid.

(1) A. Sjoerdsma and S. Udenfriend, *Biochem. Pharmacol.*, **8**, 164 (1961).

(2) S. M. Hess, R. H. Connamacher, M. Ozaki, and S. Udenfriend, *J. Pharmacol. Exptl. Therap.*, **134**, 129 (1961); C. C. Porter, J. A. Totaro, and C. M. Leiby, *ibid.*, **134**, 139 (1961).

gestion; the curve is similar to the curves for L-phenylalanine and L-tyrosine reported by Schellman.[3] The rotations for all three amino acids become strongly positive in the 300-mμ region. The dispersion curve of (+)-α-methyldopa is similar to the D-dopa[4] curve.

The assignment of the L-configuration to the active isomer is supported by three other rotational criteria. First, the Lutz–Jirgensons rule,[5] that L-amino acids show a positive shift in rotation upon going from neutral to acidic solution, is obeyed by (−)-α-methyldopa; $[\alpha]^{25}D$ −13.5° (*c* 2, phosphate buffer, pH 6.5), $[\alpha]^{25}D$ +4° (*c* 2, 6 *N* hydrochloric acid). The molecular rotation difference, [M]HCl − [M]pH 6.5, +40.5°, is larger than that of most amino acids but close to that of L-phenylalanine,[6] [M]HCl − [M]H_2O, +49.6°; D-dopa[4] shows a negative shift of the same magnitude [M]6 *N* HCl − [M]pH 6.5, −45°. It is of interest that (−)-α-methyldopa follows the rule at all the wave lengths employed (see Table I).[7] Second, L-

TABLE I

DEPENDENCY OF OPTICAL ROTATION ON ACID CONCENTRATION

Wave length, mμ	$[\alpha]^{25}$ (*c* 2) 6 *N* HCl	1 *N* HCl	0.1 *N* HCl	pH 6.5, phosphate
	A. L-α-Methyldopa			
578	+4	−0.1	−4	−14
546	+5	−0.1	−4.5	−16
436	+11.5	+1	−5.5	−25
405	+15	+3	−5	−29
	B. D-α-Methyldopa			
578	−4	+1.5	+5.5	+13
546	−4	+1.5	+6	+14
436	−10	−0.5	+8	+25
405	−15	−3	+7	+29
	C. D-Dopa[a,b]			
578	+7.5	+9.5	+13	+31.5
546	+8	+10	+14	+35.5
436	+8	+13	+19.5	+61
405	+6	+12.5	+20.5	+72.5

[a] 0.1 *N* hydrochloric acid, *c* 1.0. [b] pH 6.5, phosphate, *c* 0.5.

amino acids give hydantoin derivatives with large negative rotations.[8] The hydantoin of (−)-α-methyldopa was prepared in these laboratories[9] and has a negative rotation, $[\alpha]^{25}D$ −52.1° (*c* 1, water).

Finally, the rotatory dispersion curve for the copper salt of (−)-α-methyldopa (Fig. 2) is similar to that of L-tyrosine copper salt measured under the same conditions. Upon going from 400 mμ to longer wave lengths a positive shift in rotation occurs until, at about 600 mμ, a positive extremum is reached. The copper salt of D-dopa undergoes the opposite shift, becoming more negative as the wave length is increased from 400 mμ. Measurements of copper salt rotations have been used as evidence of configuration.[10,11] In this previous work the isolated copper salts were dissolved in water or

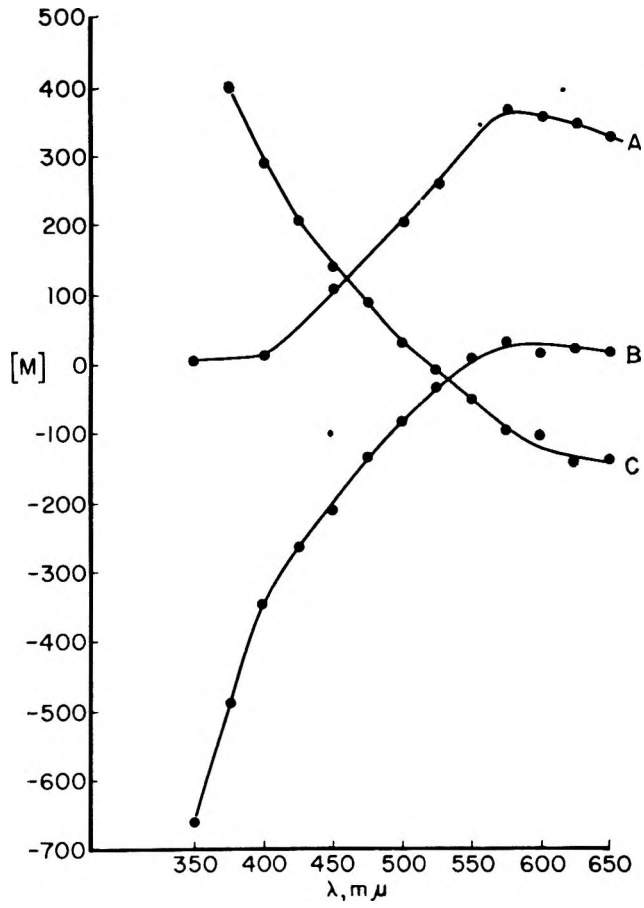


Fig. 2.—Rotatory dispersion curves of copper salts: A, L-α-methyldopa; B, L-tyrosine; C, D-dopa. Measurements were made at 25° on 0.5% solutions of the amino acids in 0.25 *M* cupric sulfate buffered at pH 3.4.

1 equiv. of cupric acetate was added to aqueous solutions of the amino acids. However solutions of the copper salt of α-methyldopa prepared in the same way were too unstable to air oxidation to be useful for rotation studies. A relatively stable solution of the copper salt can be prepared in acidic solution. Rotatory dispersion measurements were made on (−)-α-methyldopa, D-dopa, and L-tyrosine in the presence of excess cupric sulfate buffered at pH 3.4.[12] The high positive rotation of (−)-α-methyldopa at 589 mμ ($[\alpha]^{25}D$ 170–175°, for optically pure isomer) in the buffered cupric sulfate solution provides a useful assay for optical purity.

Inherent in all the rotational evidence is the assumption that the substitution of methyl for the α-hydrogen of an optically active amino acid does not alter greatly the rotatory characteristics. This assumption appears valid for amino acids in which the other alkyl substituent on the α-carbon is large compared with methyl.[13]

(3) J. A. Schellman and C. S. Schellman, *Arch. Biochem. Biophys.*, **65**, 58 (1956).

(4) Purchased from California Corporation for Biochemical Research, Los Angeles, Calif.

(5) O. Lutz and B. Jirgensons, *Ber.*, **63**, 448 (1930).

(6) J. P. Greenstein, L. M. Birnbaum, and M. C. Otey, *J. Biol. Chem.*, **204**, 307 (1953).

(7) The shift of rotation with pH has the effect of giving (−)-α-methyldopa an anomalous dispersion curve in 0.1 *N* hydrochloric acid (negative rotation in the visible region of the spectrum and a positive rotation in the ultraviolet) and a plain positive dispersion curve in 6 *N* hydrochloric acid.

(8) G. W. Clough, *J. Chem. Soc.*, **113**, 526 (1918).

(9) R. A. Vitali and T. Jacob, in press.

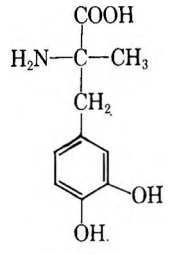
(10) P. Pfeiffer and W. Christeleit, *Z. Physiol. Chem.*, **245**, 197 (1937).

(11) N. Izumiya, M. Winitz, S. M. Birnbaum, and J. P. Greenstein, *J. Am. Chem. Soc.*, **78**, 1602 (1956).

(12) The rotations obtained for L-tyrosine differ considerably from the published values.[10] In the 400–500-mμ range rotations were negative rather than positive and the positive extremum at 525 mμ, observed by Pfeiffer and Christeleit,[10] was shifted to 575 mμ. The differences, attributable to the acidity or the excess cupric sulfate content of our solutions, emphasize the necessity of making configurational comparisons under identical conditions.

(13) M. Winitz, S. M. Birnbaum, and J. P. Greenstein [*J. Am. Chem. Soc.*, **77**, 716 (1955)], after observing the rotational shifts with change of pH for (+)-isovaline, generalized that the Lutz–Jirgensons rule applies only to α-amino acids which contain an α-hydrogen atom. However, in isovaline the two groups on the α-carbon, methyl and ethyl, are comparable in size, while for α-methylphenylalanines, methyl is small compared with benzyl.

Based on the above evidence (−)-α-methyldopa is assigned the L- or S-configuration (I).



I

The resolution of α-methyldopa[14] was achieved using 3-(3,4-dimethoxyphenyl)-2-methylalanine,[15] which was converted to the N-acetyl derivative. Upon treatment with (−)-1-phenylethylamine,[16] $[\alpha]^{25}D$ −36.5° (neat), a diastereoisomeric salt was obtained, $[\alpha]^{25}D$ +69° (*c* 1, methanol). From the salt was isolated (−)-*N*-acetyl-3-(3,4-dimethoxyphenyl)-2-methylalanine, $[\alpha]^{25}D$ −56° (*c* 1, methanol), which upon acid hydrolysis gave (−)-α-methyldopa, $[\alpha]^{25}D$ −4° (*c* 2, 0.1 *N* hydrochloric acid). Exactly the same operations using dextrorotatory 1-phenylethylamine gave (+)-α-methyldopa, $[\alpha]^{25}D$ +4° (*c* 2, 0.1 *N* hydrochloric acid).

In a second resolution, α-methyldopa[15] was the starting material. Acetylation gave N-acetyl-3-(3,4-diacetoxyphenyl)-2-methylalanine which upon treatment with quinine gave a 1:1 salt. The quinine salt of the desired enantiomer was crystalline and insoluble in acetone, $[\alpha]^{25}D$ −72.5° (*c* 1, 96% ethanol), while the undesired enantiomer formed an acetone-soluble glass. The acetylated acid, $[\alpha]^{25}D$ −74.5° (*c* 1, 96% ethanol), was liberated from crystalline quinine salt with hydrochloric acid. Acid hydrolysis of the acetyl groups gave (−)-α-methyldopa, $[\alpha]^{25}D$ −3° (*c* 2, 0.1 *N* hydrochloric acid).

Experimental

Rotatory Measurements.—Two instruments were used to measure the optical rotatory dispersion. Measurements in the range 600 to 325 mμ were made with an instrument constructed in this laboratory on the Keston[17] principle. This instrument contains ultraviolet transmitting polarizing and analyzing prisms and it was calibrated against reagent grade sucrose. The values thereby determined were checked at 405, 436, 546 and 578 mμ with a Zeiss precision photoelectric polarimeter. The pH dependency of the rotations was investigated with the Zeiss instrument.

The optical rotatory dispersions of D-α-methyldopa, L-α-methyldopa and D-dopa are plotted in Fig. 1. The rotations of these compounds at selected acid concentrations and wave lengths are summarized in Table I.

The optical rotatory dispersions of the copper salts of L-α-methyldopa, L-tyrosine, and D-dopa are plotted in Fig. 2. The copper salts were prepared at 0.5% (w./v.) concentration by dissolving the amino acid in an aqueous solution containing per liter 20 g. of anhydrous sodium acetate, 50 ml. of glacial acetic acid, and 62.5 g. of $CuSO_4 \cdot 5H_2O$. The pH of the reagent is 3.4.

DL-N-Acetyl-3-(3,4-dimethoxyphenyl)-2-methylalanine.—A mixture of 69.0 g. (0.288 mole) of DL-3-(3,4-dimethoxyphenyl)-2-methylalanine in 207 ml. (2.56 moles) of pyridine and 276 ml. (2.92 moles) of acetic anhydride was heated at 90° with stirring for 3 hr. The solution was concentrated under vacuum to a thick sirup. The residue was poured into 300 ml. of ice–water and stirred for 10 min. The product crystallized on addition of 250 ml. of 2.5 *N* hydrochloric acid.[18] The mixture was aged at 5° for 1 hr. and filtered. After washing successively with cold water and 100 ml. of ethanol, and drying over phosphorus pentoxide, the N-acetyl derivative weighed 70.0 g. (86.% yield) and melted at 213–215°; λ_{max}^{Nujol} 3.1, 3.8, 5.87, 6.1, 6.16, and 6.6 μ.

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81. Found: C, 60.05; H, 6.60.

L-N-Acetyl-3-(3,4-dimethoxyphenyl)-2-methylalanine (−)-1-Phenylethylamine Salt.—To a slurry of 77 g. (0.274 mole) of DL-N-acetyl-3-(3,4-dimethoxyphenyl-2-methylalanine) in 200 ml. of methanol slowly was added a solution of 33.2 g. (0.274 mole) of (−)-1-phenylethylamine in 50 ml. of methanol. The methanol was distilled under vacuum until copious crystallization occurred. The precipitate was dissolved in 1 l. of water at 90°. The hot solution was filtered, cooled slowly to 25°, and aged at 8° for 40 hr. The collected salt was dried under vacuum at 55°. The yield was 54.5 g. (99%); $[\alpha]^{25}D$ +55° (*c* 1, methanol). Recrystallization from water gave 42.5 g. (77%), m.p. 212–215°, $[\alpha]^{25}D$ +69° (*c* 1, methanol). Titration with base gave an equivalent weight of 396 (theory, 402.5).

Anal. Calcd. for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51. Found: C, 65.55; H, 7.43.

L-N-Acetyl-3-(3,4-dimethoxyphenyl)-2-methylalanine.—The L-N-acetyl-3-(3,4-dimethoxyphenyl)-2-methylalanine (−)-1-phenylethylamine salt (25 g., 0.062 mole) was dissolved in 100 ml. of water and 27.5 ml. of 2.5 *N* sodium hydroxide. The solution was extracted with two 50-ml. and two 25-ml. portions of chloroform. The solution was heated to 70° and 30 ml. of 2.5 *N* hydrochloric acid was added. The N-acetyl acid, which crystallized immediately, was cooled to 10°, filtered, washed with cold water, and dried under vacuum at 60°. The product weighed 16.8 g. (96%); m.p. 192–194°; $[\alpha]^{25}D$ −55° (*c* 1, methanol); $\lambda_{max}^{CH_3OH}$ 230 mμ (ε 8950), 279 (2950).

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81. Found: C, 59.74: H, 6.77.

L-(−)-3-(3,4-Dihydroxyphenyl)-2-methylalanine.—A solution of L-N-acetyl-3-(3,4-dimethoxyphenyl)-2-methylalanine (10.0 g., 0.0356 mole) in 100 ml. of 48% hydrobromic acid was heated at reflux under a nitrogen atmosphere for 12 hr. The solution was concentrated to dryness and flushed successively with 50-ml. portions of water, *t*-butyl alcohol, and water. The partly crystalline residue was dissolved in 80 ml. of water by warming. The pH was adjusted to 6.4 with 6 *N* ammonium hydroxide under a nitrogen atmosphere. The hot solution was treated with 1.2 g. of decolorizing carbon and filtered. The amber-colored filtrate was concentrated under vacuum to a volume of 30 ml. The mixture was aged in an ice bath for 1 hr., filtered, and washed with a minimum amount of cold water. After drying under vacuum at 100°, the product weighed 5.38 g. (72%); m.p. 306–308°; $[\alpha]^{25}D$ −4° (*c* 2, 0.1 *N* hydrochloric acid); λ_{max}^{Nujol} 2.79, 3.08, 4.2, 5.3, 6.17, 6.33, and 6.58 μ.

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20. Found: C, 57.06; H, 6.37.

DL-N-Acetyl-3-(3,4-diacetoxyphenyl)-2-methylalanine.—A slurry of 50 g. (0.237 mole) of α-methyldopa in 50 ml. (0.62 mole) of pyridine and 125 ml. (1.32 moles) of acetic anhydride was heated on the steam bath with stirring. The solid dissolved and the temperature rose to 118°. After 3 hr. on the steam bath (96°), the reddish solution was concentrated under vacuum. The residual oil was dissolved in 50 ml. of acetone and was diluted with 200 ml. of water and 50 ml. of 2.5 *N* hydrochloric acid.[18] After holding at 0–5° for 2 hr., the precipitated product was filtered, washed with water, and dried under vacuum at 50°. The product weighed 74 g. (92.6% yield); m.p. 197–199°; λ_{max}^{Nujol} 3.1, 3.8, 5.68, 5.86, 6.08, 6.4, and 6.61 μ; $\lambda_{max}^{CH_3OH}$ 265 mμ (ε 540), 271 (506).

Anal. Calcd. for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68. Found: C, 56.93; H, 6.00.

L-(−)-N-Acetyl-3-(3,4-diacetoxyphenyl)-2-methylalanine Quinine Salt.—Quinine (96.4 g., 0.297 mole) and 100 g. (0.297 mole) of D,L-N-acetyl-3-(3,4-diacetoxyphenyl)-2-methylalanine were placed in a 2-l. flask and 960 ml. of acetone was added. The solids dissolved upon stirring and product started to precipitate within 15 min. After stirring at 0–5° for 4 hr., the product was filtered, washed with acetone, and dried under vacuum at

(14) Merck & Co., Inc., South African Patent 61/950 (1962).

(15) G. A. Stein, H. A. Bronner, and K. Pfister, III, *J. Am. Chem. Soc.*, **77**, 700 (1955).

(16) A. W. Ingersol, "Organic Syntheses," Coll. Vol II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 506.

(17) *Cf.* Carl Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 32.

(18) The acid is added to speed hydrolysis of the azlactone.

40°. The yield was 91 g. (93%); m.p. 164–166°; $[\alpha]^{25}D$ −72.7° (*c* 1, 96% ethanol). The quinine salt titrated with base gave an equivalent weight of 665 (theory, 661.8).

L-(−)-N-Acetyl-3-(3,4-diacetoxyphenyl)-2-methylalanine.—The quinine salt of L-(−)-N-acetyl-3-(3,4-diacetoxyphenyl)-2-methylalanine (17.7 g., 0.0268 mole) was dissolved at 0–5° in 11.0 ml. of 2.5 *N* hydrochloric acid and 60 ml. of water. To the clear solution was added 10.6 ml. of 2.5 *N* hydrochloric acid which caused product to precipitate. After holding overnight at 0–5°, the product was filtered, washed with cold water, and dried under vacuum at 40°. The yield was 7.49 g. (83%); m.p. 181–183°; $[\alpha]^{25}D$ −74.5° (*c* 1, 96% ethanol). Base titration showed an equivalent weight of 336 (theory, 337.3).

L-(−)-3-(3,4-Dihydroxyphenyl)-2-methylalanine.—A solution of L-(−)-N-acetyl-3-(3,4-diacetoxyphenyl)-2-methylalanine (25.0 g., 0.074 mole) in 200 ml. of 6 *N* hydrochloric acid was refluxed for 2 hr. The solution was concentrated to dryness under vacuum and the residual yellow oil was concentrated to dryness three times with 50-ml. portions of *t*-butyl alcohol to remove hydrochloric acid. The gummy residue was dissolved in 45 ml. of water and the solution was filtered to remove a trace amount of insoluble material. The filtrate was adjusted to pH 7.0 with concentrated ammonia. After adding 1.0 g. of sulfur dioxide, the mixture was held at 0–5° overnight. The crystals were filtered, washed with cold water, and dried under vacuum at 50°. The product weighed 14.9 g., but contained 11.3% water by Karl Fischer titration (84.5% yield calculated for $C_{10}H_{13}NO_4 \cdot 1.5\ H_2O$).[19]

The L-(−)-α-methyldopa, m.p. 295° dec., $[\alpha]^{25}D$ −3° (*c* 2, 0.1 *N* hydrochloric acid) had an equivalent weight by base titration of 239 (theory, 238) and had an absorption maximum at 281 mμ (ε 2780). The dried product gave an infrared spectrum identical with material resolved through the 1-phenylethylamine salt.

(19) X-Ray analysis reveals that L-(−)-α-methyldopa exists in three crystalline forms. Normally, when isolated from aqueous solutions, a sesquihydrate is obtained. Vigorous drying of the sesquihydrate (100°, under vacuum) gives an anhydrous form which, when exposed to air, absorbs water and is transformed back to the hydrate. A second, nonhygroscopic, anhydrous form has been isolated from isopropyl alcohol solutions.

Condensation of Catechol with Phenylphosphonous Dichloride. A Novel Ring-Cleavage Reaction[1]

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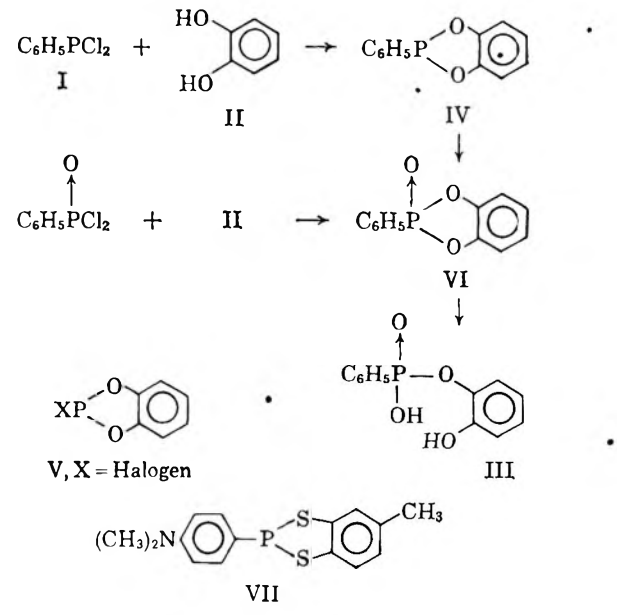
Received November 1, 1963

The chemistry of cyclic compounds derived from trivalent and pentavalent phosphorus has been investigated in some detail and an excellent review[3] has appeared recently which included data on the reaction of phosphorus trichloride with catechol (II). No detailed investigation on the synthesis of 2-aryl-substituted 1,3,2-benzodioxaphospholes has been described.

The reaction between catechol (II) and phenylphosphonous dichloride (I) is more complicated than might be anticipated. When the condensation was performed with equimolar quantities of I and II in the presence of pyridine or triethylamine in various solvents, the only isolable product was 2-phenyl-1,3,2-benzodioxaphosphole 2-oxide (VI) (Scheme I). In addition the phosphonate VI is exceedingly unstable since,

SCHEME I



upon standing for a short time (even in desiccator), it is converted quantitatively to a strong acid, *o*-hydroxyphenylhydrogen phenylphosphonate (III).[4] Reaction of I and II in bromobenzene at reflux led to the cyclic derivative IV.[5] From the cool solution, relatively pure 2-phenyl-1,3,2-benzodioxaphosphole (IV) was obtained in excellent yield. The structure of the product was tentatively established by the infrared spectral data. However, the spectrum changed rapidly when the impure ester IV was subjected to purification by recrystallization or upon storage in a desiccator. Structural confirmation of III was provided *via* hydrolysis with hydrochloric acid to yield phenylphosphonic acid and catechol. The P–O bond in III is readily cleaved by treatment with mineral acid as well as alkali. Thus, it appears that 2-phenyl-1,3,2-benzodioxaphosphole (IV) is formed initially but undergoes rapid oxidation followed by hydrolysis to III. The extreme sensitivity to oxidation of the heterocyclic ring in IV is somewhat surprising in view of the isolation of corresponding 2-halogen analogs (V),[3] although they are reported to be inherently sensitive to cleavage because of ring strain.[6] Although a related, stable sulfur compound (VII) was recorded recently, attempts to prepare other members in the series failed.[7]

Phenylphosphonic dichloride reacted with II in bromobenzene to give VI[8] (infrared analysis confirmed

(1) We gratefully acknowledge support of the National Institutes of Health, GM-10367-01. Partial support by the Research Foundation of the Oklahoma State University is also acknowledged.

(2) Postdoctorate Fellow, 1963–1964.

(3) R. S. Edmundson, *Chem. Ind.* (London), 1770 (1962).

(4) This compound may have been obtained (no analytical data) from the reaction of phenylphosphonic dichloride and II, but it now seems the previous material (m.p. 115–118°) may not have been sufficiently pure [W. W. Coover, Jr., R. L. McConnell, and M. A. McCall, *Ind. Eng. Chem.*, **52**, 409 (1960)].

(5) The procedure is similar to that used for the preparation of dihydro-1,3,2-benzodiazaphosphole 2-oxides: see R. L. Dannley and D. Zazaris, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962, p. 62-Q.

(6) The corresponding 2-alkoxy derivatives of this system were reported to be extremely sensitive at low temperature: see W. S. Reich, *Nature*, **157**, 133 (1946).

(7) I. G. M. Campbell and J. K. Way, *J. Chem. Soc.*, 5034 (1960).

(8) Actually, VI was claimed to have been prepared from phenylphosphonic dichloride and II, but the melting point was 124–125°, identical with the melting point found for III in our work [L. Anschutz and H. Walbrecht, *J. prakt. Chem.*, **133**, 65 (1932)].

its identity) which upon standing in air was converted to III quantitatively. In view of this facile cleavage of the heterocyclic ring, further work is being carried out with other aromatic dihydroxy compounds and will be reported later.

Experimental[9]

Reaction of Phenylphosphonous Dichloride with II.—A solution of phenylphosphonous dichloride (17.9 g., 0.10 mole) in 50 ml. of bromobenzene was added dropwise with vigorous stirring at room temperature under nitrogen to a solution of catechol (11.0 g., 0.10 mole) in 350 ml. of bromobenzene. The resultant clear solution was then heated to reflux at which temperature hydrogen chloride was evolved quantitatively (0.20 mole). The mixture was refluxed for 6 hr. and the evolved hydrogen chloride was passed into water and titrated with 1.0 *N* sodium hydroxide. The clear yellow solution was distilled until nearly 300 ml. of bromobenzene was removed. The solution when cooled to 0° (nitrogen atmosphere) yielded 16.1 g. of 2-phenyl-1,3,2-benzodioxaphosphole (IV), m.p. 140–145°. It was collected by suction filtration and washed with bromobenzene. The filtrate which was concentrated to 80 ml. gave 4.0 g. of IV (total 20.1 g., 93%) which was stored in vacuum desiccator; λ_{max}^{KBr} 6.23 and 6.7 (aromatic C=C), 6.92 μ (C_6H_5–P), besides other bands for substituted benzene rings.

In order to prepare the analytical sample, 2.09 g. of IV was subjected to repeated recrystallization from methylene chloride–petroleum ether (b.p. 40–60°). In spite of efforts to preserve anhydrous conditions (although nitrogen was used it was not rigorously deoxygenated and thus could cause oxidation of IV to VI) during this process, the ester IV was converted into *o*-hydroxyphenylhydrogen phenylphosphonate (III), m.p. 123.5–124.5°; λ_{max}^{KBr} 2.95 (OH), 6.92 (C_6H_5–P), 7.8 μ (P→O); pK_a 1.90 (methanol); neut. equiv. 253.2.

Anal. Calcd. for $C_{12}H_{11}O_4P$: C, 57.3; H, 4.4; P, 12.4. Found: C, 56.8; H, 4.43; P, 12.36.

In other experiments, dropwise addition of phenylphosphonous dichloride to a stirred solution of an equimolar quantity of catechol in ether, tetrahydrofuran, or benzene containing triethylamine or pyridine at 0° in an atmosphere of nitrogen resulted in the immediate precipitation of the corresponding hydrochloride salt of the amine. Filtration of the precipitate gave a clear solution which on evaporation left an oil. This was purified by distillation, b.p. 139–141° (0.3 mm.); λ_{max}^{film} 6.92 (C_6H_5–P), 7.8 (P→O), 8.2 μ (C–O–), besides other absorption bands. Immediate elemental analysis for carbon and hydrogen corresponded to VI.

Anal. Calcd. for $C_{12}H_9O_3P$: C, 62.08; H, 3.9. Found: C, 61.80; H, 3.79.

Reaction of Phenylphosphonic Dichloride with II.—A solution of phenylphosphonic dichloride (19.5 g., 0.10 mole) in 50 ml. of bromobenzene was added dropwise under nitrogen over a period of 30 min. to a well-stirred solution of catechol (11.0 g., 0.10 mole) in 350 ml. of anhydrous bromobenzene. The mixture was boiled 6 hr., and the evolved hydrogen chloride (quantitative) was titrated. Removal of the solvent left an oil and immediate infrared analysis showed that VI was formed. Upon standing it solidified, m.p. 118–121°. Recrystallization from methylene chloride–petroleum ether or from bromobenzene gave sufficiently pure acid III, m.p. 123–124°.

Hydrolysis of *o*-Hydroxyphenylhydrogen Phenylphosphonate (III).—A mixture of 6.25 g. of III and 25 ml. of hydrochloric acid was boiled 16 hr. during which period the color of the solution turned from brown to pink. After cooling, the solution was diluted with water, neutralized with sodium bicarbonate, and extracted with ether. Evaporation of solvent gave 2.3 g. of catechol, m.p. 103.5–104.5°. The aqueous layer was acidified with hydrochloric acid and extracted with ether. From the ether extract 0.4 g. of crystalline phenylphosphonic acid (m.p. 158–160.5°) was isolated.

(9) All melting points are corrected and all boiling points are uncorrected. The microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Reactions of Aryl Grignard Reagents with 2,2,4-Trimethyl-3-hydroxy-3-pentenoic Acid β-Lactone[1]

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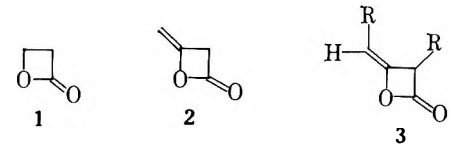
The course of reaction of β-lactone systems with organometallic reagents is not well understood and appears to depend markedly upon the β-lactone employed. β-Propiolactone (1) has been reported to react with phenyl Grignard reagent by acyl–oxygen ring-opening, to give phenyl vinyl ketone and 3-bromopropanoic acid.[3] Phenyllithium yields phenyl vinyl ketone and



the diadduct, 1,1-diphenyl-1,3-propanediol.[4] However, benzyl and allyl Grignard reagents, as well as several organic cadmium reagents, have been reported[4] to produce alkyl–oxygen fission with concomitant ring opening to form the β-substituted carboxylic acids. Diketene (2) condenses with a variety of Grignard reagents,[5] adding 3 moles to give 1,1-disubstituted ethanol derivatives and methyl ketones. Aldoketene dimers (3) with Grignard reagents[6] give diadducts and the reverse aldol cleavage products of the diadducts. In all of these processes, yields of pure compounds were quite low and considerable polymeric material was reported.

We have investigated the reaction of the highly substituted β-lactone, 2,2,4-trimethyl-3-hydroxy-3-pentenoic acid β-lactone (**4**), with aryl Grignard reagents. In view of the geminal methyl groups on the α-carbon of the β-lactone **4**, we anticipated that the reaction might terminate after monoaddition to give a highly substituted β-diketone. If diaddition occurred, dehydration was not possible and a hydroxy ketone was a conceivable product, barring intervention of carbon–carbon cleavage in a retrograde aldol decomposition. The reactions were performed by normal addition of **4** in ether to the Grignard reagent followed by hydrolysis of the reaction mixture with ammonium chloride solution. Product analysis was completed by gas chromatography.

When excess phenyl Grignard reagent was allowed to react with **4** in ether, only benzophenone and diisopropyl ketone were obtained. This is analogous to the course of the same reaction with tetramethyl-1,2-cyclo-

(1) We gratefully acknowledge partial support of this research by the Research Foundation of the Oklahoma State University.

(2) Abstracted in part from the thesis of M. H. Cooper submitted in partial fulfullment of the requirements for the Master of Science degree of the Oklahoma State University, 1964.

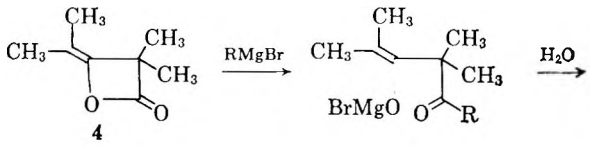
(3) T. L. Gresham, J. E. Jansen, F. W. Shaver, and R. A. Bankert, *J. Am. Chem. Soc.*, **71**, 2807 (1949).

(4) C. G. Stuckwisch and J. V. Bailey, *J. Org. Chem.*, **28**, 2362 (1963).

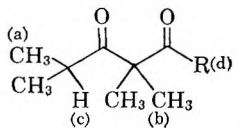
(5) A. Gibaud and A. Willemart, *Bull. soc. chim. France*, 432 (1956).

(6) D. V. Nightingale and R. H. Turley, *J. Org. Chem.*, **26**, 2656 (1961).

butanedione.[7] Diaddition of the Grignard reagent to the carbonyl group of **4** followed by immediate retrograde aldol cleavage seems reasonable. In spite of equimolar concentrations of phenyl Grignard reagent and lactone **4**, only a small quantity of monoaddition product **5** could be isolated along with cleavage products.



4



5, R = C_6H_5
6, R = *o*-$CH_3C_6H_4$
7, R = 1-$C_{10}H_7$

Small quantities of more than fifteen other compounds along with **4** were detected by gas chromatography. Compound **5** showed strong bands in the infrared region at 1718 and 1672 cm.$^{-1}$ for simple aliphatic and conjugated carbonyl functions, respectively, as well as a peak at 706 cm.$^{-1}$ for monosubstituted phenyl. Similarly, absorption for the twin carbonyl groups in **6** and **7** appeared at 1718 and 1671 cm.$^{-1}$ and at 1711 and 1671 cm.$^{-1}$, respectively. Nuclear magnetic resonance spectrograms displayed signals as expected for methyl protons in an isopropyl group, the lone tertiary hydrogen, protons on equivalent geminal methyl groups, and the aromatic protons as shown in Table I.

TABLE I

N.M.R. SPECTRA OF THE DIKETONES

Parent compound	δ-Values of protons[a] (*J* in c.p.s.) a	b	c	d
5	0.91 d (*J* = 7)	1.43 s	2.72 m	7.55 m
6[b]	0.95 d (*J* = 7)	1.40 s	2.95 m	7.26 m
7	0.95 d (*J* = 7)	1.45 s	2.97 m	7.6 m

[a] d = doublet, s = singlet, m = multiplet. [b] The *ortho* methyl group displayed a singlet at δ 2.37.

In contrast, by increasing the size of the organometallic reagent by the use of *o*-tolyl and 1-naphthyl Grignard reagents, it was possible to prepare 1-(*o*-tolyl)-2,2,4-trimethyl-1,3-pentanedione (**6**) and 1-(1-naphthyl)-2,2,4-trimethyl-1,3-pentanedione (**7**), respectively. Although the yields were less than 50% in each case, considerable tars were produced which suggests polymerization is probably competitive. As proof of structure, **6** was treated with 20% aqueous sodium hydroxide. High yields of *o*-toluic acid and diisopropyl ketone were obtained.

Thus initial reaction of the Grignard reagent occurs at the carbonyl carbon, probably with concomitant ring opening. Benzophenone could be detected by infrared analysis in the reaction mixture within minutes after the addition of **4** to the phenyl Grignard reagent. Apparently, introduction of a small amount of hindrance in the Grignard reagent permits survival of the monoaddition product, the β-diketone.

(7) J. L. E. Erickson and G. C. Kitchens, *J. Am. Chem. Soc.*, **68**, 492 (1946).

Experimental[8-10]

Reaction of Excess Phenyl Grignard Reagent with 4.—The phenyl Grignard reagent was prepared from 13.37 g. (0.55 g.-atom) of magnesium and 78.51 g. (0.5 mole) of bromobenzene in 100 ml. of anhydrous ether. The Grignard mixture was cooled to 5°, and a solution of 23.19 g. (0.165 mole) of **4** in an equal volume of ether was added dropwise with stirring to maintain the mixture temperature below 15°. When the addition was complete, the slurry was refluxed for 4 hr. The chilled mixture was hydrolyzed with cold 20% aqueous ammonium chloride and the aqueous phase was extracted with ether. Gas chromatographic analysis showed diisopropyl ketone and benzophenone as the only major products along with traces of other components. This was verified by additional experiments.

Reaction of Phenyl Grignard Reagent with 4 (1:1). Preparation of 1-Phenyl-2,2,4-trimethyl-1,3-pentanedione (5).—To the phenyl Grignard reagent (0.16 mole) was added a solution of 23.66 g. (0.16 mole) of **4** in an equal volume of ether in the manner described previously. The mixture was stirred for 6 hr. at room temperature, then boiled for 1 hr. The reaction mixture was then worked up as usual, and the resulting solution was concentrated to an oil. A mixture of the aforementioned oil, 17 g. of Girard-T reagent, 100 ml. of methanol, and 10 ml. of acetic acid was heated at reflux for 4 hr. The solution was cooled to room temperature, and 5% aqueous sodium hydroxide was added until the solution had a pH of 8. Water (100 ml.) was added and the resulting mixture was extracted with ether. When part of the ether had been distilled, a solid precipitated and was isolated by filtration. The filtrate was carefully chromatographed on acid-washed alumina. The small amount (1.7 g., 5%, based on **4**) of crude **5** was purified by preparative gas chromatography, using a 10% silicone rubber column, b.p. 81–84.5° (0.3 mm.).

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.15; H, 8.55.

1-(*o*-Tolyl)-2,2,4-trimethyl-1,3-pentanedione (6).—*o*-Tolyl Grignard reagent (0.4 mole) was prepared, and the mixture was cooled to 5°. A sample of **4** (18.48 g., 0.13 mole) dissolved in an equal volume of ether was added dropwise to the stirred Grignard reagent so that the temperature did not rise above 15°. The reaction mixture was worked up as before, and the organic phase was distilled *in vacuo* to give 1-(*o*-tolyl)-2,2,4-trimethyl-1,3-pentanedione (**6**), b.p. 158–160° at 15 mm. (12.0 g., 40%), and considerable residual tars.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.67; H, 8, 8.68.

One gram of pure diketone was refluxed in 10 ml. of 20% aqueous sodium hydroxide to give 0.584 g. (84%) of *o*-toluic acid. Diisopropyl ketone was identified in the reaction mixture by gas chromatography as the only other compound.

1-(1-Naphthyl)-2,2,4-trimethyl-1,3-pentanedione (7).—1-Naphthyl Grignard reagent (0.4 mole) was prepared in a manner as previously described.[11] The reagent was vigorously stirred to prevent solidification while cooling to 15°. An equal volume of ether was mixed with 12.6 g. (0.09 mole) of **4**, and the solution was added dropwise to the Grignard reagent (temperature was <15°). The slurry was worked up as described earlier to give an oil which was chromatographed three times on acid-washed alumina. The ketone, 1-(1-naphthyl)-2,2,4-trimethyl-1,3-pentanedione, distilled at 186–188° (4 mm.), 10.8 g. (44.8%).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.86; H, 7.51.

(8) All melting points are corrected; all boiling points are uncorrected. The lactone **4** was obtained from Eastman Chemical Products, Kingsport, Tenn., b.p. 170° (730 mm.).

(9) Gas chromatographic analyses were performed using an Aerograph Hy-Fi Model A-550 with a hydrogen flame ionization detector and an Aerograph A-350 unit. A 10% silicone rubber column on acid-washed Chromosorb W was satisfactory for the isolation of **4**.

(10) The nuclear magnetic resonance spectra were determined with a Varian Model A-60 high-resolution spectrometer fitted with a field-sensing stabilizer ("Super Stabilizer"). Carbon tetrachloride with tetramethylsilane as an internal standard was the solvent.

(11) See H. Gilman, N. B. St. John, and F. Schulze, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 425.

Acetylation of 17β-Acetoxy-5α-androstan-3-one[1]

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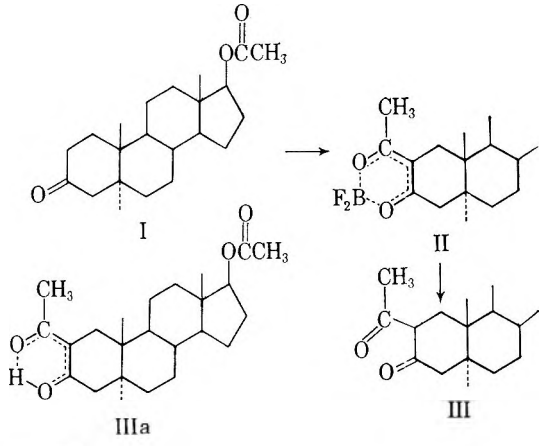
Received January 14, 1964

The familiar C-17 side chains of steroid hormones are acetyl or hydroxyacetyl functions. Marked changes in biological response usually accompany structural alteration in this side chain. We wished to investigate the effect of introducing the side chain usually associated with C-17 into position 2 of the steroid.

Syntheses of steroids substituted with the acetyl or hydroxyacetyl groups in positions other than C-17 have been reported, to our knowledge, in only a few instances. A dihydroxy acetone structure at and including C-3,[2a] 3-acetyl,[2b] and 16-acetyl and hydroxyacetyl[2c] steroids have been synthesized. To these, we wish to add the carbon acetylation of 17β-acetoxy-5α-androstan-3-one (I) by two methods, both on C-2.[2d]

Although C-acetylation of cyclohexanone and related ketones have been accomplished in low yields,[3] our many attempts to acetylate I by the alkaline condensation method were unsuccessful. It was by employing Hauser's inverse-addition method with acetic anhydride and boron trifluoride that we were able to obtain an acetylated product.[4] However, according to this method the boron fluoride complex is hydrolyzed with methanol and water, while the product we obtained following this treatment was the unhydrolyzed, acetylated steroid-boron fluoride complex (II). This was obtained in 73% yield and proved quite stable. The boron fluoride complex was characterized by strong peaks in the infrared spectrum at 1733, 1592, and 1494 cm.$^{-1}$, and an ultraviolet absorption maximum at 307 mμ in methylene chloride. Even refluxing this complex in a biphasic system of ethylene chloride and aqueous acetate buffer yielded only starting material. It was by prolonged boiling of the complex in methanol that a 40% yield of 2-acetyl-17β-acetoxy-5α-androstan-3-one (III) was obtained. A superior method of decomposing the complex was to reflux a methanolic solution with sodium acetate and acetic acid for 2 hr. Upon cooling, the β-diketone crystallized and the yield was nearly quantitative.



From spectral data III appears to exist entirely in the cyclic, hydrogen-bonded, enolic form which is formulated as IIIa. It has an ultraviolet absorption peak at 290 mμ in 95% alcohol (ε 9600) and in the infrared a broad band at 1640–1570 cm.$^{-1}$, characteristic of enolic β-diketones, and a very weak peak at 2700 cm.$^{-1}$ (bonded hydroxyl). The ultraviolet peak of IIIa (290 mμ) occurs at a longer wave length than that reported for simple aliphatic β-diketones (*ca.* 270 mμ) or the closely related 2-formyl-3-keto steroids (*ca.* 282 mμ).[5] In basic solution both the 2-acetyl (III) and the 2-formyl derivatives exhibit maxima at 315 mμ. In a hydrochloric acid solution of III, there appeared a low intensity peak at 232 mμ in addition to the characteristic maximum at 290 mμ. As shown in Table I, the molar extinction of the former peak increased by about 12% in going from 0.01 *N* to 1 *N* acid while the 290-mμ peak decreased somewhat. The change in optical rotation (Δ[M]D) of +75° in going from the 3-keto steroid to the 2-acetyl-3-keto steroid is comparable with that observed in going from the same 3-keto steroid to the 2-formyl derivative (Δ[M]D +104°).[5]

TABLE I

MOLAR EXTINCTION OF 2-ACETYL-17β-ACETOXY-5α-ANDROSTAN-3-ONE

	0.01 *N* HCl	0.1 *N* HCl	1 *N* HCl
λ_{max} 232 mμ	2080	2190	2370
λ_{max} 290 mμ	9860	9770	8970

An alternative synthesis of III was achieved through acylation of the enamine of I, with acetyl chloride. The pyrrolidine enamine (IV) of 17β-acetoxy-5α-androstan-3-one was conveniently prepared in 55% yield, according to the procedure of Heyl and Herr,[6] using benzene or toluene as solvent, a large excess of pyrrolidine, and without catalyst. Acylation of the enamine to 2-acetyl-17β-acetoxy-5α-androstan-3-one (III) was carried out with benzene or chloroform as solvent, the latter having the advantage of producing a homogeneous medium. Addition of triethylamine was found to increase the yield somewhat.

3-Keto 5α-steroids are known to enolize preferentially toward C-2.[7] That the acetylation took place on the 2-carbon rather than the 4-carbon in both syntheses was established by the following procedure: 2-acetyl-17β-acetoxy-5α-androstan-3-one (III) was treated with methyl iodide and potassium carbonate to yield 2-methyl-2-acetyl-17β-acetoxy-5α-androstan-3-one (V). The broad melting range, 128–177°, of this product

(1) This investigation was supported in part by Public Health Service Research Grants A-1113 from the National Institute of Arthritis and Metabolic Diseases, and H-2818 from the National Heart Institute, and was presented at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

(2) (a) H. B. Kagan, A. Marquet, and J. Jacques, *Bull. soc. chim. France*, 1079 (1960); (b) R. H. Baker and E. N. Squire, *J. Am. Chem. Soc.*, **70**, 1487 (1948); G. Nathansohn and O. Pirola, *Gazz. chim. ital.*, **90**, 407 (1960), and earlier papers; (c) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *J. Org. Chem.*, **26**, 2852 (1961), and earlier papers; (d) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton [*J. Med. Chem.*, **6**, (1963)] have also reported the synthesis of 2-acetyl-17β-acetoxy-5α-androstan-3-one.

(3) R. Levine, J. A. Conroy, J. T. Adams, and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 1510 (1945).

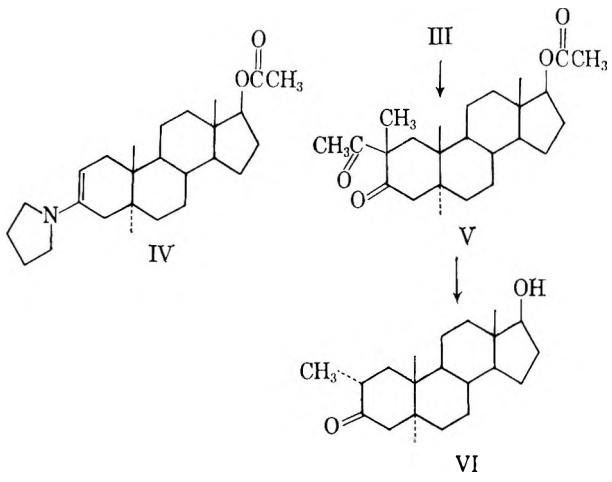
(4) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 129 (1954).

(5) R. O. Clinton, *et al.*, *J. Am. Chem. Soc.*, **83**, 1478 (1961).

(6) F. W. Heyl and M. E. Herr, *ibid.*, **75**, 1918 (1953).

(7) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 276.

indicated that it may be a mixture of the C-2 isomers. Cleavage of the acetyl group in base gave a single product which proved to be identical with an authentic sample of 2α-methyl-17β-hydroxy-5α-androstan-3-one (VI) from mixture melting point data and comparison of infrared spectra. Thus, the proton in C-2 rather than on C-4 appears to be removed, as is true in most instances with 3-keto 5α-steroids, although exceptions in special circumstances have been reported.[8]

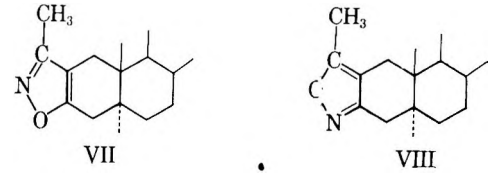


Acid hydrolysis of III at room temperature removed the 17-acetate. The resulting 2-acetyl-17β-hydroxy-5α-androstan-3-one, while having the characteristic broad β-diketone band at 1640–1540 cm.$^{-1}$, did not absorb in the "normal" carbonyl region from 1750 to 1700 cm.$^{-1}$. This apparent absence of the keto form, which was not evident before hydrolysis since the 17-acetate peak may have masked a ketone absorption peak in this region, was observed in chloroform and carbon tetrachloride. In contrast with this, two bands at about 1725 and 1700 cm.$^{-1}$ have been reported for a number of 1,3-diketones.[9] We have observed two such bands for 2-acetylcyclohexanone as well as some acyclic β-diketones. It would appear that the cyclic, hydrogen-bonded, enolic form is more stable in the 2-acetyl steroid than in 2-acetylcyclohexanone. This may be due to the greater conformational lability in the latter compound, resulting in greater tendency to open to the diketo form.

Bromine titration of III in methanol gave an average value of 87% enol. The higher proportion of ketone from titration results, as compared with spectral data, is consistent with the known shift of equilibrium toward the keto form with increasing solvent polarity.[10]

The copper chelate of III was prepared readily as a crystalline compound whose analysis revealed the expected metal–ligand ratio of 1:2. The infrared spectrum showed replacement of the "enol chelate" band with a strong but narrower band at 1578 cm.$^{-1}$ which has been characterized as due to a perturbed carbonyl.[9] A smaller band at 1530 cm.$^{-1}$ was evident, and such peaks have been assigned to perturbed carbon–carbon double bonds.

The isoxazole of III was prepared by a modification of the method of Clinton, *et al.*[11] The ultraviolet absorption maximum at 227 mμ (ε 6950) corresponds to the value obtained for 17β-hydroxy-5α-androstano-[2,3-*d*]isoxazole, 228 mμ (ε 4900), although the molar extinction coefficient of the latter is lower. The [2,3-*d*]isoxazole structure (VII) may appear to be favored over the [3,2-*c*]isoxazole (VIII); as yet, no clear structural assignment can be made on this or on molar rotation data.[12]



Experimental[13]

Borofluoride Complex of 2 Acetyl 17β-acetoxy-5α-androstan-3-one (II).—In a procedure patterned after Hauser's[4] a solution of 35 ml. of glacial acetic acid (0.611 mole) and 100 ml. of ethylene chloride in a 500-ml., three-necked flask equipped with a dropping funnel, gas-inlet tube, and stirrer was cooled in an ice bath. Boron trifluoride gas washed through sulfuric acid was passed into the stirred solution until saturation was reached. To the resulting white paste, kept under nitrogen, with continued cooling and stirring was added a solution of 21.8 g. (0.0755 mole) of 17β-acetoxy-5α-androstan-3-one and 28.7 ml. (0.306 mole) of acetic anhydride in 80 ml. of ethylene chloride. The addition required 15 min. during which time the mixture became homogeneous. After 0.5 hr. longer in the ice bath, the solution was allowed to stand at room temperature for 3 hr. under nitrogen. It was washed with water and saturated bicarbonate solution and dried, and the solvent was removed. Crystallization from acetone yielded 22.0 g. of white solid. With a second crop of 1.44 g. the combined yield was 73%. The melting range of a sample after recrystallization from acetone was 265–277°; $[\alpha]_D$ +38.7° (*c* 0.832); $\lambda_{max}^{CH_2Cl_2}$ 307 mμ (ε 12,200); infrared $\nu_{max}^{CHCl_3}$ 1733, 1592, 1494, 1156, 1052, 967, and 895 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}BF_2O_4$: C, 65.41; H, 7.88; F, 9.00. Found: C, 65.78; H, 8.14; F, 8.48.

2-Acetyl-17β-acetoxy-5α-androstan-3-one (III).—A mixture of 3.0 g. of the borofluoride complex II in 125 ml. of methanol containing 1.16 g. of sodium acetate and 0.8 ml. of glacial acetic acid was refluxed for 2.5 hr. Upon cooling and refrigerating, white crystals formed. These were filtered, washed successively with methanol and aqueous methanol, and finally dried to yield 2.52 g. (95%). Repeated crystallizations from methanol and/or acetone gave colorless needles with m.p. 180–181°; $[\alpha]^{28}D$ +43.3° (*c* 0.6116); λ_{max} 290 mμ (ε 9600); $\nu_{max}^{CCl_4}$ 2700 (very weak), 1748, 1640–1570 (broad), 1232, 1045, 1034, and 946 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.19; H, 9.34.

2-Acetyl-17β-acetoxy-5α-androstan-3-one (III) by the Enamine Method.—The pyrrolidine enamine (IV) was synthesized according to the procedure of Heyl and Herr[6] in 55% yield from 3.0 g. of I. Repeated crystallizations from ethyl acetate and methanol gave light yellow plates, the melting range of which remained broad (100–105°), $[\alpha]^{28}D$ +26.3° (*c* 0.96, chloroform) and +32.1° (*c* 1.06, methylene chloride). Neither solution

(8) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 6296 (1958).

(9) H. F. Holtzclaw, Jr., and J. P. Collman, *ibid.*, **79**, 3318 (1957).

(10) G. S. Hammond, W. G. Borduin, and G. A. Guter, *ibid.*, **81**, 4682 (1959).

(11) R. O. Clinton, A. J. Manson, F. W. Stonner, R. G. Christiansen, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Org. Chem.*, **26**, 279 (1961).

(12) The structure proposed by Manson, *et al.*,[2d] corresponding to VII would not necessarily apply in this case, since they employed acidic conditions. The melting range which they report, 189–195°, indicates that their product is probably a mixture. Under our mildly alkaline conditions, we obtained predominantly one product. This pH effect appears to be the inverse of that found with isoxazole formation from 2-hydroxymethylene steroids in the above reference. However, it is more likely that only one isoxazole is formed in acid or base and the mixture obtained by Manson, *et al.*, is due to partial hydrolysis of the 17-acetate.

(13) The infrared data taken on a Perkin–Elmer Model 21 spectrophotometer are for major bands exclusive of the usual C–H stretching frequency (*ca.* 2900 cm.$^{-1}$) and the C–H deformation bands (1370–1470 cm.$^{-1}$). Ultraviolet spectra (in 95% ethanol unless otherwise indicated) were determined on a Cary Model 14 spectrophotometer.

showed significant change in rotation after 3 hr.; $\nu_{max}^{CH_2Cl_2}$ 1730, 1646, 1370, 1040, and 1032 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.85; H, 10.26; N, 3.68.

In a 100-ml., three-neck flask equipped with a condensor, dropping funnel, gas-inlet tube, and stirrer were placed 785 mg. (2.03 mmoles) of enamine IV, 235 mg. (2.32 mmoles) of triethylamine, and 10 ml. of chloroform, the latter two being freshly distilled and dried. To the stirred solution warmed to 40° and under nitrogen was added dropwise over a 20-min. period a solution of 167 mg. (2.13 mmoles) of acetyl chloride in 10 ml. of chloroform. The reaction temperature was raised to 55° for 4 hr., then lowered to 40° overnight.

The resulting orange-red solution was hydrolyzed with 30 ml. of 4 *N* hydrochloric acid and 20 ml. of chloroform by refluxing with vigorous stirring for 4 hr. The cooled mixture was extracted with methylene chloride; the organic layer was washed with water, dried, and evaporated to dryness, giving 620 mg. of orange-brown oil. A major portion of this, 580 mg., was chromatographed on 35 g. of silica gel (80–200 mesh). Following benzene, the eluate with 0.5% ethyl acetate–benzene yielded 152 mg. of III, identified after crystallization by melting point, mixture melting point, and infrared spectra. Further elution with 2% ethyl acetate–benzene gave 190 mg. of starting material (I).

The acylation of enamine IV in benzene followed a similar procedure with the difference that a white precipitate formed upon addition of acetyl chloride and persisted throughout the reaction. After hydrolysis with hydrochloric acid, 600 mg. of crude product was chromatographed on silica gel, yielding 135 mg. of III.

Methylation of 2-Acetyl-17β-acetoxy-5α-androstan-3-one (III).—To a solution of 2.0 g. of III in 75 ml. of acetone was added 4.0 g. of pulverized potassium carbonate and 7.0 ml. of freshly distilled methyl iodide. The mixture was refluxed with stirring for 20 hr., after which an additional 3 ml. of methyl iodide was added and the stirring with reflux was continued for 20 hr. more. After approximately half of the solvent was removed by distilling, the mixture was cooled and ether was added. The organic phase was washed with water, dried with magnesium sulfate, and evaporated to dryness. The 2.0-g. yield of crude product was chromatographed on 150 g. of silica gel (80–200 mesh). Elution with benzene was followed by several liters of 3% (v./v.) of ethyl acetate–benzene from which was obtained 1.64 g. of 2-methyl-2-acetyl-17β-acetoxy-5α-androstan-3-one (V). Homogeneity throughout the fraction was established by the identity of the melting points and spectra of samples from several aliquots. Repeated crystallizations from diisopropyl ether gave an analytical sample with m.p. 194–195°; $[\alpha]^{25}D$ +83.2° (*c* 1.01); $\nu_{max}^{CCl_4}$ 1738, 1710, 1235, 1124, and 1034 cm.$^{-1}$. There was no major absorption peak in the ultraviolet.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.20; H, 9.34. Found: C, 74.17; H, 9.16.

A solution of 383 mg. of V in 40 ml. of methanol containing 4.0 g. of potassium carbonate and 17 ml. of water was refluxed for 4 hr. under nitrogen. Most of the solvent was removed by evaporation under reduced pressure. To the remainder was added methylene chloride and the organic phase was extracted with aqueous potassium carbonate, washed with water, and dried with magnesium sulfate. Evaporation of the solvent gave 289 mg. (96%) of a white solid which, without purification, had melting point and spectral properties close to those of VI. Recrystallization from diisopropyl ether gave crystals with a melting point and mixture melting point (with an authentic sample) of 148–149°. Identity of infrared spectra was established in both chloroform and carbon disulfide.

Hydrolysis of 2-Acetyl-17β-acetoxy-5α-androstan-3-one (III).—A solution of 600 mg. of III in 50 ml. of 95% ethanol and 20 ml. of 6 *N* hydrochloric acid was refluxed 6.5 hr. Approximately half the ethanol was distilled and the remaining solution was cooled, treated with 70 ml. of water, and refrigerated overnight. The solid was filtered, washed well with water, and dried, yielding 504 mg. of a glassy solid. Crystallization from hexane gave an amorphous solid of broad melting range. Recrystallizations successively from aqueous methanol and ether–hexane gave well-formed platelets, m.p. 153–154°; $[\alpha]^{24}D$ +62.4°; $\nu_{max}^{CCl_4}$ 3620, 1640–1540 (broad), 1360, 1310, 1293, 1276, 1230, 1200, 1128, 1113, 1080, 1058, 1024, and 944 cm.$^{-1}$; ultraviolet absorption, λ_{max} 291 mμ (ε 8970).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.85; H, 9.51.

The same transformation was effected under mild conditions: a solution of 200 mg. of III in 30 ml. of methanol, 15 ml. of acetone, 5 ml. of water, and 2 ml. of concentrated hydrochloric acid was allowed to stand 64 hr. at room temperature. After addition of water, the mixture was extracted with methylene chloride and the latter phase was washed with dilute bicarbonate and water. Drying with magnesium sulfate followed by evaporation of solvent gave 177 mg. of crude material, which could be crystallized from petroleum ether to give semicrystalline material, m.p. 150–152°.

Bromine Titration of III.—The procedure followed was essentially that of Smith and Shriner.[14] To a solution of 0.463 mmole of III in 60 ml. of hot methanol was added an excess of bromine–methanol solution (*ca.* 0.1 *N*, freshly prepared) and followed immediately with 3 ml. of cyclohexene. An excess of potassium iodide solution was added; the mixture was warmed to 30–35°, and allowed to stand at room temprature for 10 min. After most of the iodine was titrated with 0.100 *N* sodium thiosulfate, there was added 2 ml. of acetic acid, 250 ml. of water, and 4 ml. of starch solution, and the titration was completed. A total of 8.15 ml. of thiosulfate solution was required, indicating an enol content of 88%. A repeat run gave a value of 86.6%.

Copper Chelate of III.—A solution of 500 mg. of III in 25 ml. of hot methanol was treated with cupric acetate solution [1 g. of $Cu(OAc)_2 \cdot H_2O$ in 10 ml. of hot water, filtered]. Dilution with water caused the precipitation of the green complex which was filtered and dried. Crystallization from acetone gave 427 mg. of green needles. From repeated crystallizations from acetone there was obtained an analytical sample, m.p. *ca.* 290° (began softening and darkening at *ca.* 270°); λ_{max} 243 mμ (ε 4100) and 311 (11,200); $\nu_{max}^{CHCl_3}$ 1738, 1578, 1530, 1467, 1378, 1290, 1023, and 948 cm.$^{-1}$.

Anal. Calcd. for $C_{46}H_{66}CuO_8$: C, 68.11; H, 8.21; Cu, 7.84. Found: C, 67.75; H, 8.18; Cu, 8.13.

Isoxazole Formation from III.—A solution of 900 mg. of III and 10 g. of hydroxylamine hydrochloride in 50 ml. of pyridine and 50 ml. of ethanol was refluxed for 2 hr. After cooling, dilution with water gave a precipitate which was filtered, washed, and dried. Crystallization from acetone gave 886 mg. of isoxazole, m.p. 201–203°. Recrystallization from acetone and hexane successively gave an analytical sample, m.p. 202–203°; $[\alpha]^{24}D$ +33.6° (*c* 0.708); λ_{max} 227 mμ (ε 6950); $\nu_{max}^{CCl_4}$ 1745, 1643, 1233, 1186, 1042, 1032, and 1021 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.19; H, 8.97; N, 4.08.

(14) W. T. Smith and R. L. Shriner, "The Examination of New Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 101.

The Reaction of Schiff Bases with Dicyandiamide. A New Synthesis of 4,6-Diamino-1,2-dihydro-*sym*-triazines

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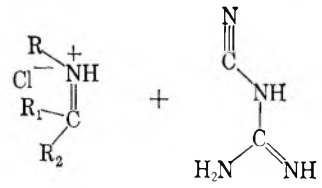
4,6-Diamino-1-aryl-1,2-dihydro-*sym*-triazine hydrochlorides[2] (I, R = aryl) have previously been prepared by either the condensation of an arylamine hydrochloride, ketone or aldehyde and dicyandiamide, or by allowing the ketone or aldehyde to react with an arylbiguanide hydrochloride.[3] The latter method was ex-

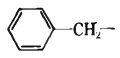
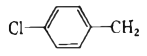
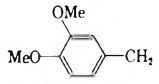
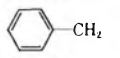
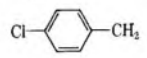
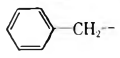
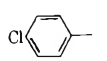
(1) Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

(2) The tautomeric form indicated is done so arbitrarily. There is no evidence to date which favors this one over the other alternatives.

(3) (a) H. C. Carrington, A. F. Crowther, D. G. Davey, A. A. Levi, and F. L. Rose, *Nature*, **168**, 1080 (1951); (b) H. C. Carrington, A. F. Crowther, and G. J. Stacey, *J. Chem. Soc.*, 1017 (1954); (c) E. J. Modest, G. E. Foley, M. M. Pechet, and S. Farber, *J. Am. Chem. Soc.*, **74**, 855 (1952); (d) E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956); (e) E. J. Modest and P. Levine, *ibid.*, **21**, 14 (1956).

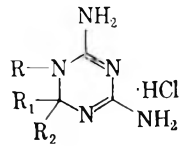
TABLE I



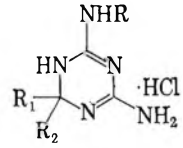
No.	R	R_1	R_2	M.p., °C.	Time, hr.	Yield, %	Calcd. / Found C	H	N	Cl	F
1			H	228–230	16	91	60.91	5.75	22.12	11.22	
							60.93	5.84	22.85	11.06	
2			H	185–187	19	78[a]	54.86	4.89	19.99	20.24	
							54.82	4.90	19.87	20.15	
3			H	183–185	27	48[a]	57.51	5.90	18.63	9.43	
							56.95	6.10	18.55	9.65	
4		CF_3	H	290 dec.	0.5	73	42.93	4.25	22.76	11.52	18.52
							43.10	3.87	22.71	11.54	18.86
5		CF_3	H	276–278	0.5	88	38.61	3.53	20.46	20.72	16.65
							38.60	3.95	20.46	20.73	16.69
6		$(CH_3)_3C$—	H	245–247	20	88	56.83	7.49	23.67	11.98	
							56.79	7.62	23.73	11.97	
7			H	232–235[b]	2.5	94	59.69	5.34	23.20	11.74	
							59.92	5.13	23.12	11.80	
8			H	245–247	72[c]	65	53.58	4.49	20.83	21.09	
							53.81	4.44	20.81	21.03	
9		CH_3	CH_3	204–206	2.0	83	*d*				

[a] Based on unrecovered starting material. [b] Lit.[2b] m.p. 232–233°. [c] Week end. [d] Identical melting point and infrared spectrum with that of the compound prepared *via* the three-component synthesis.[2d]

tended by Lombardino[4] to the preparation of 4,6-diamino-1-alkyl-1,2-dihydro-2,2-dimethyl-*sym*-triazine hydrochlorides (I, R = alkyl; $R_1 = R_2 = CH_3$) from alkylbiguanide hydrochlorides and acetone.[5]

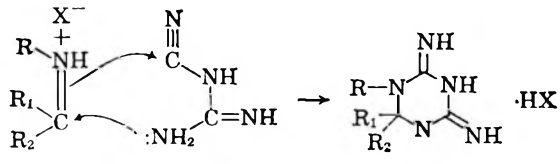


I



II

An alternate route to compounds of type I which suggested itself to us, was the reaction of dicyandiamide (III) and a protonated Schiff base of general structure IV.

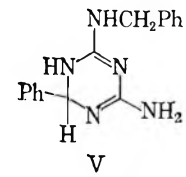


IV III

I, HX in place of HCl

The reaction proved quite satisfactory for Schiff bases in which R = aralkyl (Schiff bases in which R = alkyl was not tried), R_1 represents substituents which do not contain α-hydrogens, and R_2 = H. Thus, the 2,4-diaminodihydrotriazines listed in Table I were prepared by allowing the protonated Schiff base IV and dicyandiamide to react in dimethylformamide at room temperature.[6] The free Schiff base did not react. Earlier attempts to effect the reaction by fusing the Schiff base hydrochloride and dicyandiamide in the absence of solvent gave considerably inferior results except in the case of benzylidenebenzylamine hydrochloride (IV, R = benzyl; R_1 = phenyl; R_2 = H) and its *p*-chloro analog (IV, R = *p*-chlorobenzyl; R_1 = phenyl; R_2 = H). Here, too, no reaction was observed with the free Schiff base.

In accord with previous observations,[2d] I (R =



V

(4) J. Lombardino, *J. Med. Chem.*, **6**, 213 (1963).

(5) Unfortunately, Lombardino did not offer any evidence in support of his structural assignments, apparently assuming that the reaction course in the alkyl series parallels that observed in the aryl series, where dihydrotriazines of type I are formed exclusively. Our unpublished findings on the reaction of benzylbiguanide hydrochloride and acetone from which I (R = benzyl; $R_1 = R_2 = CH_3$) and II (R = benzyl; $R_1 = R_2 = CH_3$) was isolated in roughly equal amounts would seem to invalidate this assumption.

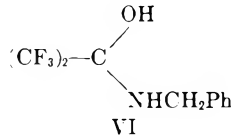
(6) Ingold and Piggott have demonstrated that benzylamine Schiff bases with a nitro substituent in either the benzylidene or benzylamine portion of the molecule are hydrolyzed back by acid to the aldehyde and amine from which they were formed [*J. Chem. Soc.*, 2381 (1922)], and we have found this to apply as well to the hydrochloride salt of the Schiff base obtained from 3,4-dimethoxybenzylamine and benzaldehyde. Cordes and Jencks [*J. Am. Chem. Soc.*, **85**, 2843 (1963)] also found no evidence for the isomerization of Schiff bases formed from ethylamine and a number of *meta*- and *para*-substituted benzaldehydes.

benzyl; R_1 = phenyl; R_2 = H) readily rearranged in base to V.

The reaction did not take place with the benzylamine Schiff bases of acetone, acetaldehyde, and acetophenone. The failure of the reaction with these α-hydrogen-containing Schiff bases is perhaps related to the previously reported difficulties encountered in the addition of nucleophiles to α-hydrogen-containing imines,[7] apparently owing to the faster attack at the α-hydrogen by the nucleophile compared to its addition across the carbon–nitrogen double bond.

As exemplified by no. 9 in the table, when R = aryl, the desired reaction does take place, in good yield, with α-hydrogen-containing R_1 and R_2 substituents.

An attempt to prepare hexafluoroisopropylidenebenzylamine (IV-HCl, R = benzyl; $R_1 = R_2 = CF_3$) under conditions (*p*-toluenesulfonic acid and benzene) satisfactorily employed for the preparation of the other Schiff bases was unsuccessful. The structure VI for the compound obtained was assigned on the basis of its infrared [sharp peak at 2.9 μ (NH), broad band at *ca.* 3.9 μ (hydrogen-bonded OH)] and n.m.r.[8] spectra [a five-proton singlet at τ 2.72 (aromatic protons), broad singlet at 5.65 (N–H), singlet at 6.00 (OH), and singlet at 6.36 (benzylic protons); the total area of the latter three peaks corresponded to four protons].[9]



VI

Experimental[10]

Reaction of Schiff Base Hydrochloride IV (X = Cl) with Dicyandiamide in Dimethylformamide.—The general method is illustrated with a description of the procedure used to prepare 4,6-diamino-1-benzyl-1,2-dihydro-2-trifluoromethyl-*sym*-triazine. A slow stream of gaseous hydrogen chloride was passed through a solution of 5.6 g. (0.03 mole) of 2,2,2-trifluoroethylidenebenzylamine in 60 ml. of anhydrous ether contained in a well-dried three-necked flask under nitrogen until it was no longer consumed. The ether and excess hydrogen chloride were removed in a stream of nitrogen and the semisolid residue dissolved in 60 ml. of dimethylformamide (dried over molecular sieves). Dicyandiamide (2.52 g., 0.03 mole) was added in one portion, with stirring, the addition being accompanied by a 30° exotherm. After being stirred for an additional 20 min., the reaction mixture, which by this time had cooled to room temperature, was poured into a fairly large amount of ether–acetone (9:1) and the resulting suspension was stirred until the suspended material solidified (in this case, 10 min.). The liquid phase was decanted and the solid was washed with a fresh portion of ether and collected to yield 6.7 g. (73%) of V (R = benzyl; $R_1 = CF_3$; R_2 = H), m.p. 290° dec., after recrystallization from ethanol–acetone (5:1).

With IV (R = *p*-chlorobenzyl or 3,4-dimethoxybenzyl; R_1 = phenyl; R_2 = H), the work-up was modified as follows. The reaction mixture containing suspended solid (unreacted Schiff base) was separated by filtration and the filtrate was poured into a large excess of ether. After being stirred for a few hours and allowed to stand for 3 days, the ether was decanted from the gummy solid, and the latter crystallized from water. Presumably a longer reaction time was necessary in these cases.

Alternatively, a solution of the Schiff base and dicyandiamide in dimethylformamide was treated with a molar equivalent of 1 *N* hydrogen chloride in dimethylformamide and the resulting reaction mixture was processed as described.

Schiff base hydrochlorides which are not very sensitive to atmospheric moisture (*e.g.*, benzylidenebenzylamine, benzylidine-*p*-chlorobenzylamine, and 2,2,2-trimethylethylidenebenzylamine) do not necessarily have to be prepared *in situ*.

4,6-Diamino-1-benzyl-1,2-dihydro-2-phenyl-*sym*-triazine Hydrochloride (V, R = Benzyl; R_1 = Phenyl; R_2 = H) by Fusion of Benzylidenebenzylamine Hydrochloride and Dicyandiamide.—An intimate mixture of 2.3 g. (0.01 mole) of benzylidenebenzylamine hydrochloride (IV, R = benzyl; R_1 = phenyl; R_2 = H) and dicyandiamide was heated at 130–135° for 2 hr. (after 45 min. the solid mixture collapsed to a yellow melt) and cooled to room temperature. The yellow solid was broken up and crystallized from ethanol to give 1.7 g. (57%) of the crystalline 4,6-diamino-1,2-dihydrotriazine hydrochloride, m.p. 227–228°.

Anal. Calcd. for $C_{16}H_{18}ClN_5$: C, 60.91; H, 5.75; N, 22.12. Found: C, 60.95; H, 5.84; N, 22.05.

4,6-Diamino-1-*p*-chlorobenzyl-1,2-dihydro-2-phenyl-*sym*-triazine hydrochloride was similarly prepared in 55% yield by fusing dicyandiamide and benzylidene-*p*-chlorobenzylamine hydrochloride.

Base-Catalyzed Isomerization of 4,6-Diamino-1-benzyl-1,2-dihydro-2-phenyl-*sym*-triazine to 4-Amino-6-benzylamino-1,2-dihydro-2-phenyl-*sym*-triazine (VI).—A solution of 1 g. (0.0032 mole) of 4,6-diamino-1-benzyl-1,2-dihydro-2-phenyl-*sym*-triazine (V, R = benzyl; R_1 = phenyl; R_2 = H) in 40 ml. of aqueous methanolic sodium hydroxide (1:2, pH of reaction mixture, *ca.* 11) was heated on a steam bath for 1 hr. and cooled. The oil which separated was dissolved in a small amount of aqueous ethanol (1:1) and the pH of the solution was adjusted to 6–7 (alkacid test paper) with 1 *N* hydrochloric acid. After 1 week in the refrigerator, 0.48 g. (48%) of crystalline 4-amino-6-benzylamino-1,2-dihydro-*sym*-triazine hydrochloride (VI + HCl) separated, m.p. 174–176°. The infrared spectra of V (R = benzyl; R_1 = phenyl; R_2 = H), and VI + HCl were clearly different.

Anal. Calcd. for $C_{16}H_{18}ClN_5$: C, 60.91; H, 5.75; Cl, 11.22; N, 22.12. Found: C, 60.95; H, 5.84; Cl, 11.16; N, 22.05.

Preparation of Schiff Bases.—The Schiff bases employed were prepared as described by Overberger, *et al.*,[11] with the exception of isopropylidenebenzylamine. The latter was prepared as described by Kuhn and Schretzmann.[12]

2,2,2-Trifluoroethylidenebenzylamine.— Commercially available (Aldrich Chemical) ethyl trifluoroacetaldehyde hemiacetal was used for Schiff base formation in the Overberger procedure. The Schiff base boiled at 49° (2 mm.).

Anal. Calcd. for $C_9H_8F_3N$: C, 57.75; H, 4.30; F, 30.45; N, 7.48. Found: C, 57.78; H, 4.34; F, 30.4; N, 7.45.

Reaction of Hexafluoroacetone with Benzylamine.—A stream of hexafluoroacetone (Allied Chemical) was slowly bubbled through a cooled solution of 21.4 g. (0.2 mole) of benzylamine in benzene (reaction was exothermic) until the ketone was no longer consumed. A catalytic amount of *p*-toluenesulfonic acid was added and the solution was heated under reflux for 17 hr., a Dean–Stark trap containing Dri-Na (Baker) providing for water separation. The liquid residue obtained by evaporating the benzene was distilled *in vacuo* to yield 37 g. of a colorless liquid, b.p. 76–78° (0.5 mm.). The compound could be stored in a dry flask under nitrogen; however, it solidified (bicarbonate?, hydrate?) on short exposure to the atmosphere.

Acknowledgment.—We thank Dr. G. Berkelhammer for his continued interest and Mr. R. Wayne for the n.m.r. spectrum.

(7) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(8) Taken in carbon tetrachloride with tetramethylsilane as an internal standard on a Varian A-60 spectrometer.

(9) While this investigation was in progress, we became aware of the work of Carrington, *et al.*,[2b] in which they prepared V (R = R_1 = phenyl; R_2 = H) in "small" yield, by the reaction of benzylideneaniline and dicyandiamide in aqueous acid. However, as they point out, the Schiff base is hydrolyzed under the reaction conditions and what is probably being observed is a three-component synthesis.[2d]

(10) Melting points are corrected. Microanalyses are by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken as mulls in Nujol with a Perkin-Elmer infracord spectrophotometer.

(11) C. G. Overberger, N. P. Marullo, and R. G. Hiskey, *J. Am. Chem. Soc.*, **83**, 1374 (1961).

(12) R. Kuhn and H. Schretzmann, *Chem. Ber.*, **90**, 557 (1957).

Investigations in Heterocycles. XVII. An Unusual Transformation of a 4-Phenylthiazole Derivative to a Tetracyclic Heteroaromatic System

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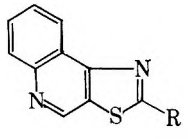
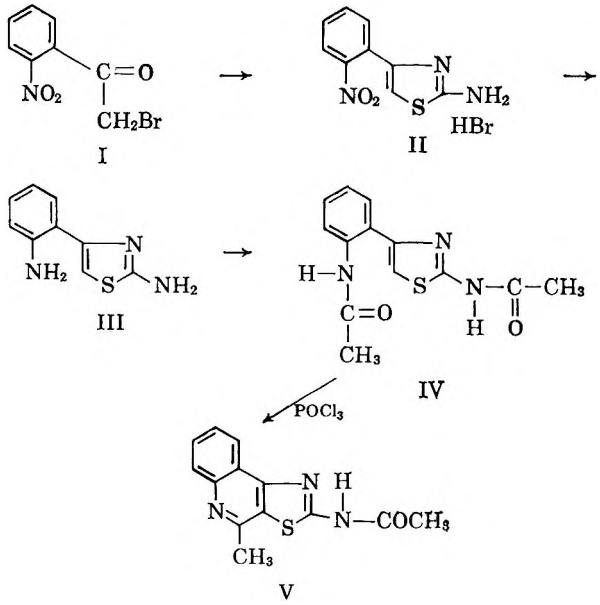
A considerable amount of interest has been deployed of late toward the synthesis of polycyclic heterocycles in which the hetero atoms are present in more than one ring. Some examples of this group of compounds are pyrrolothiophenes,[1] thiazolopyrimidines,[2] pyrazolopyrimidines,[3] and pyrazolo[1,5-*c*]quinazolines.[4] In accordance with similar studies in our laboratory, it was our intention to synthesize some quinolino[4,3-*d*]thiazoles, a heterocyclic system heretofore unreported in the literature.



Quinolino[4,3-*d*]thiazole

It appeared that the most direct route to this system would be through the 4-(2-nitrophenyl)thiazole derivatives. The sequence of reactions which could conceivably lead to a desired quinolino[4,3-*d*]thiazole (V) is shown in Scheme I.

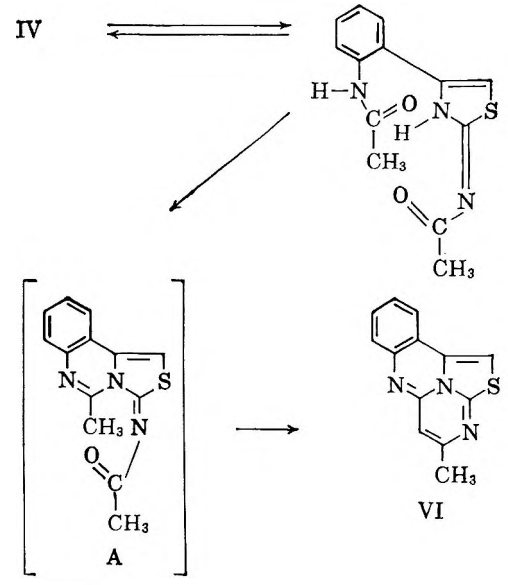
SCHEME I



Thus *o*-nitroacetophenone was brominated to form the α-bromo ketone I which was allowed to react with thiourea in refluxing ethyl alcohol to give 2-amino-4-(2-nitrophenyl)thiazole hydrobromide (II) in excellent yield. Compound II was then reduced catalytically to afford 2-amino-4-(2-aminophenyl)thiazole hydrobromide (III); the conversion in this case was virtually quantitative. Acetylation of compound III with 2 equiv. of acetyl chloride gave a diacetamide whose absorption band in the carbonyl region of the infrared was found at 1687 cm.$^{-1}$. This spectral evidence rules out a 2,2- or 4,4-diacetamide derivative, since it is well known[5] that such imido groups absorb at about 1770 cm.$^{-1}$. Therefore, the acetylation product was assigned structure IV. On treating IV with excess phosphorous oxychloride, a rather vigorous reaction occurred with the liberation of much hydrogen chloride. Work-up of the reaction mixture and fractionation of the main extract by means of thin-layer chromatography resulted in the isolation, in about 15% yield, of bright orange plates whose elemental analysis corresponded to a substance having an empirical formula of $C_{13}H_9N_3S$. Molecular weight determination by osmometry gave a value of 249. These data suggest that intramolecular condensation had occurred through the elimination of 2 equiv. of water.

Ultraviolet absorption maxima at 277 mμ (ϵ 32,050) and 347 (10,564) suggested a highly aromatic system. The N–H and OH regions of the infrared were devoid of absorption bands; only one weak absorption band was present at 3080 cm.$^{-1}$, indicative of aromatic CH. Two strong bands were noted at 1630 and 1590 cm.$^{-1}$. These are considered to be characteristic of the quinoline nucleus in polycyclic systems.[6] In the n.m.r. spectrum there is a doublet at δ 2.02 assigned to a group adjacent to a vinyl proton. This vinyl proton in turn gives a quartet at δ 5.58 due to its splitting with the methyl group. A second vinyl proton seen as a sharp singlet was shown at δ 5.90. This is characteristic of a vinyl proton adjacent to sulfur in heterocyclic systems.[7] Finally there was exhibited a complex pattern at δ 6.57 to 7.25. This corresponds to four aro-

SCHEME II



(1) W. Carpenter and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 2592 (1960).
(2) T. Takahashi, T. Maito, and S. Inoue, *Chem. Pharm. Bull.*, **6**, 334 (1958).
(3) P. Schmidt, K. Eichenberger, and M. Wilhelm, *Angew. Chem.*, **73**, No. 1, 15 (1961).
(4) G. deStevens, A. Halamandaris, M. Bernier, and H. M. Blatter, *J. Org. Chem.*, **28**, 1336 (1963).
(5) J. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1958, p. 221.
(6) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 3368 (1958).
(7) "Varian Spectra Catalog," Vol. II, No. 380 and 651.

matic protons, two of which show different chemical shifts.

The above analytical and spectral data have led us to assign structure VI to this substance. The n.m.r. strongly supports this assignment. The formation of VI can be readily explained if one considers firstly that the 2-acetamido group can readily tautomerize, and secondly that the thiazolyl and phenyl groups can and do undergo free rotation readily. Under these conditions, the initial dehydration step can occur to form intermediate A which is then favorably disposed to undergo a second dehydration to form VI. We have named this compound 4-methyl-2-thia-3,6,10c-triazoaceanthrylene. (See Scheme II.)

Experimental

2-Amino-4-(2-nitro phenyl)thiazole Monohydrobromide (II).—A solution of 2-nitro-ω-bromoacetophenone[8] (24.4 g., 0.1 mole) in ethyl alcohol (250 ml.) was treated with 7.6 g. of thiourea and the reaction mixture was heated under reflux for 4 hr. On cooling and addition of ethyl acetate to the concentrated reaction solution crystals appeared which were collected. Three recrystallizations from ethyl alcohol–ethyl acetate gave 20 g. of pure material, m.p. 179–180°.

Anal. Calcd. for $C_9H_8BrN_3O_2S$: C, 35.77; H, 2.66; N, 13.91. Found: C, 35.90, H, 2.91; N, 13.83.

2-Amino-4-(2-aminophenyl)thiazole Monohydrobromide (III).—A solution of 2-amino-4-(2-nitrophenyl)thiazole monohydrobromide (15.1 g., 0.05 mole) in 100 ml. of alcohol was shaken with hydrogen under pressure (45 lb./in.²) at room temperature using 6 g. of 10% palladium-charcoal catalyst. After the theoretical amount of hydrogen was taken up, the catalyst was filtered off and washed with 100 ml. of methanol. The washings were combined with the filtrate; the solution was evaporated to dryness to afford 12 g. of crystalline residue. Recrystallization with methanol–ethyl acetate gave a pure material, m.p. 224–225°.

Anal. Calcd. for $C_9H_{10}BrN_3S$: C, 40.16; H, 3.72; N, 15.50. Found: C, 39.95; H, 3.67; N, 15.46.

2-Acetamido-4-(2-acetamidophenyl)thiazole (IV).—The base from above salt (5.7 g.) was dissolved in tetrahydrofuran (80 ml.) and treated with pyridine (4.7 ml.). This solution was warmed to 40° and treated with 4.5 g. of acetyl chloride and boiled under reflux for 2 hr. The solvent was removed under reduced pressure; the residue was suspended in water. The suspension was extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate and evaporated to dryness. This gave 5.0 g. of diacetamide which was recrystallized from methanol–ethyl acetate to yield pure white crystals, 242–243°.

Anal. Calcd. for $C_{13}H_{13}O_2N_3S$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.48; H, 4.85; N, 15.34.

4-Methyl-2-thia-3,6,10c-triazoaceanthrylene (VI).—2-Acetamido-4-(2-acetamido phenyl)thiazole (2.0 g.) was treated with 6 ml. of phosphorus oxychloride. The reaction mixture was warmed on the steam bath for 12 min. and later boiled under reflux for 1.5 hr. The excess of phosphorus oxychloride was distilled under reduced pressure on the steam bath and the residue was carefully diluted with water (125 ml.). The gummy suspension was washed with ethyl acetate. The aqueous extract was made basic with 2 *N* sodium hydroxide solution (50 ml.) and the suspension was extracted with ethyl acetate (500 ml.). This extract was dried over anhydrous sodium sulfate and evaporated to dryness (0.8 g.). On chromatography on chromatoplates, the following fractions were obtained: fraction A, 5-cm. movement, 250 mg., highly crystalline, m.p. 208–209°; fraction B, 8-cm. movement, 140 mg., residue not crystalline; fraction C, 9-cm. movement, 140 mg., residue amorphous. Recrystallization of fraction A from ethyl alcohol gave pure material, m.p. 214–215°, which remained unchanged on repeated recrystallizations.

Anal. Calcd. for $C_{13}H_9N_3S$: C, 65.26; H, 3.79; N, 17.57; S, 13.38; mol. wt., 239.23. Found: C, 65.07; H, 3.76; N, 17.35; S, 13.55; mol. wt., 249.

(8) H. Gevekoht, *Ann.*, **221**, 327 (1883).

Mass Spectrometry for Structure Determination. Simple Nitrogen Heterocycles

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Received October 23, 1963

A number of recent studies[1-6] have demonstrated the utility of mass spectrometry in organic structure determinations. The method basically consists of the identification of modes of fragmentation which are characteristic of certain structural features. A careful study of the fragmentation patterns of related known compounds and application of the information so obtained to the spectrum of the unknown sample reveals structural information concerning the unknown.

As a basis for extension of the technique, we have examined the mass spectra of twenty simple nitrogen heterocyclic compounds, fourteen of which have not previously been reported. The instrument used in this work was a Consolidated Engineering Corp. mass spectrometer Model 21-102, modified to perform as the Model 21-103C, with the exception that the original four-coil magnet has been retained. Additionally, the instrument has been modified for high temperature sample introduction and automatic mass to charge ratio (m/e) marking.

The complete spectra obtained are too lengthy for reproduction here, but they have been submitted for distribution through Committee E-14 of the American Society for Testing Materials.[7] The purpose of this note is to point out certain features which are thought to have general structural significance. The structures of the fragments discussed are postulated from the standpoint of the driving force for their formation. This driving force is usually the formation of a very stable molecule or ion.[1] Rearrangement processes were in evidence and were particularly common when migration of hydrogen atoms was involved.[2] Since there are frequently several different fragments formed by different modes of fragmentation or rearrangement that can appear at the same m/e ratio, the absence of a peak may be of more conclusive diagnostic significance than the appearance of a peak.

As shown in Table I, a significant (greater than 5%) m/e of 28 was present in the spectra of all compounds investigated except 2-methylcarbazole. Owing to the

(1) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, and references therein.

(2) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1960.

(3) J. L. Courtney and J. A. Shannon, *Tetrahedron Letters*, **1**, 13 (1963), and references therein.

(4) F. W. McLafferty, "Determination of Organic Structures by Physical Methods," Vol. 2, F. C. Nachod and W. D. Phillips, Ed., Academic Press, New York, N. Y., 1961.

(5) T. Nakano and C. Djerassi, *J. Org. Chem.*, **26**, 167 (1961).

(6) J. H. Beynon and A. E. Williams, *Appl. Spectry.*, **13**, 101 (1959); **14**, 27 (1960).

(7) These spectra have also been deposited as Document number 7914 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $6.25 for photoprints or $2.50 for 35-mm. microfilm. Advance payment is required. Make checks or money orders payable to Chief, Photoduplication Service, Library of Congress.

TABLE I

RELATIVE INTENSITIES OF DISCUSSED FRAGMENTS[a]

Compounds	N_2^+	CNH_2^+	$C_3H_3^+$	M–HCN	M–C_2H_4	M–C_2H_3O
2-Methylcarbazole			5			
Imidazole		48		80		
2-Ethylbenzimidazole		11	12	5		
Indole		11	10	38		
3-Acetylindole		9	6			100
Pyrrole		84	84	64		
1-Methylpyrrole		17	37		28	
1-Phenylpyrrole		9	26		52	
3-Acetyl-2,4-dimethylpyrrole		17	15			100
2-Methylpyrazine		23	34	56		
2,5-Dimethylpyrazine		18	46	10		
2,6-Dimethylpyrazine		25	67	6		
Pyrazole	49[b]	49[b]	29	60		
3-Methylpyrazole	44[b]	44[b]	11	10		
3,5-Dimethylpyrazole	23		33		6	
Indazole	14[b]	14[b]	12	33		
2-Aminopyrimidine		45	15			
4,6-Dimethylpyrimidine		29	54	29		
3-Amino-1,2,4-triazole	100[b]	100[b]		28		
4-Amino-1,2,4-triazole	100[b]	100[b]		5		

[a] Intensities are given in per cent of base peak and are listed only if they are greater than 5%. [b] Combination of both N_2^+ and CNH_2^+.

improbability of intermolecular collisions, N_2^+ may be considered a significant contributor only when nitrogen atoms are adjacent in the molecule. Therefore, with the exception of such molecules, CNH_2^+ appears to be the main contributor to a *m/e* of 28. Of the compounds investigated, pyrrole had the largest *m/e* of 28 attributed to CNH_2^+. This might be anticipated, as this fragment may be formed in two ways from pyrrole and does not require rearrangement for formation. Owing to the many possible rearrangements that could occur, it does not seem feasible to make structural predictions based on the appearance of a *m/e* of 28. However, the absence of such a *m/e* of 28 could be of value. For example, based on this investigation, the absence of a *m/e* of 28 would eliminate the possibility of adjacent nitrogen atoms in a given nitrogen heterocyclic compound. Additionally, the possibility of an unsubstituted ring nitrogen atom between two carbon atoms with two hydrogen atoms attached to the C–N structure would be eliminated.

Another positive ion which appeared in significant amount was $C_3H_3^+$, which is most probably the cyclopropenium cation.[4] A peak at a *m/e* of 39 appeared in the spectra of all molecules examined in which there were three or more carbon atoms in a chain with at least three hydrogen atoms among them. A comparison of the values for the *m/e* of 39 for the various compounds studied and their structures demonstrates clearly the correlation between the number of ways a fragment may form and its probability of formation. For example, it is interesting to note that the per cent of the base peak for the $C_3H_3^+$ fragment of 2,6-dimethylpyrazine was almost twice that of the 2-methylpyrazine. Such comparisons cannot, of course, be made between unrelated compounds. The high stability of the carbazole ring structure is reflected in a lower degree of fragmentation than is observed in the pyrazines. Again, the widespread appearance of the *m/e* 39 peak makes its absence in a given spectrum especially important. Based on this investigation, the nonappearance of a significant *m/e* of 39 indicates the absence of a three-carbon chain with at least three hydrogen atoms attached.

Formation of the neutral molecule HCN was indicated several times during this investigation as a driving force for the formation of a positive ion[6]; however, the formation pattern fails to be consistent enough for correlation. This apparent inconsistency also is present in the pattern of formation of the neutral C_2H_4 molecule.

A consideration of the effects produced by the presence of an acetyl group on a nitrogen heterocyclic ring, as evidenced by both data obtained in this study and other reported spectra,[6] reveals that a correlation may be established. It may apparently be concluded that no acetyl group is present on a given nitrogen heterocyclic ring if a significant parent ion minus 43-*m/e* peak is not present in the spectrum.

8,9,10,11-Tetrahydro-12*H*-benzo[5,6]quinoxalino-[2,3-*e*][1,4]diazepin-12-ones. Examples of a New Heterocyclic Ring System

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Received March 6, 1964

The present note describes the preparation of several 8,9,10,11-tetrahydro-12*H*-benzo[5,6]quinoxalino-[2,3-*e*][1,4]diazepin-12-ones (Va–e), examples of a hitherto unreported heterocyclic ring system. The products are shown in Table III.

The first member of the new series, 8,9,10,11-tetrahydro-12*H*-benzo[5,6]quinoxalino[2,3-*e*][1,4]-diazepin-12-one (Va), was prepared by the sequence shown. Treatment of ethyl cyanoacetate with 2-amino-

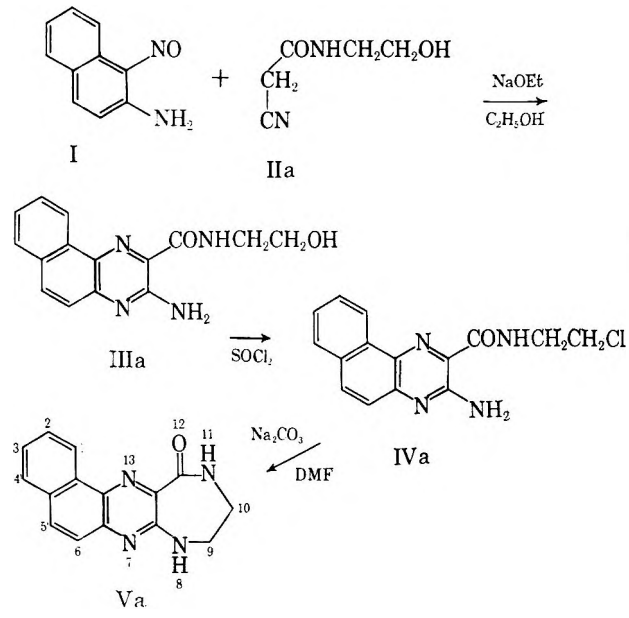
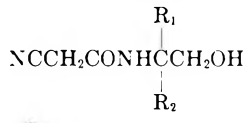


TABLE I

2-CYANO-*N*-(2-HYDROXYALKYL)ACETAMIDES

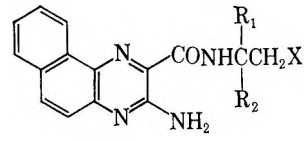


No.	R_1	R_2	M.p., °C.	Recrystg. solvent[a]	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IIa[b]	H	H	61–62	A	65	$C_5H_8N_2O_2$	46.87	6.29	21.87	46.81	6.20	21.97
b	C_2H_5	H	87–88	A, B	92	$C_7H_{12}N_2O_2$	53.83	7.74	17.94	54.08	7.76	17.83
c	CH_3	CH_3	68–70	A, B	90	$C_7H_{12}N_2O_2$	53.83	7.74	17.94	53.64	7.81	17.62
d	CH_3	CH_2OH	130.5–131.5	A, C	74	$C_7H_{12}N_2O_3$	48.83	7.03	16.27	49.02	7.30	16.42

[a] A = ethyl acetate, B = petroleum ether (b.p. 30–60°), C = ethanol. [b] O. K. Behrens, J. Corse, D. E. Huff, R. G. Jones, Q. F. Soper, and C. W. Whitehead, *J. Biol. Chem.*, **175**, 771 (1948).

TABLE II

3-AMINO-*N*-(2-SUBSTITUTED ALKYL)BENZO[*f*]QUINOXALINE-2-CARBOXAMIDES

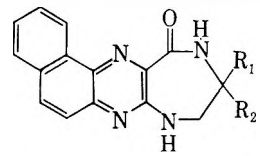


No.	R_1	R_2	X	M.p., °C.	Recrystg. solvent[a]	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IIIa	H	H	OH	181–182	C	66	$C_{13}H_{14}N_4O_2$	63.82	5.00	19.85	64.24	5.21	19.91
b	C_2H_5	H	OH	210–212	C	72	$C_{17}H_{18}N_4O_2$	65.79	5.85	18.05	65.84	5.80	18.07
c	CH_3	CH_3	OH	200–203	C	53	$C_{17}H_{18}N_4O_2$	65.79	5.85	18.05	65.75	5.82	18.16
d	CH_3	CH_2OH	OH	218–219.5	D, E	54	$C_{17}H_{18}N_4O_3$	62.56	5.56	17.17	62.55	5.27	16.90
IVa	H	H	Cl	231.5–232.5	A	75	$C_{13}H_{13}ClN_4O$	59.90	4.36	18.63	60.04	4.24	18.43
b	C_2H_5	H	Cl	211–212	B	96	$C_{17}H_{17}ClN_4O$	62.10	5.21	17.04	62.15	5.16	16.92
c[b]	CH_3	CH_3	Cl	100–105		70							
d	CH_3	CH_2Cl	Cl	183–184	A	71	$C_{17}H_{16}Cl_2N_4O$	56.20	4.44	15.42	56.36	4.49	15.60

[a] A = benzene, B = xylene, C = ethanol, D = water, E = *N*,*N*-dimethylformamide. [b] Attempts to obtain an analytically pure sample were unsuccessful. The compound was used without further purification.

TABLE III

8,9,10,11-TETRAHYDRO-12*H*-BENZO[5,6]QUINOXALINO[2,3-*e*][1,4]DIAZEPIN-12-ONES



No.	R_1	R_2	M.p., °C.	Recrystg. solvent[a]	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Va	H	H	258–260	D	75	$C_{15}H_{12}N_4O$	68.17	4.58	21.20	68.43	4.62	21.23
b	C_2H_5	H	168–170	B, D	91	$C_{17}H_{16}N_4O$	69.84	5.52	19.17	69.94	5.41	18.92
c	CH_3	CH_3	200–205	B, C	67	$C_{17}H_{16}N_4O$	69.84	5.52	19.17	69.84	5.50	19.18
d	CH_3	CH_2Cl	215–216	A	56	$C_{17}H_{15}ClN_4O$	62.48	4.63	17.15	61.96	4.59	16.60
e	CH_3		192–194	A	44	$C_{21}H_{23}N_5O_2$	66.82	6.14	18.56	66.64	6.06	18.81

[a] A = benzene, B = water, C = methanol, D = *N*,*N*-dimethylformamide.

ethanol yielded 2-cyano-*N*-(2-hydroxyethyl)acetamide (IIa). The reaction of 1-nitroso-2-naphthylamine (I) with IIa gave 3-amino-*N*-(2-hydroxyethyl)benzo[*f*]quinoxaline-2-carboxamide (IIIa).[1] 3-Amino-*N*-(2-chloroethyl)benzo[*f*]quinoxaline-2-carboxamide (IVa) was obtained by the reaction of IIIa with thionyl chloride. Cyclodehydrochlorination of IVa with sodium carbonate in boiling *N*,*N*-dimethylformamide proceeded smoothly to afford Va in excellent yield. The other examples of this new ring system (Vb–d) were prepared in similar fashion *via* the reaction sequence previously described. The intermediates IIb–d, IIIb–d, and IVb–d are given in Tables I and II.

The reaction of 10-chloromethyl-8,9,10,11-tetrahydro-10-methyl-12*H*-benzo[5,6]quinoxalino[2,3-*e*][1,4]-diazepin-12-one (Vd) with morpholine afforded 8,9,10,-11-tetrahydro-10-methyl-10-morpholinomethyl-12*H*-benzo[5,6]quinoxalino[2,3-*e*][1,4]diazepin-12-one (Ve).

8,9,10,11-Tetrahydro-12*H*-benzo[5,6]quinoxalino[2,3-*e*][1,4]diazepin-12-thione was prepared by the reaction of Va with phosphorus pentasulfide in boiling pyridine solution.

Experimental[2]

The procedures for the preparation of compounds IId, IIId, IVd, and Vd are general and were used in the preparation of the other members of the series (given in Tables I–III).

(1) D. G. I. Felton, T. S. Osdene, and G. M. Timmis, *J. Chem. Soc.*, 2895 (1954).

(2) Melting points were taken in capillary tubes (Thomas–Hoover capillary melting point apparatus) on a corrected basis.

2-Cyano-*N*-[1,1-bis(hydroxymethyl)ethyl]acetamide (IId).—A solution of 10.5 g. of 2-amino-2-methyl-1,3-propanediol and 11.3 g. of ethyl cyanoacetate in 50 ml. of absolute ethanol was heated under reflux for 1 hr. The solvent was removed *in vacuo* on a rotary evaporator. The solid residue amounted to 21 g., m.p. 127–130°. Recrystallization from ethyl acetate–ethanol afforded 12.7 g. of product, m.p. 130.5–131.5°.

3-Amino-*N*-[1,1-bis(hydroxymethyl)ethyl[benzo[*f*]quinoxaline-2-carboxamide (IIId).—To a solution of 0.9 g. of sodium metal in 200 ml. of absolute ethanol was added 6.9 g. of 1-nitroso-2-naphthylamine and 7.4 g. of 2-cyano-*N*-[1,1-bis(hydroxymethyl)-ethyl]acetamide. The reaction mixture was heated under reflux for 35 min. The solvent was removed *in vacuo* on a rotary evaporator. The solid residue was triturated with glacial acetic acid and then was washed with water. Continuous extraction of the solid with benzene afforded a total of 7 g. of product, m.p. 211–213°. Recrystallization from aqueous *N*,*N*-dimethylformamide afforded 4 g. of product, m.p. 218–219.5°.

3-Amino-*N*-[1,1-bis(chloromethyl)ethyl]benzo[*f*]quinoxaline-2-carboxamide (IVd).—A solution of 10 g. of 3-amino-*N*-[1,1-bis-(hydroxymethyl)ethyl]benzo[*f*]quinoxaline-2-carboxamide in 100 ml. of thionyl chloride was heated under reflux for 2 hr. The solvent was removed *in vacuo* on a rotary evaporator. The residue was made basic with 10% sodium carbonate solution, filtered, and washed thoroughly with water. The crude product amounted to 7.9 g., m.p. 176–181°. Several recrystallizations from benzene raised the melting point to 183–184°.

10-Chloromethyl-8,9,10,11-tetrahydro-10-methyl-12*H*-benzo-[5,6]quinoxalino[2,3-*e*][1,4]diazepin-12-one (Vd).—To a solution of 3 g. of IVd in 20 ml. of *N*,*N*-dimethylformamide was added 1.5 g. of powdered, anhydrous sodium carbonate. The reaction mixture was allowed to boil under reflux for 1 hr. and was then filtered. Water was added to the filtrate until precipitation of the product was complete. After filtration, the product had m.p. 212–214° and weighed 3.9 g. Recrystallization from benzene afforded 1.5 g. of product, m.p. 215–216°.

8,9,10,11-Tetrahydro-10-methyl-10-morpholinomethyl-12*H*-benzo[5,6]quinoxalino[2,3-*e*][1,4]-diazepin-12-one (Ve).—A solution of 3 g. of Vd in 30 ml. of morpholine was heated under reflux for 24 hr. The reaction mixture was cooled in ice and 10 ml. of water was added. A yellow precipitate was deposited which after removal by filtration amounted to 3 g., m.p. 192–193°. Several recrystallizations from benzene afforded 1 g. of product, m.p. 192–194°

8,9,10,11-Tetrahydro-12*H*-benzo[5,6]quinoxalino[2,3-*e*][1,4]-diazepin-12-thione.—To a solution of 2 g. of Va in 30 ml. of dry pyridine was added 2 g. of phosphorus pentasulfide. The reaction mixture was boiled under reflux for 80 min., cooled to room temperature, and poured into 70 ml. of hot water. The precipitate which deposited amounted to 2.5 g. After recrystallization from aqueous pyridine, the melting point was 254–256°.

Anal. Calcd. for $C_{15}H_{12}N_4S$: C, 64.26; H, 4.32; N, 19.99; S, 11.44. Found: C, 64.66; H, 4.17; N, 19.96; S, 11.55.

Acknowledgment.—The authors are indebted to Mr. Ronald D. Stewart for technical assistance and Dr. Gordon Ellis and staff for microanalytical results.

The Synthesis of a 1,3-Benzothiazine by a Novel Rearrangement of an N-Substituted Saccharin Derivative

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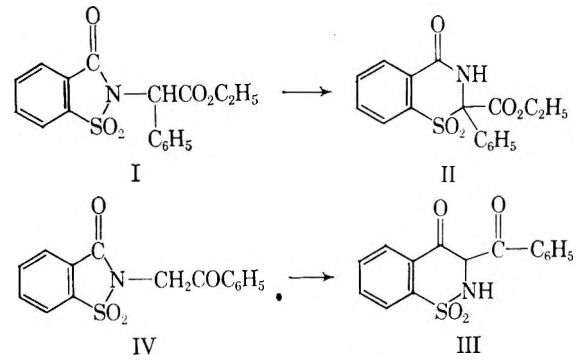
We wish to report the base-catalyzed ring expansion of an N-substituted saccharin derivative to give a 1,3-benzothiazine. Treatment of N-(α-phenylcarbethoxymethyl)saccharin (I) with sodium ethoxide in ethanol resulted in the formation of ethyl 3,4-dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-dioxide (II) in 44% yield. This is in contrast to the work of Abe, *et al.*,[1] who obtained the 1,2-benzothiazine; III, when IV was made to undergo the same reaction



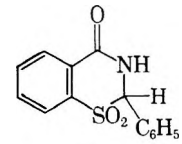
I II

IV III

conditions.[2] The latter reaction, which involves cleavage of a carboxamide linkage, has its counterpart in the phthalimide series.[3] These divergent reaction paths may be related to the relative stabilities of the carbanions formed by abstraction of an α-hydrogen from either I or IV. The formation of III from IV could arise by initial ethanolysis of the amide followed by a Dieckmann ring closure. On the other hand, the formation of the more stable carbanion from I may be favored over ethanolysis and this could react by direct attack on the electrophilic SO_2 group to give II.[4]

Reaction of II with sodium hydride in dimethylformamide followed by the addition of methyl iodide afforded the N-methyl derivative V. When this was subjected to aqueous ethanolic sodium hydroxide at room temperature, rapid saponification and decarboxylation took place to give 3-methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1,1-dioxide (VI).

Alkaline treatment of the parent compound (II) resulted in destruction of the 1,3-benzothiazine system as was shown by the rapid liberation of benzaldehyde as well as by the isolation of *o*-carboxybenzenesulfinic acid.[5] Evidently, initial saponification and decarboxylation took place to give VII. Since the N-methyl derivative (VI) was stable to base, the cleavage of the ring may have been initiated by alkaline removal of the amide proton. The instability of VII to alkali was



VII

confirmed by the immediate odor of benzaldehyde which was detected when a crystalline sample was stirred with aqueous alkali. Compound VII was isolated

(1) K. Abe, S. Yamamoto, and K. Matsui, *J. Pharm. Soc. Japan*, **86**, 1058 (1956); *Chem. Abstr.*, **51**, 3499 (1957).

(2) We have confirmed this work.

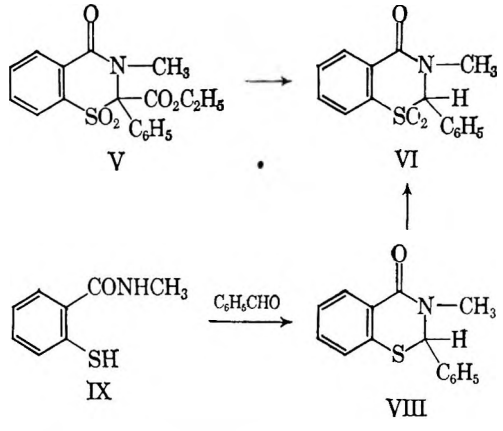
(3) S. Gabriel and J. Colman, *Ber.*, **33**, 980, 2630 (1900); **35**, 2421 (1902).

(4) Both of these mechanisms have been offered to explain the related rearrangement of α-phthalimidoacetic esters and α-phthalimido ketones to give 4-hydroxyisocarbostyrils; W. J. Gensler, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 378; C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).

(5) E. Böhme and W. Schmidt [*Arch. Pharm.*, **286**, 330 (1953)] report the formation of *o*-carboxybenzenesulfinic acid by acid hydrolysis of 3,4-dihydro-2-methyl-4-oxo-2*H*-1,3-benzothiazine 1,1-dioxide.

in small yield from a reaction in which I was treated with sodium hydride in dimethylformamide at room temperature.[6]

The structure of VI was confirmed by an independent synthesis. 3-Methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3H)-one (VIII) was prepared by the acid-catalyzed condensation of N-methylthiosalicylamide (IX) with benzaldehyde as described by Moreau and Delacoux.[7]



Treatment of this sulfide with hydrogen peroxide in acetic acid at room temperature for 24 hr. resulted in the formation of the corresponding sulfoxide. Continued oxidation for 10 days gave the sulfone VI which was identical in every respect with the product obtained from alkaline treatment of V.

Experimental[8]

N-(α-Phenylcarbethoxymethyl)saccharin (I).—A mixture of 200 g. (0.8 mole) of ethyl α-bromophenylacetate, 250 g. (1.2 moles) of sodium saccharin, and 500 ml. of dimethylformamide was heated with stirring at 105–115° for 45 min. and was poured into 5 l. of water. The resulting gum was solidified by trituration with several portions of water. The solid was dissolved in methylene chloride; the solution was washed with water, dried over sodium sulfate, and concentrated to a small volume. To this was added 300 ml. of ethanol and the resulting solution was distilled at atmospheric pressure until crystals began to separate. On cooling, there was obtained 150.5 g. of product, m.p. 127–128°. The analytical sample was prepared by dissolving a portion in a mixture of methylene chloride and ethanol and distilling at atmospheric pressure until crystals began to separate; it had m.p. 129–130°.

Anal. Calcd. for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06; S, 9.28. Found: C, 58.88; H, 4.48; N, 4.08; S, 9.42.

Ethyl 3,4-Dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-Dioxide (II).—A solution of sodium ethoxide, prepared from 6.9 g. (0.3 mole) of sodium and 135 g. of ethanol, was heated to 40° and 51.8 g. (0.15 mole) of N-(α-phenylcarbethoxymethyl)saccharin was added all at once as the powder. The mixture was quickly heated to 50–55° and maintained at this temperature for 5 min. It was then rapidly cooled to 25° and 150 ml. of 9% hydrochloric acid was added as rapidly as was consistent with maintaining the temperature at 30–35°. The ethanol was removed by distillation *in vacuo* and the remaining aqueous solution was extracted with methylene chloride. Evaporation of the dried (sodium sulfate) methylene chloride solution gave an oil which was crystallized by dissolving in 50 ml. of ethanol, concentrating to about one-half the volume, and refrigerating. There was obtained 19.5 g. (37%) of product, m.p. 137–138°. Recrystallization from ethanol gave material, m.p. 139–140°; ν_{max} 3200, 1680, and 1154 cm.$^{-1}$; λ_{max} mμ (ε), 265 sh (2860), 271 sh (2655), 278 (2540), 286 sh (2020); λ_{min} 275 (2480).

Anal. Calcd. for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06; S, 9.28. Found: C, 59.33; H, 4.34; N, 4.27; S, 9.25.

Evaporation of the solvent from the mother liquor of the initial crystallization and trituration of the residue with isopropyl ether gave a solid which was recrystallized from isopropyl alcohol to give 3.5 g. (7%) of material, m.p. 120–124°; this was shown by infrared and thin-layer chromatography to be a slightly impure sample of the first crop product. The remainder of the reaction product could not be purified further. A thin-layer chromatogram gave six spots, one of which (estimated to represent 15–20% of the total) corresponded to II.

Ethyl 3,4-Dihydro-3-methyl-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-Dioxide (V).—To a slurry of 4.0 g. of a 53.4% mineral oil dispersion of sodium hydride (0.075 mole) in 250 ml. of dimethylformamide was added a solution of 26.0 g. (0.075 mole) of ethyl 3,4-dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-dioxide (II) in 250 ml. of dimethylformamide, the temperature being maintained at 0 to 10° during the addition. The reaction mixture was stirred at room temperature for 2.5 hr. and 30 ml. of methyl iodide was added while maintaining the temperature at 0 to 10° during the addition. After stirring for 1 hr. at room temperature, the mixture was poured into 2 l. of ice–water. On stirring and scratching, a crystalline solid separated from solution. This was washed with water and dried *in vacuo* at 60° to give 24.6 g. of material, m.p. 90–93°, whose infrared spectrum was practically identical with that of the analytical sample. Recrystallization from 65 ml. of ethanol gave 17 g. of product, m.p. 103–104°. Another recrystallization from ethanol gave analytically pure material, m.p. 104–105°; ν_{max} 1744, 1674, 1235, and 1165 cm.$^{-1}$; λ_{max} mμ (ε), 266 (2900), 272 (3100), 279 (3100), 287 (2640); λ_{min} 262 (2700), 268 (2850), 275 (2920), 285 (2600).

Anal. Calcd. for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90; S, 8.92. Found: C, 60.02; H, 4.83; N, 3.76; S, 9.21.

Reaction of Ethyl 3,4-Dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-Dioxide (II) with Alkali.—When a solution of 3.5 g. (0.01 mole) of ethyl 3,4-dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-dioxide in 40 ml. of 0.05 *N* sodium hydroxide was prepared at room temperature, there was immediately noted the odor of benzaldehyde and the solution became cloudy. After standing overnight at room temperature, the mixture was extracted with ether and the ether was distilled off *in vacuo* to yield 1.0 g. of an almost colorless oil which had the characteristic odor of benzaldehyde. The oil was dissolved in 25 ml. of ethanol and was treated with excess 2,4-dinitrophenylhydrazine reagent to give 1.0 g. of benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 230–235°; recrystallization gave m.p. and m.m.p. 239–240°.

The aqueous layer from the ether extraction was acidified with hydrochloric acid, filtered, and taken to dryness at 30° using a flash evaporator. The residue was extracted with ether using a Soxhlet apparatus and evaporation of the solvent followed by drying *in vacuo* at 40° gave 1.1 g. of *o*-carboxybenzenesulfinic acid, which melted at 120–125°, resolidified, and remelted at 200°[9]; ν_{max} 2520, 1690, 1115, 1070, 1050, and 1020 cm.$^{-1}$.

Anal. Calcd. for $C_7H_6O_4S$: C, 45.16; H, 3.25; S, 17.22. Found: C, 45.25; H, 3.28; N, 0.0; S, 16.78.

3-Methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3H)-one 1,1-Dioxide (VI). A. Preparation by Alkaline Treatment of Ethyl 3,4-Dihydro-3-methyl-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-Dioxide.—To a suspension of 15 g. (0.042 mole) of the ester in 1000 ml. of ethanol was added 84 ml. of 1.0 *N* aqueous sodium hydroxide. After stirring at room temperature for a few minutes, a precipitate began to separate from the solution. The stirring was continued overnight and the precipitate, which was identified as sodium carbonate, was filtered off. The filtrate was concentrated *in vacuo* to a small volume and 3000 ml. of water was added. The resulting white precipitate was col-

(6) Here the same rearrangement took place as with sodium ethoxide in ethanol. The only isolable product (VII) probably arose through saponification and decarboxylation in the alkaline solution resulting from the hydrolysis of the reaction mixture.

(7) R. C. Moreau and E. Delacoux, *Bull. soc. chim. France*, 502 (1962).

(8) Melting points were determined using the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. The infrared spectra were all carried out as Nujol mulls and the ultraviolet spectra were determined as solutions in 95% ethanol. Homogeneity of the analytical samples was checked by thin-layer chromatography on silica gel G (Stahl) using a 50:50 mixture of *n*-heptane and acetone as the eluent. Chromatograms were developed by placing them in a closed vessel containing iodine crystals. We are indebted to Mrs. U. Zeek for the microanalyses and to Mr. R. Puchalski for the spectral data.

(9) Ref. 5 reports m.p. 124–126° followed by resolidification and remelting at 287–291°.

lected by filtration, washed with water, and dissolved in methylene chloride, and the dried (sodium sulfate) methylene chloride solution was distilled to dryness. Trituration of the residue with petroleum ether (b.p. 40–60°) gave 9.7 g. of white crystals, m.p. 170–171°. Recrystallization from ethanol gave material with m.p. 170–171°; ν_{max} 1671 and 1156 cm.$^{-1}$; λ_{max} mμ (ϵ), 270 (3270), 277 (3180), 286 (2680); λ_{min} 268 (3250), 274 (3180), 283 (2500).

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87; S, 11.16. Found: C, 62.61; H, 4.66; N, 4.93; S, 11.21.

B. Preparation by Oxidation of 3-Methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one.—To a solution of 3.5 g. (0.014 mole) of the thioether[7] in 25 ml. of glacial acetic acid was added 20 ml. of 30% hydrogen peroxide. The solution was allowed to stand at room temperature for 10 days and was then poured into 300 ml. of water. The resulting white precipitate was collected, washed well with water, and dissolved in methylene chloride, and the dried (sodium sulfate) methylene chloride solution was distilled to dryness. The residue was triturated with low boiling petroleum ether to give 3.3 g. of product, m.p. 170–171°, which was shown by mixture melting point and by comparison of infrared and ultraviolet spectra to be identical with material prepared by A.

2-Phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1,1-Dioxide (VII).—To a suspension of 0.8 g. of 53.4% mineral oil dispersion of sodium hydride (0.015 mole) in 50 ml. of dimethylformamide was added a solution of 5 g. (0.015 mole) of N-(α-phenylcarbethoxymethyl)saccharin in 25 ml. of dimethylformamide, the temperature being maintained between 0 and 10°. The orange solution was stirred at room temperature for 3 hr. and then was poured into 1000 ml. of absolute ether. A gum separated, and this became a semisolid after several triturations with fresh portions of ether. The semisolid was dissolved in 150 ml. of water and on acidification of this solution with dilute hydrochloric acid there was obtained a white precipitate. This was filtered off, washed with water, and was dried *in vacuo* at 60° to give 0.7 g. of material, m.p. 177–178°. Recrystallization from ethanol yielded a product, m.p. 185–186°; ν_{max} 3200, 1680, and 1154 cm.$^{-1}$; the ultraviolet spectrum was identical with that of the corresponding N-methyl compound (VI).

Anal. Calcd. for $C_{14}H_{11}NO_3S$: C, 61.53; H, 4.06; N, 5.12; S, 11.73. Found: C, 61.37; H, 4.23; N, 5.15; S, 11.64.

On stirring a portion of this compound with 1 *N* sodium hydroxide, there was immediately noted the odor of benzaldehyde.

3-Methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1-Oxide.—To a solution of 5.2 g. (0.02 mole) of 3-methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one in 60 ml. of glacial acetic acid was added 20 ml. of 30% hydrogen peroxide. The solution was allowed to stand at room temperature for 24 hr. and was then poured into 400 ml. of ice–water. Extraction with methylene chloride followed by drying over sodium sulfate and evaporation of the solvent gave an oil. This was crystallized from 40 ml. of ethanol to yield 3.0 g. of product, m.p. 170–172°. Recrystallization did not change the melting point. Mixture melting point with a sample of the corresponding sulfone gave a 20° depression; ν_{max} 1656, 1640, 1052, no significant absorption at 1100–1200 cm.$^{-1}$; λ_{max} mμ (ϵ), 272 (2800), 280 (2750), 289 sh (2420); λ_{min} 276 (2700), 285 (2490).

Anal. Calcd. for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; S, 11.82. Found: C, 66.23; H, 4.80; S, 11.85.

N-Nitrosoamides. VI. Nitrosocarbamates and Nitrosoamides of Amino Acids. The Preparation of Diazoacetic and Diazopropionic Esters[1]

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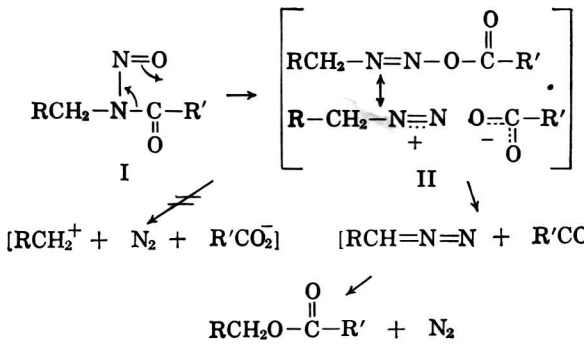
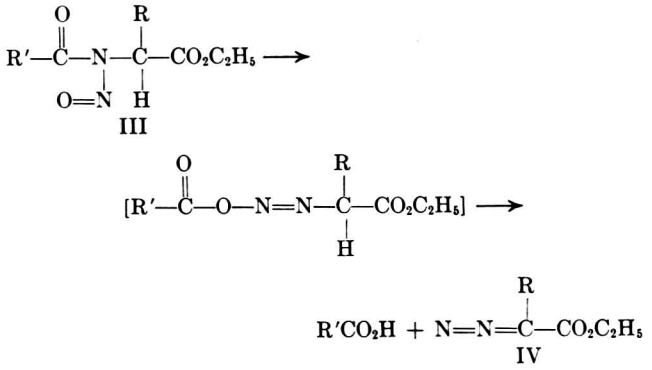
Received January 24, 1964

N-Nitrosoamides of primary carbinamines (I) decompose to give the corresponding esters *via* a reaction

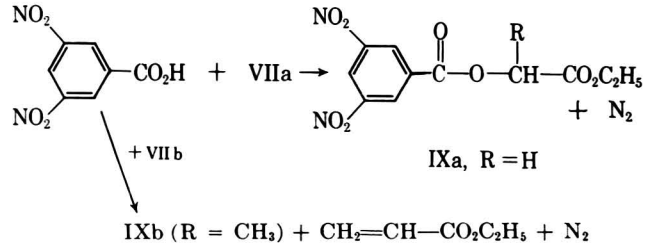


series involving diazo alkanes as intermediates.[3] The carbonium ion pathway, found for the decomposition of nitrosoamides of secondary carbinamines,[1] is not followed, presumably because of the relatively high energy of a primary carbonium ion (formed by the loss of nitrogen from II). The decomposition of nitrosoamides or nitrosocarbamates of amino acid esters (III) also yields the corresponding diazo compound (IV), which, in this case, can be isolated because of the low general reactivity of α-diazocarbonyl compounds. We report here the decomposition of several of these nitroso compounds.[4]



N-Nitrosocarbamates.—These derivatives of glycine and alanine were readily prepared by the acylation of the corresponding esters, and subsequent nitrosation of the carbamates with either nitrogen tetroxide or nitrous acid. The pyrolysis of compounds VIa and VIb at 125–135° and 50–100 mm. (under conditions whereby the product was distilled from the reaction vessel) led to *ca.* 70% yields of the corresponding diazo esters (Scheme I).

The diazo esters were identified through their infrared spectra, and assayed by the reaction with 3,5-dinitrobenzoic acid. These dinitrobenzoate derivatives, which apparently have not been reported previously, were prepared from ethyl chloroacetate and ethyl lactate for comparison purposes. The diazo



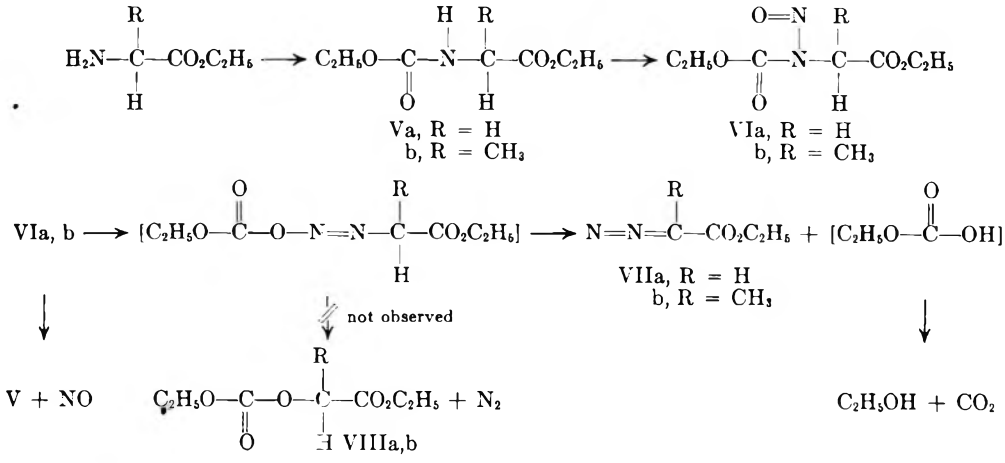
(1) Paper V in this series: E. H. White and C. A. Aufdermarsh, Jr., *J. Am. Chem. Soc.*, **83**, 1179 (1961).

(2) Taken in part from a thesis submitted by R. J. Baumgarten to the Faculty of the Graduate School at The Johns Hopkins University in partial fulfillment of the requirements for the Ph.D. degree.

(3) E. H. White and C. A. Aufdermarsh, Jr., *J. Am. Chem. Soc.*, **83**, 1174 (1961).

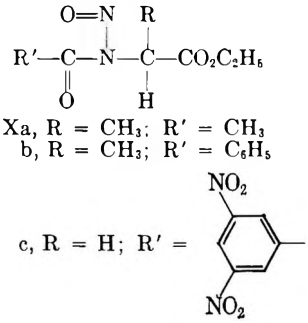
(4) Preliminary results were given by E. H. White, *ibid.*, **77**, 6013 (1955).

SCHEME I



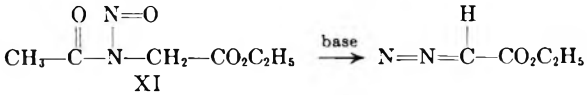
esters were pure as obtained from the reaction. The reaction sequence represents, therefore, a convenient method for the preparation of diazoacetic esters and related compounds. One by-product was found; this is the relatively nonvolatile carbamate V. We have observed the thermal denitrosation of N-nitrosocarbamates in a number of other cases, and, in addition, Newman and Weinberg[5] have shown that some related N-nitrosooxazolidones also undergo pyrolytic denitrosation. The corresponding carbonates (VIII) were not detected among the reaction products.

N-Nitrosamides.—Extension of the reaction to several N-nitrosoamides was less successful. Com-



pounds Xa and Xb yielded mixtures of ethyl diazopropionate and the corresponding acid ($R'CO_2H$) on pyrolysis, whereas compound Xc yielded principally the starting amide, presumably a result of denitrosation catalyzed by the rather strong acid, 3,5-dinitrobenzoic acid.

Ethyl Diazoacetate.—This compound has usually been made by the reaction of nitrous acid with ethyl glycinate.[6] Recently, Reimlinger[7] reported a synthesis based on the reaction of ethyl N-acetyl-N-nitrosoglycinate (XI) with barium oxide. We have found



that sodium ethoxide may also be used as the base; however, the simplest method proved to be the reaction of tetraethylenepentamine with the nitrosoamide under conditions whereby the ethyl diazoacetate could be distilled out of the reaction vessel as it was formed.[8]

(5) M. S. Newman and A. E. Weinberg, *J. Am. Chem. Soc.*, **79**, 2814 (1957).
(6) N. E. Searle, *Org. Syn.*, **36**, 25 (1956).
(7) H. Reimlinger, *Angew. Chem.*, **72**, 33 (1960).
(8) We thank Dr. G. Maier for this experiment.

Experimental

Ethyl N-carbethoxyglycinate (Va) ($n^{19.6}D$ 1.4379, d^{20}_4 1.135, b.p. 78–80° (0.3 mm.), m.p. 26–27°; lit.[9] b.p. 126° (12 mm.), m.p. 27–28°) and **ethyl N-carbethoxyalanate (Vb)**[10] ($n^{12}D$ 1.4391, d^{20}_4 1.080, b.p. 65–70° (0.1 mm.), m.p. 24–25°; lit.[11] b.p. 123° (10 mm.), m.p. 25°) were prepared in 50–80% yields by the method of Fisher and Otto.[9] **Ethyl carbethoxymethyl carbonate (VIIIa)** and **ethyl 1-carbethoxyethyl carbonate (VIIIb)** were prepared by the method of Rehberg, Dixon, and Fisher.[12]

Ethyl N-Carbethoxy-N-nitrosoglycinate (VIa).[13]—Anhydrous sodium acetate (13 g., 0.16 mole) was added to a solution of 10 g. (0.11 mole) of nitrogen tetroxide in 50 ml. of methylene chloride.[14] The solution was cooled to −70° at which time 10 g. (0.057 mole) of carbamate Va was added dropwise while the solution was being stirred. The solution was warmed to 0° and the reaction was allowed to proceed for 20 min. after which most of the nitrogen tetroxide and methylene chloride were evaporated *in vacuo*. The residue was extracted with ether and the extract was washed with sodium carbonate solution and water. After the extract was dried over sodium sulfate, the ether was evaporated *in vacuo* to give nitrosocarbamate VIa which was distilled to yield 11 g. (0.054 mole, 95%) of the yellowish pink nitrosocarbamate, b.p. 60–62° (0.1 mm.), $n^{14}D$ 1.4456, λ_{max} 242 mμ (ε 6.0 × 10³). Compound VIa was also prepared by the aqueous method of White[14] and by the method of Hantzsch and Metcalf.[15]

Ethyl N-Carbethoxy-N-nitrosoalanate (VIb).[13]—The nitrogen tetroxide and nitrous acid methods of White[14] were used to obtain nitrosocarbamate VIb in 55–90% yields [$n^{13}D$ 1.4446, b.p. 38–40° (0.01 mm.), λ_{max} 243 mμ (ε 4.01 × 10³)]. Compound VIb was unstable and decomposed slowly at room temperature.

Pyrolysis of Ethyl N-Carbethoxy-N-nitrosoglycinate (VIa).—Nitrosocarbamate VIa (290 mg., 1.42 mmoles) was heated for 10 hr. at 125–140° (50–100 mm.) in a 2-ml. pear-shaped flask equipped with a fractionating column and a receiver cooled by a Dry Ice–acetone bath. The yellow liquid product was collected in three fractions, and the ethanol was removed from the product by evaporation at 20 mm. The yield of ethyl diazoacetate (VIIa) was 120 mg. (1.05 mmoles, 74%), $n^{21}D$ 1.4611, lit.[6] $n^{25}D$ 1.4616. The infrared spectrum of this sample was identical with the spectrum of ethyl diazoacetate prepared by the reaction of nitrous acid with ethyl glycinate.[6] Treatment of the entire distillate with 3,5-dinitrobenzoic acid yielded 69 mole % of the ester IXa. The infrared spectrum of the brown residue in the distillation flask (60 mg., 0.34 mmole, 24%) was identical with the infrared spectrum of the carbamate Va.

Runs were also made at pressures ranging from atmospheric to 0.2 mm. and at temperatures ranging from 90 to 145°; however, the conditions reported above were optimum. At high pressures and temperatures, the yields were lower, and at pressures less than 1 mm., the reactant distilled.

(9) E. Fisher and E. Otto, *Ber.*, **36**, 2107 (1903).
(10) We wish to thank Donald E. Schmelz for preparing this compound.
(11) E. Fisher and W. Axhausen, *Ann.*, **340**, 139 (1905).
(12) C. E. Rehberg, M. B. Dixon, and C. H. Fisher, *J. Org. Chem.*, **13**, 261 (1948).
(13) Repeated contact with these nitroso compounds led to skin rashes.
(14) E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955); see also ref. 3.
(15) A. Hantzsch and W. V. Metcalf, *Ber.*, **29**, 1682 (1896).

Pyrolysis of Ethyl N-Carbethoxy-N-nitrosoalanate (VIb).—Nitrosocarbamate VIb (2.12 g., 9.72 mmoles) was heated for 8 hr. at 125–135° (50–100 mm.) in the same apparatus used in the pyrolysis of the nitrosocarbamate VIa. The yield of yellow ethyl α-diazopropionate (VIIb) (n^{18}D 1.4489, lit.[16] n^{18}D 1.4472) was 0.89 g. (6.9 mmoles, 71%); the infrared spectrum was consistent with the structure assigned. Treatment with 3,5-dinitrobenzoic acid yielded the ester IXb, m.p. 74.5–76°. An infrared spectrum of the dark residue (0.45 g., 2.4 mmoles, 25%) was identical with the spectrum of carbamate Vb; distillation of the brown residue gave the carbamate Vb (n^{14}D 1.4397). Pyrolyses in the presence of solid sodium carbonate led to essentially the same results. For optimum yields in the pyrolyses, temperatures between 115 and 140° and pressures between 50 and 150 mm. should be used.

Reaction of Ethyl Diazoacetate (VIIa) with 3,5-Dinitrobenzoic Acid.—Ethyl diazoacetate (0.101 g., 0.89 mmole) was mixed with 0.188 g. (0.89 mmole) of 3,5-dinitrobenzoic acid and the stirred mixture was kept at 0°. After 1 day, 10 ml. of ether was added and the mixture was stirred at 25–30° for 1 day. Ether was added to a total volume of 50 ml. and the solution was washed with cold sodium bicarbonate solution and water, and then dried. When the ether was evaporated *in vacuo*, 0.249 g. (0.84 mmole, 94%) of light yellow crystals was obtained, m.p. 59–60°. The infrared spectrum of this ester (IXa) was identical with the spectrum of ester prepared from ethyl chloroacetate (*vide infra*).

Reaction of Ethyl α-Diazopropionate (VIIb) with 3,5-Dinitrobenzoic Acid.—Compound VIIb (0.50 g., 3.9 mmoles) and 3,5-dinitrobenzoic acid (0.83 g., 3.9 mmoles) were dissolved in 25 ml. of dry dioxane and the solution was kept at 25–30° for 2 days. The volatiles were evaporated *in vacuo* to give 0.17 g. (0.54 mmole 14%) of ester IXb, m.p. 74.5–76°. The infrared spectrum was identical with that of a sample of the ester prepared from ethyl lactate (*vide infra*).

Carbethoxymethyl 3,5-Dinitrobenzoate (IXa).—Sodium 3,5-dinitrobenzoate (2.8 g., 12 mmoles) was dissolved in 50 ml. of 50% aqueous ethanol. After 1.2 g. (9.8 mmoles) of ethyl chloroacetate and 1.5 g. (10 mmoles) of sodium iodide were added, the mixture was heated on the steam bath for 4 hr. Most of the solvent was removed *in vacuo*, after which the residue was extracted with ether. The ether was removed to give 1.4 g. (4.7 mmoles, 48%) of yellow crystalline ester, m.p. 48–51°. After three recrystallizations from methylene chloride–hexane, 0.13 g. (0.44 mmole) of very light yellow needles of ester IXa was isolated, m.p. 59–60°.

Anal. Calcd. for $C_{11}H_{10}N_2O_8$: C, 44.30; H, 3.38; N, 9.40. Found: C, 44.36; H, 3.65; N, 9.46.

1-Carbethoxyethyl 3,5-Dinitrobenzoate (IXb).—Ethyl lactate (3.5 g., 0.030 mole) and 4.0 g. (0.020 mole) of 3,5-dinitrobenzoyl-chloride were added to 25 ml. of dry pyridine. The reaction was allowed to proceed with stirring at room temperature for 2 hr. after which the pyridine was removed *in vacuo* to give a highly viscous residue. This residue was dissolved in methylene chloride and washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and water. The solution was then dried and evaporated to a yellow-brown solid (4.1 g., 0.013 mole, 65%; m.p. 66–70°) which was fractionally crystallized from methylene chloride–hexane at 0°. White needles of ester IXb were obtained, m.p. 75–76° (0.80 g., 2.6 mmoles, 13.0%).

Anal. Calcd. for $C_{12}H_{12}N_2O_8$: C, 46.16; H, 3.38; N, 8.97. Found: C, 46.02; H, 3.66; N, 8.95.

An attempt to prepare ester IXb from excess ethyl lactate and 3,5-dinitrobenzoyl chloride in the absence of pyridine at 70° yielded mainly ethyl 3,5-dinitrobenzoate.

Ethyl N-(3,5-Dinitrobenzoyl)glycinate.—This compound (light yellow needles from methylene chloride–hexane, m.p. 152–154°) was prepared in 56% yield from ethyl glycinate hydrochloride and 3,5-dinitrobenzoyl chloride in dry pyridine (4-hr. reaction time).

Anal. Calcd. for $C_{11}H_{11}N_3O_7$: C, 44.45; eq. H, 3.73; eq. N, 14.13. Found: C, 44.51; H, 3.71; N, 13.97.

Ethyl N-(3,5-Dinitrobenzoyl)-N-nitrosoglycinate (Xc).—This compound was prepared in 73% yield by the nitrogen tetroxide nitrosation of the corresponding amide (see above) in methylene chloride.[14] Recrystallization from ether–hexane mixtures yielded light yellow crystals of Xc, m.p. 68–70° (followed by gas evolution at 78°). This compound was unstable, and samples showed signs of decomposition (NO_2) after several days.

Anal. Calcd. for $C_{11}H_{10}N_4O_8$: C, 40.50; H, 3.10; N, 17.17. Found: C, 40.42; H, 3.04; N, 16.28.

Pyrolysis of this compound at 75° (100 mμ) yielded principally the parent amide. Recrystallization of the product yielded pure amide, m.p. 151–154°.

The Nitrosoacetamide and Benzamide of Ethyl Alanate.[13]—These compounds were prepared by the nitrogen tetroxide nitrosation of the acetyl and benzoyl derivatives of methyl alanate. Pyrolyses at 50–90° (100–200 mm.) yielded a mixture of ethyl diazopropionate and the carboxylic acids; the acid could be removed with dilute solutions of sodium carbonate.

Ethyl Diazoacetate (VIIa).—In addition to the pyrolytic methods outlined above, this compound can be prepared in 50–75% yields by the dropwise addition of ethyl N-nitroso-N-acetylglycinate to an excess of tetraethylenepentamine under high vacuum. The mixture is stirred vigorously and the product collected in a cooled receiver; about 4–8 hr. are required for the reaction.

Acknowledgment.—This work was supported by a grant from the National Institutes of Health (CY 3554). Analyses were performed by Joe Walter, The Johns Hopkins University, and the Galbraith Laboratories, Knoxville, Tennessee.

(16) T. Curtius and E. Müller, *Ber.*, **37**, 1269 (1904).

Action of Nitrous Acid on Osazone Acetates. A New Synthesis of Osotriazoles

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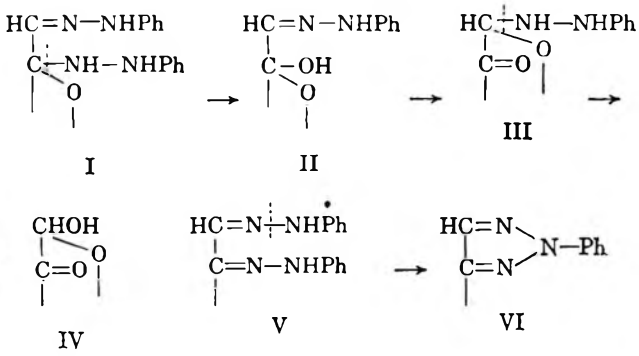
Osazones are known[1] to react with nitrous acid to give first the aldosulose ("osone") 1-hydrazone (II) and then with excess reagent to yield the aldosulose (IV) in yields up to 65%. We have now carried out this reaction with the tetra-*O*-acetylphenylosazones from D-galactose, D-glucose, and L-sorbose, but, instead of the expected aldosulose tetraacetates, we obtained the corresponding phenylosotriazole tetraacetates in about 80% yields. The D-galactose derivative crystallized from the crude reaction mixture and the D-glucose and L-sorbose derivatives were identified by deacetylation to the free osotriazoles. The different course followed by the reaction with osazone acetates seems to be due to the absence in the molecule of free hydroxyl groups which allow the formation of cyclic modifications. Osazone acetates have been shown[2] to possess acyclic bis(hydrazone) structures (V), whereas the unacetylated derivatives may form in solution some of the cyclic hydrazino hydrazone forms (I). If we now assume that nitrous acid reacts more rapidly with the labile and highly reactive hydrazino group,[3] than with a true hydrazone residue, we would expect the unacetylated osazones to undergo a series of cyclizations and eliminations of hydrazino groups leading first to the aldosulose hydrazone (II) and finally to the aldosulose (IV). Scission of the hydrazino groups is probably achieved through the intermediate

(1) H. Ohle, G. Henseke, and A. Czyzewski, *Ber.*, **86**, 316 (1953); G. Henseke and M. Winter, *ibid.*, **89**, 956 (1956).

(2) M. L. Wolfrom, M. Konigsberg, and S. Soltzberg, *J. Am. Chem. Soc.*, **58**, 490 (1936).

(3) H. S. Isbell, *Ann. Rev. Biochem.*, **12**, 205 (1943); F. Weygand, *Ber.*, **73**, 1284 (1940).

formation of *N*-nitroso compounds on the β-hydrazino nitrogen followed by hydrolytic splitting of the C–N bond. In the case of acetylated osazones which have only hydrazone groups, nitrous acid would be expected to attack the α-nitrogen of the phenylhydrazone residue and cause the hydrolytic scission of the N–N bond and closure of the triazole ring.



The high yields of osotriazole obtained with osazone acetates render this reaction of value for preparative purpose.

Experimental[4]

D-*lyxo*-**Hexose Phenylosotriazole Tetraacetate.**—A suspension of D-*lyxo*-hexose phenylosazone tetraacetate[2] (5.3 g.) in a mixture of ethanol (40 ml.), water (20 ml.), and concentrated hydrochloric acid (2.4 ml.) was treated, with stirring, at 50–55° with a solution of sodium nitrite (1.4 g.) in water (10 ml.) during the course of 30 min. The now clear reddish brown solution was treated with 1.5 g. of sodium acetate trihydrate in water (50 ml.) and extracted with chloroform. The chloroform layer which contained the osotriazole tetraacetate was washed successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water. The residue obtained after solvent removal from the dried extract crystallized from methanol–ether in needles, m.p. 106° undepressed with authentic D-*lyxo*-hexose phenylosotriazole tetraacetate,[5] yield 3.5 g.

Anal. Calcd. for $C_{20}H_{23}N_3O_8$: C, 55.42; H, 5.35; N, 9.70; CH_3CO, 39.73. Found: C, 55.27; H, 5.00; N, 9.54; CH_3CO, 39.57.

Deacetylation.—The acetate (3 g.) in methanol (50 ml.) was treated with concentrated aqueous ammonia (20 ml.) and the mixture kept overnight at room temperature. On evaporation and distillation of the residue under reduced pressure at 190–200° (0.05 mm.), D-*lyxo*-hexose phenylosotriazole was obtained in needles, m.p. 111–112° undepressed on admixture with an authentic specimen.[6] Both products had identical infrared spectra.

Anal Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.20; H, 5.94; N, 15.94.

D-*arabino*-**Hexose Phenylosotriazole.**—D-*arabino*-Hexose phenylosazone tetraacetate[6] (5.3 g.) was treated with nitrous acid in exactly the same manner as the D-*lyxo*-hexose derivative and the residue, after evaporation of the chloroform, was subjected directly to deacetylation with ammonia in aqueous methanol. D-*arabino*-Hexose phenylosotriazole was obtained by evaporation and crystallization from water or ethanol in needles, m.p. 196° undepressed on admixture with an authentic specimen,[7] yield 2 g. Both products had identical infrared spectra.

Anal. Found: C, 54.29; H, 5.79; N, 15.96.

L-*xylo*-**Hexose Phenylosotriazole.**—Amorphous L-*xylo*-hexose phenylosazone tetraacetate (about 5 g.), obtained by the action of acetic anhydride and pyridine on the osazone and carefully washed with water, was treated in exactly the same manner as the D-*arabino*-hexose derivative, yielding finally L-*xylo*-hexose phenylosotriazole. This crystallized from water in needles, m.p. 159° undepressed on admixture with an authentic specimen,[5] yield 2 g. Both products gave identical infrared spectra.

Anal. Found: C, 54.82; H, 6.03; N, 16.02.

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(4) Microanalyses were by W. N. Rond, The Ohio State University; infrared spectra were measured with a Perkin-Elmer Infracord spectrophotometer.

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(7) R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 735 (1944).

Benzoylation of Sugar Phenylhydrazones

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Acyclic sugar hydrazones when acetylated with pyridine and acetic anhydride yield *O*-acetylated derivatives[2] which can be converted to tetraacetoxy-1-phenylazo-1-hexene.[3] The more drastic reaction with boiling acetic anhydride[4] yields derivatives having acetyl groups attached to the nitrogen as well as to the oxygen which no longer undergoes this conversion. To study the behavior of sugar hydrazones toward benzoylation, the phenyl hydrazones of D-mannose, D-arabinose, and L-rhamnose were treated with benzoyl chloride in pyridine, and the structure of their crystalline benzoates investigated. D-Mannose phenylhydrazone yielded a hexabenzoate (I) which showed in the infrared spectrum a C=N band at 1610, an ester band at 1725, and an amide band at 1660 cm.$^{-1}$, denoting the presence of *O*- and *N*-benzoyl groups in an acyclic hydrazone. This was confirmed by trans-hydrazonation; the hexabenzoate was treated with *p*-nitrophenylhydrazine, which replaced the *N*-benzoyl phenylazo residue yielding a *p*-nitrophenylhydrazone pentabenzoate (II). This showed the C=N band at 1605 and the ester band at 1730 but not the amide absorption at 1660 cm.$^{-1}$, denoting that all five benzoyl groups were linked to oxygen. The presence of five *O*-benzoyl groups on a hexose aryl hydrazone excludes the possibility of cyclic structures, which would have yielded a benzoate having fewer *O*-benzoyl groups. Accordingly the hexabenzoate (I) was formulated as *N*-benzoylpenta-*O*-benzoyl-*aldehydo*-D-mannose phenylhydrazone (I), and the transhydrazonation product as penta-*O*-benzoyl-*aldehydo*-D-mannose *p*-nitrophenylhydrazone (II). Similarly, D-arabinose and L-rhamnose phenylhydrazones yielded pentabenzoates which showed the C=N bands at 1605 and 1610, the ester bands at 1725 and 1730, and the amide bands at 1670 and 1680 cm.$^{-1}$, respectively, denoting that, like the mannose

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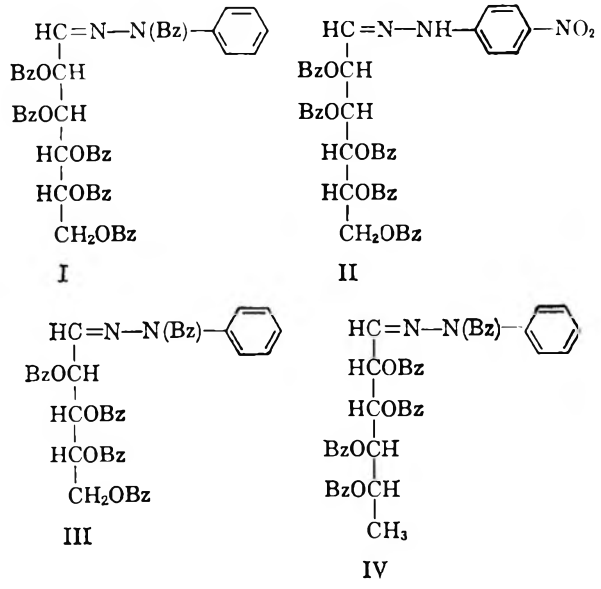
(2) M. L. Wolfrom and C. C. Christman, *J. Am. Chem. Soc.*, **53**, 3413 (1931).

(3) M. L. Wolfrom, A. Thompson, and D. R. Lineback, *J. Org. Chem.*, **24**, 2563 (1962); M. L. Wolfrom, G. Fraenkel, D. R. Lineback, and F. Komitsky, Jr., *J. Org. Chem.*, **29**, 457 (1964).

(4) H. El Khadem, Z. M. El-Shafei, and M. M. Mohammed-Ali, *J. Org. Chem.*, **29**, 1565 (1964).

derivative, they were acyclic and possessed both *O*- and *N*-benzoyl groups. They were therefore designated *N*-benzoyltetra-*O*-benzoyl-*aldehydo*-D-arabinose phenylhydrazone (III) and *N*-benzoyltetra-*O*-benzoyl-*aldehydo*-L-rhamnose phenylhydrazone (IV), respectively. It seems that benzoyl chloride in pyridine,



being a more vigorous reagent than acetic anhydride in pyridine, leads in the case of acyclic sugar hydrazones to the acylation of the OH and NH groups and not merely the former ones. The *N*-benzoylated derivatives produced like the *N*-acetylated ones studied earlier[3] do not give azoethylene compounds on boiling with ethanolic pyridine.

Experimental[5]

N-Benzoylpenta-*O*-benzoyl-*aldehydo*-D-mannose Phenylhydrazone (I).—D-Mannose phenylhydrazone[6] (10 g.) was suspended in pyridine (70 ml.) and treated with benzoyl chloride (40 ml.). The reaction mixture warmed up spontaneously, darkened, and after 2 hr. returned to room temperature. It was left overnight, then poured onto crushed ice (1 kg.). The viscous residue that separated was washed repeatedly with water, then with aqueous sodium hydrogen carbonate to remove benzoic acid. After 2 days the *N*-benzoylpenta-*O*-benzoyl-*aldehydo*-D-mannose phenylhydrazone solidified and crystallized from ethanol as needles, yield 30 g. (91%), $[\alpha]^{20}D$ 62.5° (*c*, 1, chloroform), m.p. 169°; λ_{max}^{KBr} 1610 (C=N), 1660 (NBz), 1725 (OBz) cm.$^{-1}$; X-ray powder diffraction pattern[7]: 13.50 s, 12.11 w, 9.80 m, 8.00 vw, 6.86 w, 6.11 w, 5.54 m, 5.12 w, 4.82 s, 4.75 s, 4.08 s, 3.65 m, 3.59 m, 3.43 w, 3.11 m, 2.93 w.

Anal. Calcd. for $C_{54}H_{42}N_2O_{11}$: C, 72.47; H, 4.73; N, 3.13. Found: C, 72.35; H, 4.90; N, 3.18.

Penta-*O*-benzoyl-*aldehydo*-D-mannose *p*-Nitrophenylhydrazone (II).—*N*-Benzoylpenta-*O*-benzoyl-*aldehydo*-D-mannose phenylhydrazone (1 g.) was refluxed for 3 hr. with a solution of *p*-nitrophenylhydrazine (0.4 g.) in ethanol (50 ml.). The mixture was concentrated to 20 ml., whereupon some unchanged hydrazone separated and was filtered. The penta-*O*-benzoyl-*aldehydo*-D-mannose *p*-nitrophenylhydrazone subsequently crystallized from ethanol as yellow needles, yield 0.4 g. (48%), m.p. 105°; λ_{max}^{KBr} 1605 (C=N), 1730 (OBz) cm.$^{-1}$.

Anal. Calcd. for $C_{47}H_{37}N_3O_{12}$: C, 67.54; H, 4.46; N, 5.03. Found: C, 67.56; H, 4.59; N, 5.29.

N-Benzoyltetra-*O*-benzoyl-*aldehydo*-D-arabinose Phenylhydrazone (III).—D-Arabinose phenylhydrazone[8] (10 g.) was treated with pyridine (70 ml.) followed by benzoyl chloride (40 ml.), left to stand overnight at room temperature, then poured onto crushed ice (1 kg.). The viscous residue that separated was washed repeatedly with water, and crystallized by the addition of a few drops of ethanol. The *N*-benzoyltetra-*O*-benzoyl-*aldehydo*-D-arabinose phenylhydrazone was recrystallized from a mixture of ethanol and acetone as needles, yield 30 g. (95%), $[\alpha]^{20}D$ 52.5° (*c* 1, chloroform), m.p. 134°; ν_{max}^{KBr} 1605 (C=N), 1670 (NBz), 1725 (OBz) cm.$^{-1}$; X-ray powder diffraction pattern: 11.79 vs, 9.10 m, 8.67 vw, 7.90 m, 6.92 vw, 6.24 w, 5.80 w, 5.15 s, 5.07 s, 4.79 w, 4.55 vs, 4.13 m, 3.76 m, 3.49 m.

Anal. Calcd. for $C_{46}H_{36}N_2O_9$: C, 72.61; H, 4.77; N, 3.68. Found: C, 72.42; H, 4.64; N, 3.82.

N-Benzoyltetra-*O*-benzoyl-*aldehydo*-L-rhamnose Phenylhydrazone (IV).—L-Rhamnose phenylhydrazone[9] (10 g.) was benzoylated by the procedure used for the arabinose derivative and the product was purified by repeatedly dissolving it in ethanol and precipitating with water. After four such precipitations *N*-benzoyl tetra-*O*-benzoyl-*aldehydo*-L-rhamnose phenylhydrazone was dried in a vacuum desiccator, yield 25 g. (86%), $[\alpha]^{20}D$ 31.6° (*c* 1.3, chloroform), m.p. 95°; λ_{max}^{KBr} 1610 (C=N), 1680 (NBz), 1730 (OBz) cm.$^{-1}$.

Anal. Calcd. for $C_{47}H_{38}N_2O_9$: C, 72.85; H, 4.95; N, 3.62. Found: C, 72.14; H, 5.21; N, 3.36.

Acknowledgment.—The author is indebted to the Educational and Cultural Exchange Program for a Fulbright Grant, to Professor M. L. Wolfrom and Dr. D. Horton for valued counsel, and to The Ohio State University for laboratory facilities provided.

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(9) E. Fischer and J. Tafel, *Ber.*, **20**, 2566 (1887).

5-Deoxy-D-glucose (5-Deoxy-D-*xylo*-hexose)[1]

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Deoxy sugars and their derivatives have been evaluated in biological systems as potent glycolytic inhibitors of various tumor tissues,[2-4] as intermediates for the preparation of antimetabolites, and as potential anticancer agents.[5]

This paper describes a convenient method for the preparation of 5-deoxy-D-*xylo*-hexose. The yield from D-glucose is 25%.

3-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose[6] (I), prepared from 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, is the starting compound. It is tritylated and tosylated in one operation to produce 3-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolyl-

(5) Melting points are corrected; infrared spectra were measured with a Perkin-Elmer Infracord spectrophotometer. Microanalyses were by W. N. Rond, The Ohio State University.
(6) E. Fisher, *Ber.*, **20**, 821 (1887); E. Fischer and J. Hirshberger, *ibid.*, **21**, 1805 (1888).
(7) Interplanar spacing, Å., Cu Kα radiation. Relative intensities estimated visually: s, strong; m, medium; w, weak; v, very.

(1) Journal Paper No. 2297 of the Purdue University Agricultural Experiment Station.
(2) G. E. Woodword and M. T. Hudson, *Cancer Res.*, **14**, 599 (1954).
(3) J. O. Ely, *J. Franklin Inst.*, **258**, 157 (1954).
(4) J. Laszlo, B. Landau, K. Wight, and D. Burk, *J. Natl. Cancer Inst.*, **21**, 475 (1958).
(5) M. Dahlgard and E. Kaufmann, *J. Org. Chem.*, **25**, 781 (1960).
(6) K. Josephson, *Ann.*, **472**, 217 (1929).

sulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose (II) in 67% yield. Desulfonyloxylation and β-elimination of compound II with sodium methoxide affords crystalline 5-deoxy-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuran-5-enose (III) in 90% yield. A complete structure proof of compound III is described elsewhere.[7]

Hydrogenation of compound III, with palladium-on-carbon catalyst, produces pure, crystalline 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (5-deoxymonoacetone-D-glucose, IV) in 80% yield. This compound on hydrolysis of the isopropylidene group with Amberlite IR-120(H^+) resin produces 5-deoxy-D-*xylo*-hexose.

Experimental

Analytical Methods.—Purity of crystalline products was determined by thin layer chromatography on silica gel G-coated[8] glass plates, irrigated with (A) chloroform–acetone (1:1 v./v.) and (B) 1-butanol saturated with water. Plates were sprayed with 5% ethanolic sulfuric acid and charred at 110° until permanent spots were visible. A calibrated Fisher-Johns apparatus was used for melting point determinations. Evaporations were done at reduced pressure.

3-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (I).—Acetylation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in acetic anhydride and pyridine gave 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.[6] The acetyl derivative was dissolved in a 60% solution of aqueous acetic acid, allowed to stand for 5 hr. at 37°, and evaporated below 50° to a sirup which crystallized as a solid white mass of compound I. This was recrystallized from warm ethyl acetate, m.p. 126°, lit.[6] m.p. 125–126°.

3-*O*-Acetyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose (II).—Compound I (180 g.) was dissolved in 900 ml. of dry pyridine to which was added 200 g. of trityl chloride (chlorotriphenylmethane). After 2 days at 25°, 400 ml. of pyridine was added and the solution was cooled to 5°. While the mixture was continuously stirred, 500 ml. of alcohol-free chloroform containing 350 g. of tosyl chloride (*p*-tolylsulfonyl chloride) was slowly added. After 3 days at 37°, the reaction mixture was cooled to 0° and 20 ml. of water was added to hydrolyze excess tosyl chloride. Within 0.5 hr., the solution was poured into a mixture of ice and water. The water layer was drawn off, extracted twice with chloroform, and the chloroform solution washed free of pyridine with several portions of chilled 15% aqueous acetic acid. Upon neutralization with a solution of sodium bicarbonate, the chloroform was washed free of salts and dried over anhydrous magnesium sulfate. After filtration and evaporation, a dark brown sirup was obtained; the yield was 450 g. which contained 300 g. of solids (compound II).

5-Deoxy-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuran-5-enose (III).—A 225-g. portion of this dark brown sirup, obtained above was dissolved in 1685 ml. of chloroform. While this solution was stirred continuously and externally cooled, 900 ml. of a methanol solution containing 12.5% of sodium methylate was added. After 2 hr., the reaction mixture was slowly warmed to 25° where it was held for 16 hr. Then 100 ml. of a saturated solution of potassium bicarbonate was added and the mixture evaporated to remove methanol. The residue was extracted four times with chloroform, the chloroform was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was crystallized from a mixture of benzene and petroleum ether (b.p. 40–60°) yielding 90 g. (90%), of III, m.p. 83°, $[\alpha]^{25}D$ −15.4° (*c* 1.4, chloroform).

Anal. Calcd. for $C_{28}H_{28}O_5$ (444.50): C, 75.66; H, 6.34. Found: C, 75.4; H, 6.42.

5-Deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (IV).—Compound III (45 g.) was dissolved in 325 ml. of absolute ethanol to which was added 325 ml. of an ethanol slurry containing 20 g. of 5% palladium on carbon. This mixture was subjected to 600 p.s.i. of hydrogen pressure and stirred for 2 hr. at 60°. During this period, the pressure dropped about 400 p.s.i. The pressure was again adjusted to 600 p.s.i. and the hydrogenation continued at 60° for 18 hr. The mixture was filtered and evaporated to a sirup which was dissolved in a mixture of petroleum ether and water. Triphenylmethane was reclaimed from the ether phase. The water phase contained compound IV. This solution was evaporated to a colorless sirup which was crystallized from a mixture of benzene and petroleum ether yielding 16 g. of IV, m.p. 94°, $[\alpha]^{25}D$ −10.0° (*c* 0.71, chloroform). The yield from compound I was 48%. The product migrated as a single component in irrigants A and B. An X-ray powder diffraction pattern of compound IV and an authentic sample[9] was identical.

Anal. Calcd. for $C_9H_{16}O_5$ (204.22): C, 52.94; H, 7.89. Found: C, 53.0; H, 7.98.

5-Deoxy-D-*xylo*-hexose.—Two grams of compound IV was dissolved in 50 ml. of water and stirred for 2.5 hr. at 60° with 8 g. of Amberlite IR-120(H^+) resin. The solution was filtered and concentrated to a colorless sirup, $[\alpha]^{25}D$ +40° (*c* 1.7, in water). The sugar was converted to the known[10] crystalline 5-deoxy-D-*threo*-hexose phenylosazone, m.p. 151°.

Acknowledgment.—This work was supported in part by the U. S. Department of Health, Education, and Welfare under Grant AM 06782-01.

(7) R. E. Gramera, T. R. Ingle, and R. L. Whistler, *J. Org. Chem.*, **29** 1083 (1964).

(8) Brinkmann Instruments, Inc., Great Neck, Long Island, N. Y.

(9) T. E. Whiteley (Ohio State University, Columbus): *Univ. Microfilms*, Ann Arbor Mich., L. C. Card No. Mic. 60-6419, 122 pp.; *Dissertation Abstr.*, **21**, 2121 (1961).

(10) P. P. Regna, *J. Am. Chem. Soc.*, **69**, 246 (1947).

3-Deoxy-D-*glycero*-D-*ido*-octonic γ-Lactone

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Recently Richtmyer and Bodenheimer[2] described an octosaccharinic lactone isolated from the mother liquors of the sodium amalgam reduction of D-*erythro*-L-*talo*-octonic lactone, it being the first higher carbon saccharinic acid obtained from a sugar–alkali reaction.[3] The lactone[4] consumed 3 moles of sodium periodate in 15 min. and this value remained constant for 8 hr. Since Richards, *et al.*,[5] have shown that D-glucoisosaccharinic lactone is rapidly and completely degraded by periodate ion, the isosaccharinic acid structure is excluded for Richtmyer's lactone, **1**. The decision between the metasaccharinic acid and the saccharinic acid structure was made by comparing the proton magnetic resonance spectra of 3-deoxy-D-*arabino*-hexonic γ-lactone[6a] (β-D-glucometasaccharin),[6b] 2-*C*-methyl-D-*ribo*-pentonic γ-lactone[7a] (α-D-glucosaccharin),[7b] and the octonic lactone in the region τ 8.0–

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(2) N. K. Richtmyer and T. S. Bodenheimer, *J. Org. Chem.*, **27**, 1892 (1962).

(3) J. C. Sowden, *Advan. Carbohydrate Chem.*, **12**, 35 (1957).

(4) The author is indebted to Dr. N. K. Richtmyer, NIAMD, National Institutes of Health, for a gift of this lactone.

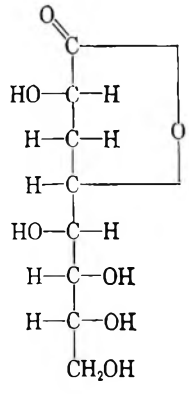
(5) G. N. Richards and H. H. Sephton, *J. Chem. Soc.*, 4492 (1957).

(6) (a) A gift from Dr. H. G. Fletcher, Jr., NIAMD, National Institutes of Health; (b) J. U. Nef, *Ann.*, **376**, 1 (1910).

(7) (a) J. C. Sowden and D. R. Strobach, *J. Am. Chem. Soc.*, **82**, 3707 (1960); (b) H. Kiliani, *Chem. Ber.*, **15**, 2953 (1882).

10.0. Both 3-deoxy-D-*arabino*-hexonic γ-lactone and **1** were devoid of resonance signal in this region while 2-*C*-methyl-D-*ribo*-pentonic γ-lactone showed the expected *C*-methyl signal as a singlet at τ 8.08. The lack of *C*-methyl signal in the p.m.r. spectrum of **1** eliminates the saccharinic acid structure and the metasaccharinic acid structure is established.

That **1** is a γ-lactone is indicated by its lack of mutarotation[2] and the presence of a band at 1765 cm.$^{-1}$ in the infrared.[8] The phenylhydrazide derivative of the octonic lactone is levorotatory and, by the phenylhydrazide rule,[9] the hydroxyl on C-2 is to the left in the Fischer projection formula. If one assumes the formation of the lactone *via* the Nef–Isbell mechanism,[6b,10] **1** is then 3-deoxy-D-*glycero*-D-*ido*-octonic γ-lactone.



1

It is interesting to note that Hudson's lactone rule[11] predicts the metasaccharinic acid structure as the only possibility for the octonic lactone. Its specific optical rotation was reported as +27° [2]; the γ-lactones of the two branched chain structures would both have negative optical rotations.

Experimental[12]

3-Deoxy-D-*glycero*-D-*ido*-octonic Phenylhydrazide.—A mixture of 3-deoxy-D-*glycero*-D-*ido*-octonic lactone (20 mg.), phenylhydrazine (25 mg.), and acetic acid (0.40 ml.) in water (1 ml.) was heated at 100° for 1 hr. The solution was cooled and concentrated *in vacuo* at 60° to an oil which crystallized upon addition of ethanol. The crystals (18 mg.) were collected, washed with ethanol, and dried. Two recrystallizations from methanol produced pure product, m.p. 153–154°, $[\alpha]^{20}D$ −8.8° (H_2O, *c* 1).

Anal. Calcd. for $C_{14}H_{22}O_7N_2$: C, 50.90; H, 6.71; N, 8.48. Found: C, 50.67; H, 6.68; N, 8.70.

Acknowledgment.—This work was done in the laboratories of Dr. H. E. Carter and was supported by Public Health Service grants.

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 178.

(9) P. A. Levene, *J. Biol. Chem.*, **23**, 145 (1915); C. S. Hudson, *J. Am. Chem. Soc.*, **39**, 462 (1917); P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **31**, 623 (1917).

(10) H. S. Isbell, *J. Res. Natl. Bur. Std.*, **32**, 45 (1944).

(11) C. S. Hudson, *J. Am. Chem. Soc.*, **32**, 338 (1910); E. Anderson, *ibid.*, **34**, 51 (1912).

(12) Proton magnetic resonance spectra were taken in deuterium oxide on a Varian A-60 instrument by the spectroscopy laboratory, Department of Chemistry.

Nucleosides. V. The Monomesylates of 1-(2′-Deoxy-β-D-lyxofuranosyl)thymine[1,2]

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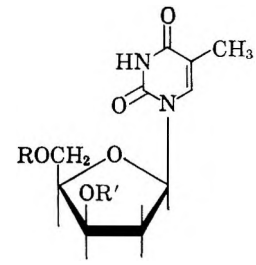
A recent study in this laboratory corrected the identity of 3′-*O*-mesyl- and 5′-*O*-mesylthymidine.[3] Efforts were then directed toward the synthesis of the corresponding mesylates of the 2′-deoxylyxosyl epimer (**4**) of thymidine. In fact, an unsuccessful attempt to prepare 1-(2′-deoxy-5′-*O*-mesyl-β-D-lyxofuranosyl)thymine (**5**) has since been recorded.[4] However, the simultaneous disclosure[4,5] of a practical route to 1-(2′-deoxy-β-D-lyxofuranosyl)thymine (**4**) by two laboratories provided an approach to the desired monomesyloxy derivatives.



1, R = $(C_6H_5)_3C$; R′ = H
2, R = $(C_6H_5)_3C$; R′ = CH_3SO_2
3, R = H; R′ = CH_3SO_2
4, R = R′ = H
5, R = CH_3SO_2; R′ = H

The mesylation of 1-(2′-deoxy-5′-*O*-trityl-β-D-lyxosyl)thymine (**1**), the direct precursor[4,5] of **4**, afforded the sulfonate **2** in high yield. Detritylation of **2** with anhydrous hydrogen chloride in chloroform at −5° gave 1-(2′-deoxy-3′-*O*-mesyl-β-D-lyxofuranosyl)-thymine (**3**) in 66% yield. Unimolar mesylation of **4** in a mixture of chloroform and pyridine at −5° produced a single[6] monomesylate (73% yield) with chromatographic (*cf.* Table I) and spectral (infrared) properties distinctly different from those of **3**. Accordingly, it is concluded that selective esterification of the primary (C′-5) alcohol function in **4** was effected and structure **5** is assigned to the product.

The acquisition of **2** provided the opportunity of studying the replacement of the mesyloxy group by nucleophiles such as azide, iodide, and benzoate ions. These transformations are of interest in view of the fact that recent studies have emphasized the difficulty of promoting the displacement of secondary sulfonates

(1) This work was supported in part by Research Grants CA-02903 and CY-5943 from the National Cancer Institute, Public Health Service, and in part by an institutional grant from the United Foundation of Greater Detroit allocated through the Michigan Cancer Foundation.

(2) Presented, in part, before the Division of Medicinal Chemistry, 144th National Meeting, American Chemical Society, Los Angeles, Calif., April, 1963.

(3) J. P. Horwitz, J. A. Urbanski, and J. Chua, *J. Org. Chem.*, **27**, 3300 (1962).

(4) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *ibid.*, **28**, 942 (1963).

(5) J. J. Fox and N. C. Miller, *ibid.*, **28**, 936 (1963).

(6) The same reaction conditions applied to thymidine produced a mixture of mesylates.

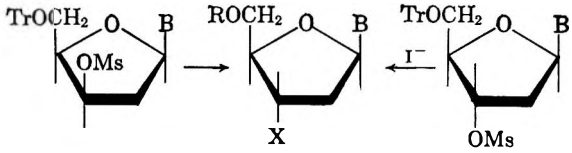
TABLE I

$R_{thymidine}$ VALUES FOR THE MONOMESYLATES OF 1-β-D-(2′-DEOXYALDOPENTOFURANOSYL)THYMINE[a]

Thymine derivative	Solvent system[b] A	B
3′-*O*-Mesylthymidine	1.02	1.52
3	0.82	1.06
5′-*O*-Mesylthymidine	0.92	1.19
5	0.90	1.37

[a] Ascending thin-layer chromatograms were run on silica gel G (Research Specialties Co.). The compounds were located on the chromatogram either by ultraviolet light alone or in conjunction with a fluorescein–bromine spray technique [J. G. Kirchner, J. M. Miller, and G. J. Keller, *Anal. Chem.*, **23**, 420 (1951)]. Each chromatogram included thymidine and the results represent the average of several determinations. [b] Two solvent systems were employed: A, *n*-butyl alcohol–water (86:14); and B, benzene–ethanol (7:3).

of cyclic carbohydrate derivatives in the absence of anchimeric assistance to the reaction.[7–10] A *cis* relationship between the aglycon and mesyloxy moieties in **2** obviously precludes the possibility of participation by the 2-carbonyl of the pyrimidine in these replacements.



B = thymine
Tr = $(C_6H_5)_3C$
MS = CH_3SO_2

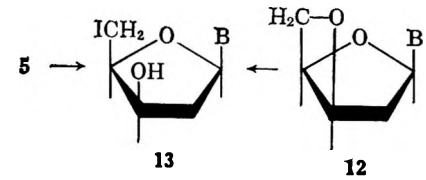
6, R = Tr; X = N_3
7, R = H; X = N_3
8, R = H; X = NH_2·HCl
9, R = Tr; X = I
10, R = H; X = I
11

Treatment of **2** with lithium azide in N,N-dimethylformamide at 100° for 3 hr. led to a solid that was characterized by a strong azide absorption at 4.76 μ and the disappearance of mesylate absorption at 7.35 and 8.48 μ. The crude[11] product (**6**), on detritylation, gave a crystalline solid (62% yield based on **2**) with properties consistent with those of 1-(3′-azido-2′,3′-dideoxy-β-D-*erythro*-pentosyl)thymine (3′-azido-3′-deoxythymidine, **7**). The latter, on catalytic reduction, gave 3′-amino-3′-deoxythymidine (**8**),[12] which was isolated as a hydrochloride.

The interaction of **2** and sodium iodide in acetone at 100° for 16 hr. gave a product identical in every respect with the known 3′-deoxy-3′-iodo-5′-*O*-tritylthymidine (**9**) obtained from 3′-*O*-mesyl-5′-*O*-tritylthymidine[13] (**11**). Moreover, **9**, obtained by either route, yielded the same 3′-deoxy-3′-iodo nucleoside (**10**) on detritylation. It was originally assumed[13] that the action of sodium iodide on **11** led to 3′-iodo derivative of the "down" or *ribo* configuration. The present findings lend credence to the original structural assignment and provide additional support for the view[5] that displacement on **11** by iodide ion proceeds through a 2,3′-anhydro nucleoside under acid catalysis.

Treatment of **2** with sodium benzoate in refluxing DMF led only to partial replacement of the sulfonyloxy group after 70 hr. It is apparent, then, that the displacement of this function requires the use of strong nucleophilic reagents under forcing conditions. The present observations are in accord with the concept that ring sulfonates are, in general, relatively unreactive in the absence of neighboring group participation.[7–9]

The synthesis of **5** provided an alternate route to an iodo nucleoside (**13**) obtained in a previous study[4] from the action of sodium iodide on 1-(2′-deoxy-3′,5′-epoxy-β-D-lyxofuranosyl)thymine (**12**). It was suggested that opening of the epoxide ring in **12** occurred as a result of attack at C′-5 to form 1-(2′,5′-dideoxy-5′-iodo-β-D-lyxosyl)thymine (**13**). It was found that **5**, on treatment with sodium iodide in butanone, yielded an identical product.



B = thymine

Experimental[14]

1-(2′-Deoxy-3′-*O*-mesyl-5′-*O*-trityl-β-D-lyxosyl)thymine (2).—To a cold solution of 9.0 g. (18.6 mmoles) of **1**[4,5] in 50 ml. dry pyridine was added 4.2 ml. (57.2 mmoles) of methanesulfonyl chloride and the reaction mixture was held at 0° for 16 hr. The amber solution was then allowed to reach room temperature and held there for 3 hr.[15] The reaction mixture was again cooled to 0°, treated with *ca.* 2 ml. of ice–water, refrigerated for an additional hour, and finally poured slowly, with vigorous stirring, into 1.5 l. of ice–water. After 1 hr. of stirring the product was collected, air-dried, and crystallized from ethanol, 9.25 g. (80% yield), m.p. 108–110°. Material in this form was sufficiently pure for succeeding transformations. Three recrystallizations from ethanol provided analytical material, m.p. 116–118°, $[\alpha]^{26}D$ −14° (*c* 0.5, ethanol); $\lambda_{max,\,min}^{EtOH}$ 266 mμ (ε 10,000), 243 (5015).

Anal. Calcd. for $C_{30}H_{30}N_2O_7S \cdot C_2H_5OH$: C, 63.34; H, 5.98; N, 4.61. Found: C, 63.05; H, 5.38; N, 4.94.

1-(2′-Deoxy-3′-*O*-mesyl-β-D-lyxofuranosyl)thymine (3).—To a solution of 2.0 g. (3.76 mmoles) of **2** (once recrystallized) in 25 ml. of chloroform, chilled to 0°, was added a cold solution of chloroform (22 ml.) containing 5.4 mequiv. of dry hydrogen chloride, and the mixture was held at −5° for 16 hr. The solution was decanted from an oil that lined the reaction vessel and the oil then triturated with cold chloroform. The addition of a small quantity (*ca.* 10 ml.) of ethanol and scratching effected solidification of the oil. The amorphous solid was collected, washed with cold ethanol, and air-dried, 0.735 g. (61%), m.p. 156–158° dec. Evaporation of the original chloroform solution in a stream of air left a residue which, on recrystallization from ethanol, gave an additional crop (0.055 g., 5%) of solid, m.p. 157–160° dec. Recrystallization of the first crop from ethanol gave material, m.p. 161–162°, in the form of transparent plates, $[\alpha]^{26}D$ −40° (*c* 0.5, ethanol); $\lambda_{max,\,min}^{EtOH}$ 265 mμ (ε 10,550), 234 (2500); λ_{max}^{KBr} 7.35, 8.48 μ (sulfonate).

Anal. Calcd. for $C_{11}H_{16}N_2O_7S$: C, 41.24; H, 5.04; N, 8.75. Found: C, 41.19; H, 5.16; N, 8.92.

1-(2′-Deoxy-5′-*O*-mesyl-β-D-lyxofuranosyl)thymine (5).—To a solution of 1.53 g. (6.32 mmoles) of **4**[4,5] in 5 ml. of dry pyridine

(7) For a summary of earlier work related to this subject, see S. R. Tipson, *Advan. Carbohydrate Chem.*, **8**, 107 (1953).

(8) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963).

(9) M. L. Wolfrom, J. Bernsmann, and D. Horton, *ibid.*, **27**, 4505 (1962).

(10) W. M. Zu Reckendorf and W. A. Bonner, *Tetrahedron*, **19**, 1711 (1963).

(11) No attempt was made to purify this product.

(12) The synthesis of this compound by an alternate route was recently announced by N. C. Miller and J. J. Fox, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 21D.

(13) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(14) Melting points are corrected. Infrared spectra were recorded by a Perkin-Elmer Model 21 spectrophotometer (KBr) and ultraviolet spectra by a Cary Model 11 spectrophotometer. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(15) It was found that mesylation was incomplete after 16 hr. at 0°.

cooled to −12° was added dropwise with magnetic stirring and over a period of 0.5 hr. a solution of 0.54 ml. (7.4 mmoles) of methanesulfonyl chloride in 3 ml. of chloroform. The reaction mixture was held overnight (16 hr.) at −5°. Methanol (5 ml.) was then added and the solution evaporated to dryness *in vacuo*. This procedure was repeated twice with ethanol after which the residue crystallized from the same solvent as colorless irregular prisms, 1.45 g. (73% yield), m.p. 142–145° dec. Two recrystallizations from ethanol provided analytical material, m.p. 148–149°, $[\alpha]^{26}D$ +10° (*c* 0.5, ethanol); $\lambda_{max,\,min}^{EtOH}$ 266 mμ (ε 9700), 234 (2230).

Anal. Calcd. for $C_{11}H_{16}N_2O_7S$: C, 41.24; H, 5.04; N, 8.75. Found: C, 41.47; H, 5.00; N, 8.73.

3′-Azido-3′-deoxythymidine (7).—A solution of 3.27 g. (6.7 mmoles) of **2** in 20 ml. of DMF containing 1.0 g. of lithium azide[16] was stirred for 3 hr. at 100° under an atmosphere of nitrogen. The cooled reaction mixture was poured, with stirring, into 600 ml. of ice–water and the product (**6**) was collected. The air-dried, off-white solid (3.4 g.), which showed a prominent azide peak (λ_{max}^{Nujol} 4.76 μ), was dried (P_2O_5) for 4 hr. at 50° (0.1 mm.) and used without further purification.

To a solution of 3.4 g. (6.7 mmoles) of **6** in 5 ml. of chloroform cooled to 0° was added 36 ml. of a cold chloroform solution containing 8.6 mmoles of hydrogen chloride. The cloudy reaction mixture was refrigerated for 1 hr. and then poured into 5 ml. of a saturated solution of sodium bicarbonate. The two-phase mixture was evaporated to dryness in a stream of air and the residue triturated with four 10-ml. portions of acetone. The acetone extract was treated with Norit and concentrated to *ca.* one-half of the original volume. The addition of petroleum ether (b.p. 30–60°) caused the slow deposition of the product in the form of a mat of colorless needles, 1.34 g. (62% yield based on **2**), m.p. 106–112°. Recrystallization of the product from ether did not change the melting point. However, material of m.p. 119–121° was obtained after drying at 100° (1×10^{-2} mm.) for 16 hr., $[\alpha]^{25}D$ +99° (*c* 0.5, water); λ_{max}^{Nujol} 4.76 μ (azide); $\lambda_{max,\,min}^{H_2O}$ 266.5 mμ (ε 11,650), 234.5 (2610).

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.98; H, 4.74; N, 26.22.

3′-Amino-3′-deoxythymidine Hydrochloride (8).—A solution of 0.6 g. (1.9 mmoles) of **7** in 25 ml. of ethanol containing 0.25 g. of platinum oxide was shaken under 3 atm. of hydrogen for 2.5 hr. The catalyst was removed by filtration; the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 5 ml. of 2-propanol and to this solution was added an equal volume of cold, saturated 2-propanolic hydrogen chloride. The salt that was deposited was collected, 0.35 g. (57% yield), m.p. 240–245° dec. Two recrystallizations from methanol–2-propanol provided an analytical sample, m.p. 248–249° dec., $[\alpha]^{25}D$ +11° (*c* 0.58, H_2O); $\lambda_{max,\,min}^{H_2O}$ 265.5 mμ (ε 10,015), 234.5 (2320).

Anal. Calcd. for $C_{10}H_{16}N_3O_4Cl$: C, 43.24; H, 5.80; N, 15.13. Found: C, 43.07; H, 6.12; N, 14.83.

3′-Deoxy-3′-iodo-5′-*O*-tritylthymidine (9) from 2.—A solution of 0.335 g. of **2** and 0.2 g. (1.33 mmoles) of anhydrous sodium iodide in 15 ml. of dry acetone was heated at 100° in a pressure bottle for 15 hr. The inorganic salts were removed and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with water and the yellow amorphous solid was collected. The product crystallized from acetone–methanol in the form of colorless cubes, 0.13 g. (37% yield), m.p. 145–148° (lit.[13] m.p. 147°). Recrystallization from the same solvent system raised the melting point to 148–150°, $[\alpha]^{25}D$ +59° (*c* 0.42, acetone); $\lambda_{max,\,min}^{EtOH}$ 266 mμ (ε 10,110), 244 (4650).

From 3′-*O*-Mesyl-5′-*O*-tritylthymidine (11).—A solution of 0.335 g. (0.6 mmoles) of **11** and 0.2 g. (1.3 mmoles) of anhydrous sodium iodide in 15 ml. of acetone was treated in a pressure bottle at 100° for 18 hr.[17] The work-up and recrystallization of the product was identical with that described above, 0.15 g. (44% yield), m.p. and m.m.p. 148–150°, $[\alpha]^{24}D$ +59° (*c* 0.51, acetone); $\lambda_{max,\,min}^{EtOH}$ 266 mμ (ε 10,500), 244 (4900).

Samples of **9** obtained by the two routes gave 3′-deoxy-3′-iodothymidine (**10**) as a colorless crystalline solid on detritylation with 80% acetic acid, m.p. 166–167° dec. (lit.[13] m.p. 166–167° dec.).

1-(2′,5′-Dideoxy-5′-iodo-β-D-lyxosyl)thymine (13) from 5.—A solution of 0.32 g. (1 mmole) of **5** and 0.3 g. (2 mmoles) of anhydrous sodium iodide in 15 ml. of butanone was refluxed for 17 hr. under an atmosphere of nitrogen. The inorganic salts were removed by filtration and the solution was evaporated to dryness *in vacuo*. The residue was triturated with *ca.* 5 ml. of ice–water; the solid was collected and then recrystallized from ethanol, 0.20 g. in two crops (57% yield), m.p. 154–157° dec. A second recrystallization from ethanol provided an analytical sample, m.p. 156–157° dec., $[\alpha]^{25}D$ −38° (*c* 0.53, ethanol); $\lambda_{max,\,min}^{EtOH}$ 266 mμ (ε 10,930), 234 (3160).

Anal. Calcd. for $C_{10}H_{13}N_2O_4I$: C, 34.11; H, 3.72; N, 7.96. Found: C, 34.11; H, 3.78; N, 7.81.

From 12.—A solution of 1.0 g. (4.5 mmoles) of **12**[4] and 2.0 g. (13.3 mmoles) of sodium iodide in 25 ml. of butanone containing 0.4 ml. of glacial acetic acid was refluxed under an atmosphere of nitrogen for 16 hr. The inorganic salts were removed; the filtrate was evaporated to dryness *in vacuo*. The gummy residue solidified on trituration with *ca.* 5 ml. of ice–water. The solid was collected, washed with two 5-ml. portions of water, and sucked dry, 1.04 g. (66% yield), m.p. 156–157° dec. The product obtained by this procedure gave spectrophotometric and polarimetric data identical with that obtained above.

(16) J. P. Horwitz, A. J. Tomson, J. A. Urbanski, and J. Chua, *J. Org. Chem.*, **27**, 3045 (1962).

(17) A reaction period of 2 hr. as employed by the English workers (see ref. 13) gave **9** in only 24% yield.

Monoglucose Derivatives of Gentisic Acid

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A glucoside of gentisic acid (2,5-dihydroxybenzoic acid) has been found to accumulate in sunflower leaves that have become deficient in boron.[1] As the position of attachment of the glucose unit in the unknown glucoside was not determined, synthesis of the hitherto unknown monoglucosides of gentisic acid for use as reference standards was undertaken. Gentisic acid-5-β-D-glucopyranoside (I), gentisic acid-2-β-D-glucopyranoside (II), and 1-*O*-gentisoyl-β-D-glucopyranose (III) have been prepared.

Glucosides I and II were obtained from their known methyl esters[2] by de-esterification with barium hydroxide. Compound III was produced by the condensation of 2,5-dibenzyloxybenzoyl chloride with the sodium salt of 4,6-*O*-benzylidene-α-D-glucopyranose in chloroform, followed by the catalytic reduction of the product. It was then purified on a polyamide column. Acetylation of III produced the hexaacetate, 1-*O*-(2′,5′-diacetylgentisoyl)-β-D-glucopyranose tetraacetate. This derivative was identical with that obtained by the condensation of gentisic acid diacetate with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of silver oxide and quinoline. Steps in the preparation of monoglucosides of gentisic acid are summarized in Fig. 1.

Experimental

Melting points are not corrected and were taken in open capillary tubes. No efforts were made to obtain maximum possible yields.

2,5-Dibenzyloxybenzoic Acid.—To a solution of 61.6 g. (0.4 mole) of gentisic acid in 800 ml. of absolute ethyl alcohol was added 228 ml. of freshly distilled benzyl chloride, followed by 332 g. of anhydrous potassium carbonate. The mixture was refluxed for 20 hr. under anhydrous conditions and cooled to room

(1) R. Watanabe, W. Chorney, J. Skok, and S. Wender, *Phytochemistry*, in press.

(2) G. Wagner, *Arch. Pharm.*, **291**, 278 (1958).

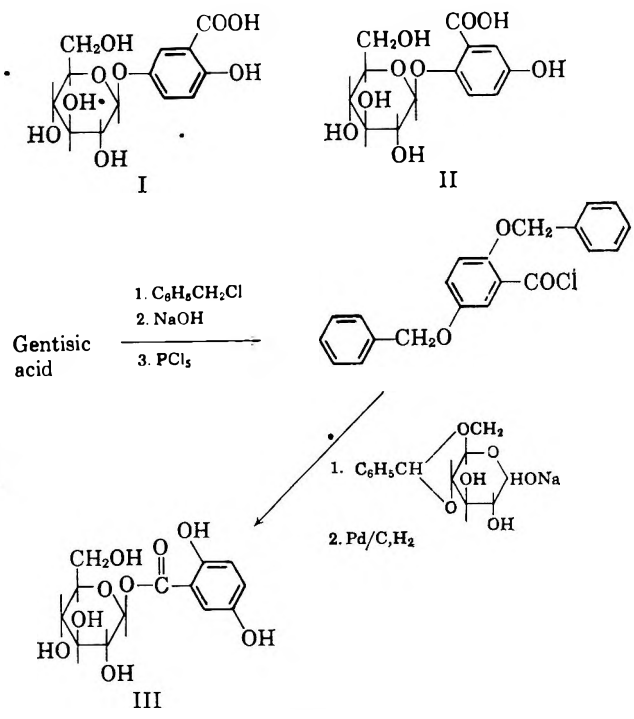

Fig. 1.—Summary of steps in synthesis of monoglucose derivatives of gentisic acid.

temperature; 900 ml. of cold water was added. Three phases were formed. After separation, the middle yellow layer was refluxed for 45 min. in 680 ml. of ethyl alcohol–water (100:70 v./v.) containing 60 g. of sodium hydroxide. After cooling the reaction mixture to room temperature, 800 ml. of cold water was added. Neutralization with concentrated hydrochloric acid produced a pale yellow product which was filtered off, washed with water, and air-dried to yield 92 g. (69%) of a pale yellow powder. Crystallization from benzene–isooctane gave a white crystalline product (82 g., 61%), m.p. 108–109°.

Anal. Calcd. for $C_{21}H_{18}O_4$ (334.37): C, 75.43; H, 5.43. Found: C, 75.61; H, 5.45.

2,5-Dibenzyloxybenzoyl Chloride.—To a solution of 40 g. (0.12 mole) of 2,5-dibenzyloxybenzoic acid in 160 ml. of anhydrous benzene–isooctane (1:1 v./v.) was added 29 g. (0.14 mole) of phosphorus pentachloride. When the initial reaction had subsided, the solution was refluxed for 1 hr. and then left overnight at 5°. Filtration yielded 30 g. (71%) of a pale yellow crystalline product, m.p. 83–86°. Crystallization from hexane produced granular white crystals (24 g., 57%), m.p. 86–88°.

Anal. Calcd. for $C_{21}H_{17}ClO_3$ (352.81): C, 71.49; H, 4.86; Cl, 10.05. Found: C, 71.64; H, 4.98; Cl, 9.88.

Sodium Salt of 4,6 *O*-Benzylidene-α-D-glucopyranose.—The 4,6-*O*-benzylidene-α-D-glucopyranose was prepared by the method of Zervas.[3] The crude product was crystallized twice from hot water and once from ethyl acetate to yield white crystals, m.p. 184–185°, lit. m.p. 188°. The sodium salt was obtained by the Zervas method.

1-*O*-Gentisoyl-β-D-glucopyranose (III).—To a solution of 10 g. (0.0286 mole) of 2,5-dibenzyloxybenzoyl chloride in 35 ml. of anhydrous chloroform was added 8.3 g. (0.0286 mole) of freshly prepared sodium salt of 4,6-*O*-benzylidene-α-D-glucopyranose. The suspension was shaken for 2 days at room temperature and then concentrated under reduced pressure to a thick sirup. Ethyl acetate (800 ml.) was added, and the cloudy solution then was washed three times with distilled water. The organic layer was dried over anhydrous sodium sulfate and then hydrogenated at room temperature and atmospheric pressure in the presence of 2 g. of 10% palladium on charcoal until absorption had substantially ceased (3 hr.). The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to a small volume. The addition of excess benzene produced a white precipitate which was filtered off, washed with benzene, and air-dried to give a white powder (5.7 g., 63%). Purification of III was achieved by chromatography on a column packed with "Ultramidpulver" (Badische-Anilin and Soda-Fabrick AG, Ludwigshafen am Rhein) in water, under a pressure of 2 p.s.i. The absorbent was washed with five column lengths of dimethylformamide–acetic acid–water–ethyl alcohol (1:2:6:4, v./v./v./v.) under gravity, followed by distilled water. Impure III (1 g.), dissolved in 50 ml. of distilled water, was added onto the polyamide. On development of the chromatogram with distilled water, two zones formed which fluoresced blue under ultraviolet light (3660 Å.). The major zone was eluted in 1300 ml. of colorless solution. On "freeze-drying," a white product (0.7 g.) resulted. Paper chromatography showed the presence of only one compound. Using descending chromatography and Whatman No. 1 chromatography paper, R_f values for the glucoside were 0.62 in *n*-butyl alcohol–acetic acid–water (6:1:2 v./v./v., called BAW), 0.83 in 2% acetic acid–water, and 0.38 in isobutyl methyl ketone–formic acid–water (3:1:2 v./v./v., called IBFW). The glucoside III showed $[\alpha]^{25}D$ −17.3° (distilled water).

Anal. Calcd. for $C_{13}H_{16}O_9$ (316.27): C, 49.37; H, 5.10. Found: C, 49.16; H, 5.19.

After spraying III on paper chromatograms with a 0.2% aqueous solution of β-glucosidase (Calbiochem, Los Angeles, Calif.) and leaving for 1 hr. in a moist chamber, gentisic acid was obtained.

1-*O*-(2′,5′-Diacetylgentisoyl)-β-D-glucopyranose Tetraacetate.—To a suspension of 0.5 g. of 1-*O*-gentisoyl-β-D-glucopyranose in 5 ml. acetic anhydride was added 1 drop of concentrated sulfuric acid. The solid dissolved rapidly, and the solution was kept at 50–60° for 30 min., and then quenched in 100 ml. of ice–water. Filtration yielded a white product (0.7 g.). Two crystallizations from hot methyl alcohol yielded a white crystalline product (0.2 g.), m.p. 158–159°.

In another preparation, gentisic acid diacetate[2] (19 g., 0.08 mole) and tetra-*O*-acetyl-α-D-glucopyranosyl bromide (32.8 g., 0.08 mole) were dissolved in warm quinoline (55 ml.) The addition of silver oxide (10 g.) with stirring produced heating and thickening of the reaction mixture. After 2 hr., the dark viscous material was extracted with 200 ml. of hot acetic acid and filtered. Quenching in 2.5 l. of ice–water produced a brown precipitate. After filtration and air-drying, the brown material (28.1 g.) was crystallized from methyl alcohol and charcoal to produce 20 g. (44%) of white crystals, m.p. 156–157°. Recrystallization from methyl alcohol gave a product melting at 158–159°.

Anal. Calcd. for $C_{25}H_{28}O_{15}$ (568.50): C, 52.82; H, 4.96. Found: C, 52.99; H, 4.97.

A mixture melting point determination of the 1-*O*-(2′,5′-diacetylgentisoyl)-β-D-glucopyranose tetraacetate samples prepared by the two different pathways showed no depression of melting point of either sample.

(3) L. Zervas, *Ber.*, **64**, 2289 (1931).

Isolation of Gentiobiose from Gentian Root

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The trisaccharide, gentianose, was isolated in 1882 from roots of *Gentiana lutea*[2] and shown later to give rise when treated with invertase to a disaccharide, gentiohexobiose, now called gentiobiose, and fructose.[3] Later work confirmed this, a yield of 1.2 g. of gentiobiose octaacetate being obtained from a kilogram of the root.[4]

The relative inaccessibility of the gentian plant and the uncertainty of the presence of gentianose in the

(1) Paper No. 5286, Minnesota Agriculture Experiment Station.
(2) A. Meyer, *Z. physiol. Chem.*, **6**, 135 (1882).
(3) E. Bourquelot and H. Hérissey, *Compt. rend.*, **132**, 571 (1901).
(4) G. Zemplén, *Z. physiol. Chem.*, **85**, 402 (1913); *Ber.*, **48**, 233 (1915).

powdered gentian root of commerce,[5] which may depend upon the stage of development of the plant, has led to the suggestion that the best way to prepare gentiobiose is to synthesize it by treating 2,3,4,6-tetra-*O*-acetyl-α-glucosyl bromide with 1,2,3,4-tetra-*O*-acetyl-D-glucose. This provides the crystalline octaacetate[6,7] from which the free disaccharide may be obtained by deacetylation. A recent modification of this synthetic approach involving the interaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide with 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-β-D-glucose in the presence of silver perchlorate is worthy of note.[7] A biochemical synthesis effected by the action of almond emulsin (β-D-glucosidase) on D-glucose has also been recommended,[8] and recently controlled hydrolysis of yeast glucan[9] and of the $\beta 1 \rightarrow 6$ linked D-glucan (pustulan) from *Umbilicaria pustulata*[10] has been shown to give gentiobiose.

During the summer of 1961, roots of the yellow gentian (*Gentiana lutea*) were collected in the area of Lausanne, Switzerland, and shown to contain gentiobiose in such amounts that acetylation of the 50% aqueous ethanol extract readily afforded crystalline gentiobiose octaacetate, the yield amounting to 23 g./kg. of dried roots.

Roots of a second species of gentian (*Gentiana andrewsii*) collected in September, 1963, in New Hampshire (U. S. A.) have also been found to be a good source of gentiobiose. In this case, the roots were extracted with water and the extract was treated with ethanol to precipitate a polysaccharide which was composed of arabinose, galactose, glucose, and traces of rhamnose. Acetylation of the mixture of sugars recovered from the aqueous ethanolic solution readily afforded gentiobiose β-octaacetate, the yield of the latter corresponding to 26 g./kg. of dried roots. Thus, treatment of the material with yeast invertase as formerly recommended[3-5] is unnecessary.

Experimental

All evaporations were carried out under reduced pressure at about 40°.

Isolation of Gentiobiose from Gentian Roots.—**A. From *Gentiana lutea*.** Roots were collected from flowering plants of the yellow gentian found in the vicinity of Lausanne, Switzerland, during the first week of July, 1961. The partially dried roots (150 g.) were cut into small pieces and extracted with 50% aqueous ethanol (900 ml.) at room temperature during 12 hr. The extract was decanted and the residue was ground in a mortar and a second extraction was carried out in the same manner. After three extractions had been made, the combined solutions were concentrated *in vacuo* at 40° to a volume of about 200 ml. This solution was treated with ethanol (400 ml.) and, after adding charcoal, the solution was filtered and concentrated to 100 ml. Paper chromatography showed that this solution contained glucose, sucrose, and gentiobiose, and smaller porportions of other slow moving components. The solution (100 ml.) was treated with water (100 ml.) and invertase (10 mg.) was added. Addition of invertase is believed to be unnecessary (see B below). After keeping overnight, the solution was concentrated to dryness and the residue was dissolved in pyridine (30 ml.) and treated with acetic anhydride (20 ml.) at room temperature for 12 hr. The reaction mixture was poured with stirring into water and after 2 hr. the product was extracted with chloroform (200 ml.) The chloroform solution was washed with water (three times), dried ($MgSO_4$), and concentrated to a sirup. This sirupy product was dissolved in warm methanol and after nucleating with β-gentiobiose octaacetate, the solution was allowed to crystallize. After keeping for 12 hr., filtration and washing gave a crude product (3.5 g.) which when recrystallized from methanol gave β-gentiobiose octaacetate, m.p. 192.5–194°, $[\alpha]^{25}D$ −5.6° (*c* 1.3, chloroform); lit.[5] (β-gentiobiose octaacetate) m.p. 193°, $[\alpha]D$ −5.3° (chloroform); yield 2.5 g. of octaacetate from 250 g. of gentian root of unspecified origin; lit.[5,7] (α-octaacetate) m.p. 188–189°, $[\alpha]D$ +52.4° (chloroform).

B. From *Gentiana andrewsii*.—Roots of this species of blue gentian were collected from flowering plants found in the mountains of New Hampshire, U. S. A., in September, 1963. The partially dried roots (77 g.) which had been kept at room temperature for about 7 days were heated with water (500 ml.) on a steam bath for 5 hr. The swollen roots were disintegrated in a Waring Blendor in the presence of added water (total volume 1000 ml.). The mixture was filtered through a linen cloth and the filtrate was concentrated to a volume of 500 ml. and treated with ethanol (1000 ml.). The polysaccharide which was precipitated at this stage was recovered (centrifuge) and purified by reprecipitation (twice) from aqueous solution with ethanol and then dried *in vacuo* after washing successively with ethanol, ether, and petroleum ether. This polysaccharide, which readily dissolved in water, showed $[\alpha]^{24}D$ +157° (*c* 1, water), and, upon hydrolysis by heating (sealed tube) with 0.5 *N* H_2SO_4 for 5 hr. in a boiling water bath, it gave rise to arabinose, galactose, glucose, and traces of rhamnose as revealed by paper chromatography.

Evaporation of the aqueous ethanolic solution from the first precipitation of the polysaccharide gave a sirupy product which was dissolved in methanol (250 ml.). After removing a small proportion of insoluble precipitate, the methanolic solution was concentrated to dryness and the yellowish brown residue was subjected to acetylation by heating for 2 hr. with a mixture of acetic anhydride (135 ml.) and anhydrous sodium acetate (11 g.). The reaction mixture was poured with stirring into water (1000 ml.) and, after the excess of acetic anhydride had decomposed, the acetylated product was extracted with chloroform (500 ml.). The chloroform solution was washed with an aqueous solution of sodium bicarbonate and with water. The dried ($MgSO_4$) chloroform extract was treated with charcoal, filtered, and concentrated to remove the solvent. The residue was dissolved in a small volume of methanol and the solution, after nucleation with β-gentiobiose octaacetate, was kept at room temperature for 2 days until crystallization was complete. The crystalline mass was diluted with methanol and the crystals were recovered by filtration. Recrystallization of the product from methanol gave β-gentiobiose octaacetate (2.0 g.), m.p. 195° and $[\alpha]^{25}D$ −6.4° (*c* 2, chloroform).

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(6) B. Helferich and W. Klein, *Ann.*, **450**, 219 (1926); D. D. Reynolds and W. L. Evans, *J. Am. Chem. Soc.*, **60**, 2559 (1938).

(7) H. Bredereck, A. Wagner, G. Faber, H. Ott, and J. Rauther, *Ber.*, **92**, 1135 (1959).

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Synthesis of α-Keto Acids from Diethyl Alkylidenemalonates

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An earlier paper[1] described the preparation of α-keto amides by epoxidation of ethyl alkylidenecyanoacetates and subsequent decarboxylation of the epoxy acids thus obtained. This procedure has now been extended to the synthesis of α-keto acids by the use of diethyl alkylidenemalonates.

(1) M. Igarashi and H. Midorikawa, *J. Org. Chem.*, **28**, 3088 (1963).

TABLE I

EPOXIDATION OF DIETHYL ALKYLIDENEMALONATES

Diethyl alkylidenemalonate	Epoxy compound	B.p., °C. (mm.)	Yield, %	Formula	Anal., % Calcd. C	Calcd. H	Found C	Found H
Propylidene[a]	IIa	123–129 (8)	64	$C_{10}H_{16}O_5$	55.54	7.46	55.61	7.32
Butylidene[c]	IIb	130–133 (6)	75[b]	$C_{11}H_{18}O_5$	57.38	7.88	57.42	7.51
Isobutylidene[a]	IIc	120–122 (6)	72	$C_{11}H_{18}O_5$	57.38	7.88	57.73	7.89
Isopentylidene[a]	IId	129–133 (5)	58	$C_{12}H_{20}O_5$	59.00	8.25	59.34	8.15
n-Hexylidene[a]	IIe	150–155 (7)	70	$C_{13}H_{22}O_5$	60.44	8.59	60.77	8.40
n-Heptylidene[c]	IIf	153–157 (6)	72	$C_{14}H_{24}O_5$	61.74	8.88	62.00	8.63

[a] Ref. 2. [b] When trisodium phosphate and potassium carbonate as a catalyst were used, the yields were 37 and 3%, respectively. [c] B. Wojcik and H. Adkins, *J. Am. Chem. Soc.*, 56, 2424 (1934).

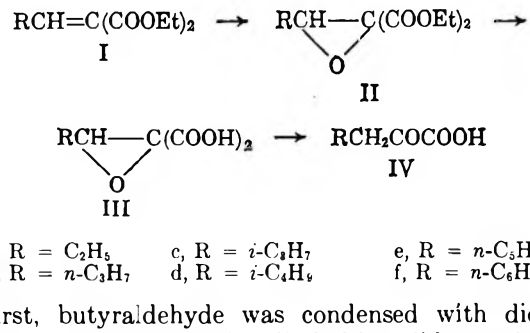
TABLE II

PREPARATION OF α-KETO ACIDS FROM EPOXY ESTERS (II)

α-Keto acid	B.p. (mm.) or m.p., °C.	Yield,[a] %	Formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa	58–61 (5)[b]	42 (A)	$C_5H_8O_3$	51.72	6.94		51.27	6.80	
Oxime	143 dec.[c]		$C_5H_9NO_3$			10.68			10.60
IVb	99–102 (20)[d]	46 (A) 35 (B)	$C_6H_{10}O_3$	55.37	7.75		54.98	7.56	
Oxime	132 dec.[e]		$C_6H_{11}NO_3$			9.65			9.43
IVc	97–98 (26)[f]	60 (A) 47 (B)	$C_6H_{10}O_3$	55.37	7.75		55.21	7.63	
Oxime	148 dec.[g]		$C_6H_{11}NO_3$			9.65			9.57
IVd	98–100 (11)[h]	58 (B)	$C_7H_{12}O_3$	58.31	8.39		57.89	8.01	
IVe	101–103 (4)[i]	65 (B)	$C_8H_{14}O_3$	60.74	8.92		60.33	8.76	
IVf	41–42[j]	60 (B)	$C_9H_{16}O_3$	62.76	9.36		62.57	9.22	
Oxime	97[k]		$C_9H_{17}NO_3$			7.48			7.34

[a] Capital letters refer to decarboxylation methods designated by these letters in the Experimental section. [b] F. Adickes and G. Andresen [*Ann.*, 555, 41 (1944)] report b.p. 66° (6 mm.). [c] K. E. Hamlin and W. H. Hartung [*J. Biol. Chem.*, 145, 351 (1942)] report m.p. 145° dec. [d] Lit.[b] b.p. 101–102° (20 mm.). [e] Lit.[b] m.p. 132–133° dec. [f] J. Schreiber [*Ann. Chem.* (Paris), [12]2, 98 (1947)] reports b.p. 84° (15 mm.). [g] T. Uyemura [*Bull. Agr. Chem. Soc. Japan*, 15, 353 (1939)] reports m.p. 147° dec. [h] R. Locquin [*Bull. soc. chim. France*, [3]31, 1153 (1904)] reports b.p. 101–102° (12 mm.). [i] Lit.[b] b.p. 118–123° (13 mm.). [j] Lit.[b] m.p. 43–44°. [k] Lit.[b] m.p. 98–98.5°.

Diethyl alkylidenemalonates (I) have been prepared in good yield by using the conditions developed by Cope, *et al.*[2] Epoxidation of these unsaturated esters with hydrogen peroxide proceeded smoothly in the presence of sodium tungstate to give the epoxy esters (II). Alkaline hydrolysis of the epoxy esters afforded the corresponding acids (III) which were readily decarboxylated to α-keto acids (IV).



a, R = C_2H_5 c, R = *i*-C_3H_7 e, R = *n*-C_5H_{11}
b, R = *n*-C_3H_7 d, R = *i*-C_4H_9 f, R = *n*-C_6H_{13}

First, butyraldehyde was condensed with diethyl malonate, and the resulting diethyl butylidenemalonate was treated with 30% hydrogen peroxide at 70–80° giving ethyl 2,3-epoxy-2-ethoxycarbonylcaproate (IIb).

Payne[3] showed that ethanolysis of ethyl 2,3-epoxy-2-ethoxycarbonylbutyrate leads to ethyl 3-ethoxy-2-ethoxycarbonyl-2-hydroxybutyrate or its isomer, ethyl 2-ethoxy-2-ethoxycarbonyl-3-hydroxybutyrate. When the ethanolysis was carried out with IIb, the product was a mixture of ethyl 2-ethoxy-2-ethoxycarbonyl-3-hydroxycaproate and ethyl 3-ethoxy-2-ethoxycarbonyl-2-hydroxycaproate.

The epoxy ester (IIb), on treatment with alcoholic potassium hydroxide, gave a potassium salt of 2-carboxy-2,3-epoxycaproic acid. The epoxy acid produced by acidification of the salt was decarboxylated on heating in an oil bath, giving 2-oxocaproic acid, identical (physical constants, infrared spectrum, and oxime derivative) with the compound prepared previously from α-oxocaproamide.[1]

These techniques have also been successfully applied to other α,β-unsaturated diesters. These results are summarized in Tables I and II.

An attempt was then made to modify the above approach to diethyl 3-methylpropylidenemalonate. The ester was recovered unchanged, however, after prolonged treatment with 30% hydrogen peroxide. This result is in accord with the observation of Payne.[3] He has reported that, whereas diethyl ethylidenemalonate on treatment with 50% hydrogen peroxide gave the epoxy compound in high yield, diethyl isopropylidenemalonate under similar conditions failed to undergo epoxidation because of a steric inhibition of coplanarity.

A convenient and direct synthesis of α-keto esters from epoxy esters (II) was also investigated. Ethyl

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2,3-epoxy-2-ethoxycarbonylcaproate (IIb) and 0.5 mole of alkali in ethanol at room temperature afforded ethyl 2-carboxy-2,3-epoxycaproate. The monoester was converted, by heating, into the known ethyl 2-oxocaproate, on decarboxylation and rearrangement of oxygen. In a similar reaction sequence, isopropyl 4-methyl-2-oxovalerate was prepared in good yield from isopropyl 2,3-epoxy-2-ethoxycarbonyl-4-methylvalerate.

In an attempt to obtain α-keto esters from ethyl 2-carbamoyl-2,3-epoxycarboxylate,[1] selective hydrolysis of the carbamoyl group by Fischer's procedure[4] was examined. Reaction of ethyl 2-carbamoyl-2,3-epoxy-3-methylvalerate with nitrous acid in ether at 0° gave a 50% yield of ethyl 2-carboxy-2,3-epoxy-3-methylvalerate which could be converted into ethyl 3-methyl-2-oxovalerate on decarboxylation.

Experimental

General Procedure. Epoxidation.—Diethyl alkylidenemalonate (0.01 mole), 15 ml. of 30% hydrogen peroxide, 15 ml. of ethanol, and 0.7 g. of sodium tungstate dihydrate were placed in a round-bottom flask, fitted with a reflux condenser and thermometer. The mixture was heated to 70–80° on a water bath for about 1 hr. After an additional hour, ethanol was removed by distillation. The oily layer was separated from the aqueous layer, the aqueous layer was extracted with two portions of ether, and the combined extracts and oil were dried over calcium chloride. The ether was removed by distillation. Fractional distillation of the residue gave epoxy ester (II).

Hydrolysis.—The epoxy ester (II) was dissolved in an ethanolic solution of potassium hydroxide and allowed to saponify overnight at room temperature (or elevated temperature). The resulting precipitate was dissolved in water and acidified with dilute hydrochloric acid. The aqueous solution was extracted with ether. The ether was distilled and all low-boiling material was removed from the residue on a water bath under reduced pressure. The epoxy acid which remained in the flask was used without further purification for the preparation of α-keto acid. The yields of crude epoxy acids were 80–90%.

Decarboxylation. A.—In a Claisen flask was placed the epoxy acid. When it was heated in an oil bath at 180–200° under reduced pressure, evolution of carbon dioxide was observed. The product was removed by distillation. The distillate was dissolved in an aqueous sodium carbonate solution and then shaken with ether. The alkali solution was acidified with dilute hydrochloric acid and again extracted with ether. The ether was removed by distillation. Fractional distillation of the residue gave α-keto acid.

B.—Epoxy acid (III) was heated with 50% sulfuric acid for 2–3 hr. The solution was cooled and extracted with ether. The ethereal solution was shaken with an aqueous sodium carbonate solution. The aqueous layer was acidified and then extracted with ether. Fractional distillation of the extract gave α-keto acid.

Ethyl 2-Oxocaproate from Ethyl 2,3-Epoxy-2-ethoxycarbonylcaproate (IIb).—In a three-necked flask equipped with a sealed stirrer, dropping funnel, and a reflux condenser, 24.5 g. of ethyl 2,3-epoxy-2-ethoxycarbonylcaproate (IIb) and 100 ml. of ethanol were charged, and a solution of 5.6 g. of potassium hydroxide in 60 ml. of ethanol was added at room temperature with stirring. After the mixture had stood overnight, it was heated to boiling on a water bath and filtered. A sirup was obtained by concentrating the mother liquor. The sirup was dissolved in water and shaken with ether. The aqueous layer was cooled to 5° and a slight excess of hydrochloric acid was added while the temperature was maintained below 10°. The aqueous solution was then extracted with ether. The ethereal solution was concentrated to give the monoethyl ester. The yield was 15 g. The product was used without further purification for the following reaction.

Decarboxylation of the monoester was carried out as in the above experiment A. The fraction distilling at 103–110° (35 mm.) was collected (10 g.), lit.[5] b.p. 83.5–84° (10 mm.).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.41; H, 8.80.

2,4-Dinitrophenylhydrazone had m.p. 120°, lit.[5] m.p. 120.5–121°.

Anal. Calcd. for $C_{14}H_{18}N_4O_6$: N, 16.56. Found: N, 16.24.

Ethyl isopropyl isobutylidenemalonate was prepared by Cope's method[2] from ethyl isopropyl malonate and isobutyraldehyde. The yield was 87%, b.p. 106–107° (4 mm.).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.89; H, 8.63.

Isopropyl 2,3-Epoxy-2-ethoxycarbonyl-4-methylvalerate.—Epoxidation of ethyl isopropyl isobutylidenemalonate was carried out, by using trisodium phosphate, as described above. The fraction distilling at 115–116° (4 mm.) was collected. The yield was 70%.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.26; H, 8.23.

Isopropyl 4-Methyl-2-oxovalerate.—Hydrolysis of isopropyl 2,3-epoxy-2-ethoxycarbonyl-4-methylvalerate was carried out as above. The resulting crude isopropyl 2-carboxy-2,3-epoxy-4-methylvalerate was heated at 180–200° in an oil bath, and then the fraction distilling at 88–89° (23 mm.) was collected. The yield was 51%.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.09; H, 9.11.

The product gave a green color with ferric chloride in ethanol.

Ethyl 3-Methyl-2-oxovalerate from Ethyl 2-Carbamoyl-2,3-epoxy-3-methylvalerate.[1]—Ten grams of ethyl 2-carbamoyl-2,3-epoxy-3-methylvalerate was dissolved in 75 ml. of ether containing 5 ml. of water and then the solution was cooled in an ice bath. A steady stream of nitrous acid was introduced into the cold solution while cooling was continued for a period of 14 hr. The ethereal solution was then washed with water and the ether was removed by distillation. The residue was dissolved in an aqueous sodium hydrogen carbonate solution, and the alkaline solution was extracted with ether to remove any material not soluble in alkali. The aqueous solution was then acidified with dilute hydrochloric acid and again extracted with ether. The ether was removed to give the crude product. The above purification procedure was repeated. Ethyl 2-carboxy-2,3-epoxy-3-methylvalerate was obtained in 50% yield as an oil.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.01; H, 6.77.

The compound was decarboxylated by heating in an oil bath (bath temperature, 180–190°) giving ethyl 3-methyl-2-oxovalerate, 2 g., b.p. 75–80° (15 mm.), lit.[6] b.p. 78–79° (15 mm.).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.31; H, 8.44.

The ester gave a dark green color with ferric chloride in ethanol.

Ethyl 4-Methyl-2-oxovalerate from Ethyl 2-Carbamoyl-2,3-epoxy-4-methylvalerate.[1]—The procedure was carried out as above. Ethyl 4-methyl-2-oxovalerate, b.p. 100–104° (35 mm.), was obtained in 42% yield, lit.[5] b.p. 76–77° (10 mm.).

2,4-Dinitrophenylhydrazone had m.p. 79°, lit.[5] m.p. 79.5–80°.

Anal. Calcd. for $C_{14}H_{18}N_4O_6$: N, 16.56. Found: N, 16.31.

Ethanolysis of Ethyl 2,3-Epoxy-2-ethoxycarbonylcaproate (IIb).—A solution of 4.4 g. of IIb in 25 ml. of ethanol containing 1 ml. of concentrated sulfuric acid was refluxed for 8 hr. The solution was then neutralized with calcium carbonate. After filtration and concentration, the resulting residue was taken up in warm ether and filtered. Distillation of the filtrate gave 4.0 g. of material, b.p. 136–138° (6 mm.), having an analysis in agreement with ethyl 2-ethoxy-2-ethoxycarbonyl-3-hydroxycaproate and its isomer. Hell-Urech's, Diniges', Chancel's, and Nessler's reactions[7] were all positive.

Anal. Calcd. for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 61.46; H, 10.31.

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Transacetalation of Methyl 9,9-Dimethoxynonanoate

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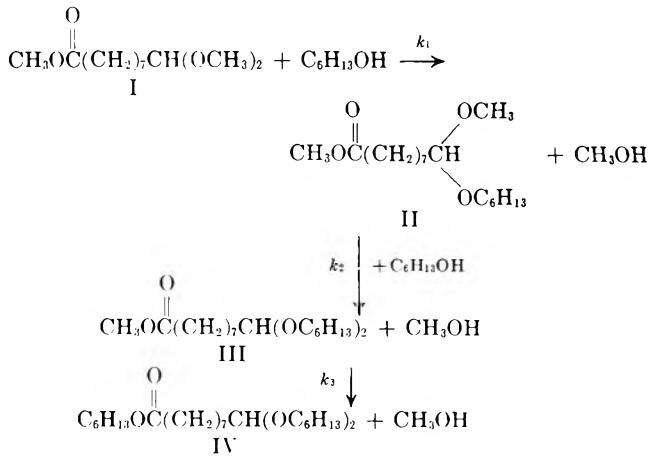
The stability of acetals, especially cyclic acetals, in the presence of alkaline and neutral reagents is well known.[2,3] This stability makes possible the reactions of other functional groups in compounds containing carbonyl groups protected in the acetal form. Although considerably fewer in number, selective reactions of the acetal group in a polyfunctional compound also are recorded. For example, selective hydrolysis[4,5] and transacetalation to form acyclic[6] as well as cyclic[7,8] acetals in compounds also containing an ester group have been described. The ease with which 1,2- and 1,3-diols form cyclic acetals and their stability in general have been noted.[9,10] However, we have reported a special case of transacetalation of cyclic acetals in the presence of an ester group: the cross linking of poly(ester acetals) and poly(amide acetals) with certain metal oxides and salts.[11-13]

Selective transacetalation to form acyclic acetals with acidic catalysts has been noted only for certain β,β-dialkoxypropionate and β-alkoxyacrylate derivatives.[6] Since alkoxide catalysts cause both transacetalation and transesterification, β-alkoxy esters cannot be considered representative members of a homologous series of ω-dialkoxy esters. We therefore report our findings on selective alcoholysis with acidic and alkaline catalysts of a more representative homolog, methyl 9,9-dimethoxynonanoate (I), and discuss the kinetics of the reaction in a quantitative sense. We also describe the cleavage of I to form enol ethers.

Alcoholysis of the acetal group of I was carried out in the presence of potassium acid sulfate catalyst, 100% excess of alcohol, and a slow stream of nitrogen to aid removal of methanol. A study of time and temperature effects was carried out with 1-hexanol (Table I). A 95% conversion to methyl 9,9-(1-hexoxy)nonanoate (III) was obtained in 4 hr. at 75° with none of the hexyl ester (IV) *or of the mixed acetal* (II) detected by gas–liquid chromatography (g.l.c.) at any point during this



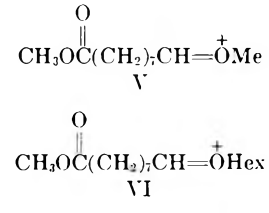
period. Higher reaction temperatures and longer heating periods resulted in the formation of increasing amounts of IV. Similar conversions were obtained with other alcohols, including butyl, 2-ethylhexyl, and *n*-octadecyl alcohols, ethylene glycol, glycerol, and 2-methoxyethanol. Ester formation was more significant with ethyl and allyl alcohols.

TABLE I

EFFECT OF REACTION CONDITIONS ON ACETAL ALCOHOLYSIS

Reaction temp., °C.	Reaction time, 4 hr. Total conversion, %	Ester acetal IV, %	Reaction time, 7 hr. Total conversion, %	Ester acetal IV, %
50	82.5	0.0	87.0	0.0
75	95.0	0.0	95.6	0.8
85	94.5	2.9	97.0	3.5
115	88.0	4.4	92.5	18.0
155	92.0	21.2	92.5	33.0

The absence of a detectable quantity of the mixed acetal II leads to the conclusion that $k_2 > k_1$. A semiquantitative value for the ratio $K = k_2/k_1$ may be calculated from the equations developed for series first-order reactions.[14] Thus, at $K = 30$, for 75% completion of the reaction, the concentration of II should be about 0.9%; 2.6% at 25% completion. Assuming the limit of detection of the gas chromatograph to be about 1%, then K must be at least 30. This difference in reaction rates is in qualitative accord with the findings of Juvet and Chiu,[15] who studied the methanolysis of the diethyl acetal of acetaldehyde. On the basis of several rate determinations, they concluded that alcoholysis rate depends on the remaining alkoxy group rather than on the leaving or attacking group. Thus, inductive stabilization by the *n*-hexyl group makes VI (and the transition states leading to it from II and from it to III) more stable than V (and its corresponding transition states).



However, Juvet and Chiu found that conversion of the mixed acetal to the diethyl acetal occurred at a rate

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only 1.6 times faster than the conversion of the dimethyl to the mixed acetal. The larger ratio of 30 for the corresponding two steps as described herein may be due to the greater steric effect of the hexyl group as compared to ethyl. The steric effect would cause the methyl hexyl acetal II to be less stable than the methyl ethyl acetal of acetaldehyde relative to their respective carbonium ions VI and CH_3CHOEt^+.

Our results are also in qualitative accord with those of Salomaa,[16] who found a ratio of *ca.* 6 for the rate constants in acid-catalyzed hydrolysis of $EtOCH_2OEt$ compared to $MeOCH_2OMe$, and with Jansson's,[17] who found ratios ranging from 5 up to 9 for the rate constants in acid-catalyzed hydrolysis of $CH_3CH(OEt)_2$ compared to $CH_3CH(OMe)(OEt)$.

Alcoholysis of the ester group was carried out in the presence of sodium methoxide with *n*-butyl and 2-ethylhexyl alcohols, ethylene glycol, glycerol, and 2-methoxyethanol. Heating at about 100° for up to 10 hr. was required to obtain yields comparable to those obtained in transacetalation. No evidence for transacetalation with the alkaline catalysts showed by g.l.c., in contrast to the results reported for β,β-dialkoxypropionates.[6]

Analogous to the cracking reaction that simple acetals undergo,[18] I underwent a cracking reaction to form the enol ether (VII). The cracking reaction was carried out

$$CH_3OCH{=}CH(CH_2)_6COOCH_3$$
VII

in the liquid phase with heating in the presence of potassium acid sulfate. Cracking at 150° was quite pronounced, and crude yields of 80–90% were obtained in 8 hr. Under the same heating conditions but in the absence of catalyst or acidic substance, no significant cracking occurred.

The apparently homogeneous cracked product VII contained two components by g.l.c. analysis. These components are believed to be the *cis* and *trans* isomers. Evidence for this conclusion was obtained from the infrared spectrum, by ozonation, and by re-formation of the dimethyl acetal. Infrared analysis of both I and VII indicated several changes. Bands at 1130, 1055, and 950 cm.$^{-1}$ in the spectrum of I no longer appeared in the spectrum of VII, and new bands at 1667, 1266, 1115, 1025, and 934 cm.$^{-1}$ appeared for VII. The band at 934 cm.$^{-1}$ is attributed to the *trans* configuration, the shift from the normal 965 cm.$^{-1}$ resulting from the presence of the ether group.[19] This assignment of structure is in agreement with an absorption at 930 cm.$^{-1}$ for certain *trans* alkenyl ethers as reported by Warner and Lands.[19b] Position of the double bond was established by ozonizing VII and oxidatively decomposing the ozonolysis products by the method of Ackman, *et al.*[20] G.l.c. analysis of the product methyl esters showed the presence of the expected C_8 diester and the complete absence of the C_7 diester, which would have resulted if the double bond had shifted to give a positional isomer. The enol ether VII added methanol rapidly and quantitatively at room temperature in the presence of hydrochloric acid to re-form I[21]; it was also hydrogenated to give methyl 9-methoxynonanoate in good yields.

The cyclic acetal from ethylene glycol was considerably more stable and not subject to cracking under the conditions used. The infrared spectrum before and after treatment, under conditions known to produce enol ethers from dialkyl acetals, showed no enol ethers present. This stability was useful in the preparation of high-boiling ester derivatives, which otherwise would crack at the elevated temperatures necessary for distillation.

Experimental

Methyl 9,9-Dimethoxynonanoate (I).—A mixture consisting of methyl azelaaldehydate[22] (233.5 g., 1.25 moles), 500 ml. of methanol, 250 ml. of 2,2-dimethoxypropane, and 5 ml. of 5% methanolic hydrogen chloride was refluxed for 4 hr. The dimethoxypropane served as a water scavenger for the acetalation reaction similar to its use in the preparation of methyl esters.[23] To the product solution was added about 500 ml. of methylene chloride, and the solution was washed with water several times until the aqueous wash became neutral. Each water wash was backwashed with methylene chloride. This solution was distilled to remove methylene chloride, and the residue was distilled under reduced pressure through a 1 × 6 in. glass helices-packed column. There was recovered 271.8 g. (1.17 moles, 93.4% yield) of product distilling at 78–80° at 0.13 mm., $n^{30}D$ 1.4294. G.l.c. analyses did not indicate any detectable impurities.

Effect of Temperature and Reaction Time upon Selectivity of Acetal Alcoholysis.—Ester acetal I (15.0 g., 0.065 mole), *n*-hexyl alcohol (26.15 g., 0.260 mole), and potassium hydrogen sulfate (0.1 g.) were heated at a predetermined temperature for 12 hr. The removal of methanol was assured by using a steam-heated condenser between the reaction flask and the take-off head. Samples were withdrawn every 0.5 hr. for the first 3 hr., every hour for the next 4 hr., and at the end of the heating period. For samples, 2 ml. were taken up in methylene chloride and washed three times with water. The methylene chloride layer was dried over anhydrous sodium sulfate. After filtering off the sodium sulfate and removing solvent, g.l.c. analysis was carried out on each sample. An F and M Model 500 temperature programmed gas chromatograph with a 2-ft. silicone gum rubber column was used. Compositions obtained from g.l.c. analysis were plotted for each reaction temperature. Information taken from the composition curves are summarized in Table I. Conversions of 95% are obtained in 4 hr. at 75° with no ester acetal IV detected. None of the mixed acetal II was found, even with the starting material I still present in the mixture.

In a preparative run at 75° for 4 hr., there was obtained a 95% yield of crude methyl 9,9-(di-1-hexoxynonanoate). Distillation gave a pure product boiling at 115–116° (0.03 mm.), $n^{30}D$ 1.4440, d^{20}_{20} 0.9046.

Anal. Calcd. for $C_{22}H_{44}O_4$: C, 71.25; H, 11.95. Found: C, 71.04; H, 11.79.

Cracking Procedure.—The acetal ester I (69.12 g., 0.298 mole) and potassium acid sulfate (0.20 g.) were heated in a three-necked round-bottom flask fitted with a capillary inlet for nitrogen, a thermometer, and a distillation head. Heating was carried out at 135–150° under reduced pressure for 7 hr. The product was taken up in methylene chloride and washed several times with water. After drying over anhydrous sodium sulfate, the solution was filtered and the solvent was stripped. Flash-distilled, the product left a polymeric residue of 23.3% based on starting material. The distillate contained 70.3% cracked product; the remainder was starting material and a trace of

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dimethyl azelate. The distillate was redistilled on a spinning band Podbielniak column without further condensation. The main fraction boiled at 107–109° (4.5 mm.), $n^{30}D$ 1.4434, and contained 98.6% cracked product.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 66.05; H, 10.08; hydroxylamine value, 200.2 g./equiv. Found: C, 66.14, H, 10.06; hydroxylamine value, 205.0 g./equiv.

G.l.c. analyses of the mixture during the cracking step showed two new peaks, believed to be the isomeric-substituted enol ether VII. Attempts to separate the isomers by fractional distillation were unsuccessful although *cis*- and *trans*-methyl propenyl ether have been successfully separated by this means.[24]

Methyl 9-Methoxynonanoate.—The enol ether VII (11.50 g. of 90.6% cracked products) was dissolved in 100 ml. of diethyl ether. Hydrogenation over 0.2 g. of platinum oxide was carried out at ambient temperature and 40 p.s.i. in a Parr low-pressure hydrogenation apparatus. The product was distilled through a spinning band Podbielniak column. The main fraction boiled from 109–110° (5.5 mm.), $n^{30}D$ 1.4282. The purity was 98% calculated from g.l.c. data.

Anal. Calcd. for $C_{11}H_{22}O_3$: C, 65.30; H, 10.90; sapon. equiv., 202.3. Found: C, 65.15; H, 10.87; sapon equiv., 201.3.

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Synthesis of 5-Substituted Derivatives of 3-Acetamido-1-methyl-2,4-dioxopyrrolidine[1]

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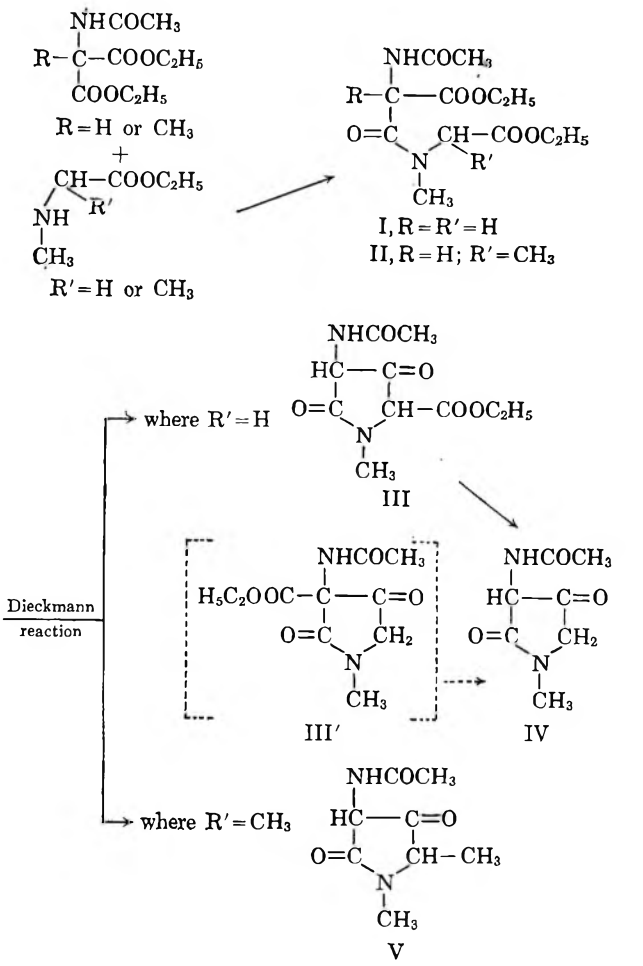
The structures of thiolutin and aureothricin, both yellow crystalline sulfur-containing antibiotics, were elucidated by Celmer and Solmons,[2] respectively, as 3-acetamido and 3-propionamido derivatives of 3-amino-5-methylpyrrolin-4-oxo[4,3-*d*]-1,2-dithiol (Ic). It is of interest that they are the first recognized examples of microbiologically active unsaturated lactams.

As part of investigation on the synthesis of thiolutin, the Dieckmann reaction of some N-(α-acetamido-α-ethoxycarbonylacetyl)-N-methylamino acid ethyl esters (I, R = R′ = H; II, R = H, R′ = CH_3) was carried out.

First, N-(α-acetamido-α-ethoxycarbonylacetyl)-N-methyl derivatives of glycine and alanine ethyl esters (I and II) were prepared from the corresponding amino acid esters and diethyl acetamidomalonates. Some 5-substituted 3-acetamido-1-methyl-2,4-dioxopyrrolidines (III, IV, and V) were prepared by the Dieckmann cyclization of the above ester derivatives. The product of this Dieckmann reaction of N-(α-acetamido-α-ethoxycarbonylacetyl)-N-methylglycine ethyl ester (I) was found to be 3-acetamido-5-ethoxycarbonyl-1-methyl-2,4-dioxopyrrolidine (III) and not 3-acetamido-3-ethoxycarbonyl-1-methyl-2,4-dioxopyrrolidine (III′), which is also a possibility. In this connection, compound III was found to be a useful intermediate for the preparation of α-amino-α'-methylamino-β-hydroxyglutaric acid. These 2,4-dioxopyrrolidines form a tautomeric system and derivatives of both ketonic and enolic tautomers were also prepared.

The sequence of reactions leading to 5-substituted derivatives of 3-acetamido-1-methyl-2,4-dioxopyrrolidine is shown in Scheme I.

SCHEME I



The starting materials, N-methylamino acid esters, were prepared *via* the α-methylamino derivatives of acetonitrile from formaldehyde or of propionitrile from acetaldehyde. In the case of the N-methylalanine ethyl ester, isolation of the intermediate, α-methylaminopropionitrile, was necessary in order to reduce the by-product formation to a minimum during esterification of the nitrile.

The condensation of N-methylamino acid ethyl esters and diethyl acetamidomalonates was effected in xylene at a refluxing temperature by the dropwise addition of the ester into the boiling xylene solution of the acetamidomalonate so as to avoid the formation of diketopiperazines by self-condensation. Completion of the reaction required more than 24 hr. of heating. The

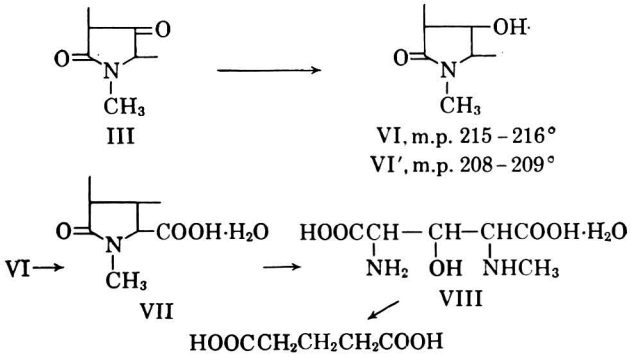
(1) Part of this paper was read at the 11th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1958.

(2) W. D. Celmer and I. A. Solmons, *J. Am. Chem. Soc.*, **77**, 2861 (1955).

products were highly viscous oils, distillable under high vacuum. The condensation failed with methyl derivatives of diethyl acetamidomalonate, possibly due to the steric effect.

Cyclization of the condensation products (I, II) progressed smoothly in an inert solvent in the presence of sodium ethoxide at room temperature. Cyclization of N-(α-acetamido-α-ethoxycarbonylacetyl)-N-methylalanine ethyl ester (II, R = H; R′ = CH_3) was attended with decarboxylation and the product thereby obtained was 3-acetamido-1,5-dimethyl-2,4-dioxopyrrolidine (V).

Similar treatment of N-(α-acetamido-α-ethoxycarbonylacetyl)-N-methylglycine ethyl ester (I, R = R′ = H) gave only one compound with an ethoxycarbonyl group, $C_{10}H_{14}N_2O_5$, which was one of the two isomers (III and III′). In order to determine which of these two alternative structures was correct, the following experiment was carried out.



Catalytic hydrogenation of III over Raney nickel at 1500 lb./in.^{2} afforded two diastereoisomeric dihydro compounds, $C_{10}H_{16}N_2O_5$, one (VI) of m.p. 215–216° and the other (VI′) of m.p. 208–209°. The former, produced in a larger amount, was converted by mild alkaline hydrolysis into a free acid (VII), which was further hydrolyzed with 6 *N* hydrochloric acid to α-amino-α′-methylamino-β-hydroxyglutaric acid (VIII). Thin layer chromatography of VIII on silica gel gave a spot near that of serine by development with water saturated with phenol. The chromatogram gave a positive reaction to the Ninhydrin reagent and to the Nessler reagent for hydroxyamino acid. Reduction[3] of this diaminodicarboxylic acid with hydriodic acid (sp. gr. 1.7) at 200° gave a straight-chain dibasic acid which was identified by infrared spectrum with authentic glutaric acid, and also by a mixture melting point test.

From the other possible structure (III′), glutaric acid could never be derived by the same procedure. These experiments leave no doubt that the Dieckmann reaction product of I (R = R′ = H) is 3-acetamido-5-ethoxycarbonyl-1-methyl-2,4-dioxopyrrolidine (III).

III is easily decarboxylated by treatment with dilute alkali and forms 3-acetamido-1-methyl-2,4-dioxopyrrolidine (IV), which was also obtained in a small amount, together with III, by the Dieckmann reaction of I. In view of the fact that the cyclization of II (R = H, R′ = CH_3) is always attended with decarboxylation, it seems reasonable to assume that IV in the Dieckmann reaction mixture may have been derived from the unstable isomer (III′) by decarboxylation. It may be possible that the two substituents, $-COOC_2H_5$ and $-NHCOCH_3$, cannot occupy the same 3-position owing to steric hindrance.

These 5-substituted 3-acetamido-1-methyl-2,4-dioxopyrrolidines (III, IV, and V) are acidic and decompose sodium hydrogen carbonate. They all show an intense blue coloration with ferric chloride solution. To confirm further their enolic character, these compounds were treated with diazomethane and the formation of enol ethers, along with the formation of 2,4-dinitrophenylhydrazones, indicated that they form tautomeric systems. The ultraviolet spectra (in water) of III, IV, and V, respectively, show absorption maxima at 274 mμ (log ε 3.84), 266 (3.85), and 268 (3.76). These spectral data provide strong evidence for the presence of the chromophor $-\overset{\alpha}{C}=\overset{\beta}{C}-\overset{R}{\underset{|}{C}}=O$ in these molecules in spite of the weak activating effect of the lactam carbonyl [α = OH, β = $NHCOCH_3$, R = $N(CH_3)$—]. Presence of the chromophor in these compounds was also suggested by their infrared spectra, carbonyl bands of which are shown in Table I.

TABLE I

CARBONYL BANDS OF III, IV, V, VI, AND VI′ (CM.$^{-1}$)

Compound	Bands A	B	C
IV		1661	1630
V		1674	1630
III	1740	1675	1635
VI	1742	1691	1638
VI′	1734	1700	1640

It is seen that the B-band of III shows a shift from those of VI and VI′ which show the normal γ-lactam carbonyl absorption near 1700 cm.$^{-1}$.[4] If III, IV, and V have an α,β-unsaturated carbonyl as their structural unit, this shift of a lactam carbonyl band will be expected. It seems reasonable, therefore, to assume that the B-band is associated with the γ-lactam carbonyl absorption. Since the infrared spectra of III, IV, and V lack normal carbonyl absorption in the 1725–1705-cm.$^{-1}$ range, the 4-oxo group in these compounds must be largely in the enolic form. As the A-band is an ester carbonyl band, the C-band is assigned to the 3-acetamido group.

Experimental

N-(α-Acetamido-α-ethoxycarbonylacetyl)-N-methylglycine Ethyl Ester (I).—A mixture of 76.2 g. (0.351 mole) of diethyl acetamidomalonate and 163 ml. of xylene was heated in an oil bath at 150°. A solution of 20.6 g. (0.176 mole) of N-methylglycine ethyl ester[5] in 40.8 ml. of xylene was added dropwise during 2.5 hr., and the mixture was heated for a further 20 hr. Most of the unchanged diethyl acetamidomalonate, which crystallized upon cooling the clear, slightly yellow solution, was filtered off, and the xylene was then distilled. The residue was distilled under high vacuum, and 32.5 g. (64.1%) of the main distillate was obtained as a very viscous yellow oil of b.p. 156–158° (0.02 mm.). The total amount of diethyl acetamidomalonate recovered as crystals and as the first distillate amounted to 43.3 g. (0.199 mole). Several redistillations produced an almost colorless viscous oil, b.p. 150–151° (0.01 mm.), $n^{23}D$ 1.4765.

(3) G. Hüfner, *J. prakt. Chem.*, **109**, 6 (1870).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 176.

(5) S. M. McElvain and P. M. Laughton, *J. Am. Chem. Soc.*, **73**, 449 (1951).

Anal. Calcd. for $C_{12}H_{20}N_2O_6$: C, 49.99; H, 6.99; N, 9.72. Found: C, 49.95; H, 6.91; N, 10.03.

3-Acetamido-5-ethoxycarbonyl-1-methyl-2,4-dioxopyrrolidine (III).—To a solution of sodium ethoxide, prepared from 1.78 g. (0.077 g.-atom) of sodium and 22.5 ml. of absolute ethanol and diluted with 30 ml. of benzene, a solution of 22.3 g. (0.077 mole) of I in 50 ml. of benzene was added dropwise during 1 hr. During this time, a yellowish white solid of the sodio derivative of the reaction product gradually formed in the orange-yellow solution. After completion of the addition, the reaction mixture was left overnight and then distilled to dryness. The residue was dissolved in a small amount of water, and the solution was acidified with 10% hydrochloric acid. Crude crystals usually began to precipitate at once and amounted to 12.9 g., m.p. 146–157°.

Recrystallization from absolute alcohol gave 8.2 g. (43.8%) of 3-acetamido-5-ethoxycarbonyl-1-methyl-2,4-dioxopyrrolidine (III), m.p. 156–158°. It gave an intense blue coloration with ferric chloride solution. Further recrystallization from benzene raised the melting point to 160–161°; ν_{max}^{KBr} 3285, 1740, 1675, 1635, 1401, and 1205 cm.$^{-1}$; $\lambda_{max}^{H_2O}$ 274 mμ (log ε 3.84).

Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.85; N, 11.57; mol. wt., 242.23. Found: C, 49.43; H, 5.77; N, 11.45; mol. wt., 266.1.

An effort was made to find another isomer from the ethanolic mother liquid of recrystallization, by fractional crystallization. A compound with m.p. 195–200° was found besides the additional crops of III. Recrystallization of the compound from absolute ethanol raised the melting point to 206–208°, undepressed on admixture with the decarboxylated III, 3-acetamido-1-methyl-2,4-dioxopyrrolidine (IV).

The 2,4-dinitrophenylhydrazone of III was prepared by treating the compound with Baeyer's reagent. Recrystallization from 99% ethanol produced orange-yellow needles, m.p. 212–213°.

Anal. Calcd. for $C_{16}H_{18}N_6O_8$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.45; H, 4.49; N, 19.87.

3-Acetamido-5-carbethoxy-4-methoxy-1-methyl-2-oxo-3(or 4)-pyrroline.—The enol ether of III was prepared by the use of an ether solution of diazomethane[6] prepared from nitrosomethylurethan and distilled before use. To a suspension of 200 mg. of III in 10 ml. of ether, the solution of diazomethane was added in small portions with stirring, to a slight excess. Stirring was continued for an additional 0.5 hr. Excess diazomethane was decomposed by adding a few drops of acetic acid and the mixture was allowed to stand in a refrigerator. The crystals amounted to 70 mg., m.p. 107–110°. Recrystallization from carbon tetrachloride produced colorless prisms, m.p. 108–110°.

Anal. Calcd. for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.68; H, 6.26; N, 10.78.

3-Acetamido-1-methyl-2,4-dioxopyrrolidine (IV).—One gram (0.0041 mole) of III was added to a solution of 0.46 g. (0.0082 mole) of potassium hydroxide in 0.82 ml. of water. The mixture was heated on a water bath for 0.5 hr. After cooling, the resultant solution was acidified with 1.5 ml. of 10% hydrochloric acid. After several hours, the crude deposit of 3-acetamido-1-methyl-2,4-dioxopyrrolidine (IV) amounted to 0.53 g. Recrystallization from ethanol gave 0.42 g. (59.7%) of IV as white needles, m.p. 204–206°. Further recrystallization from benzene raised the melting point to 206–208°. It gave an intense blue coloration with the ferric chloride solution; ν_{max}^{KBr} 3285, 1661, 1630, and 1330 cm.$^{-1}$; $\lambda_{max}^{H_2O}$ 266 mμ (log ε 3.85).

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.46; mol. wt., 170.17. Found: C, 49.77; H, 6.10; N, 16.42; mol. wt., 181.1.

The 2,4-dinitrophenylhydrazone of IV was prepared by the standard procedure. The crude brown product was recrystallized from tetrahydrofuran as orange-yellow prisms, m.p. 224–225° dec.

Anal. Calcd. for $C_{13}H_{14}N_6O_6$: C, 44.57; H, 4.03; N, 23.99. Found: C, 44.56; H, 3.94; N, 23.69.

3-Acetamido-4-methoxy-1-methyl-2-oxo-3-pyrroline.—From 200 mg. of IV and an excess of an ether solution of diazomethane, 200 mg. (92.4%) of crude 3-acetamido-4-methoxy-1-methyl-2-oxo-3-pyrroline, m.p. 203–212°, was obtained. Crystallization from chloroform–carbon tetrachloride gave colorless prisms, m.p. 209–211°.

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.34; H, 6.14; N, 15.22.

Acetaldehyde cyanohydrin was prepared by the conventional method.[7] The yield was 60%, b.p. 75–77° (7 mm.), lit.[8] b.p. 79° (25 mm.).

α-Methylaminopropionitrile was prepared by a method similar to that for methylaminoacetonitrile.[9] The yield was 77.3%, b.p. 73–75° (52 mm.).

N-Methylalanine Ethyl Ester.—The hydrochloride of N-methylalanine ethyl ester was prepared by introduction of dry hydrogen chloride below 10°, with vigorous stirring, into a solution of 60.8 g. of α-methylaminopropionitrile in 400 ml. of absolute ethanol until the precipitate of the hydrochloride of α-methylaminopropionitrile initially formed disappeared to give a saturated solution of hydrogen chloride. After removal of ammonium chloride, the reaction mixture was evaporated to dryness under reduced pressure, leaving a light yellow sirup, which crystallized very slowly. Unpurified sirup was converted immediately to a free amino acid ethyl ester. A suspension of the hydrochloride in dry ether was treated with dry ammonia gas until all of the hydrochloride appeared to be replaced by the precipitate of ammonium chloride. After removal of ammonium chloride, the ether solution was evaporated at room temperature and the residue was fractionally distilled to yield 35.7 g. (37.5%) of a colorless liquid, b.p. 79–81° (70 mm.).

N-(α-Acetamido-α-ethoxycarbonylacetyl)-N-methylalanine Ethyl Ester (II).—A solution of 14.3 g. (0.109 mole) of N-methylalanine ethyl ester in 28 ml. of xylene was allowed to react with 47.4 g. (0.218 mole) of diethyl acetamidomalonate in 100 ml. of xylene for 24 hr., as described for I. After completion of the reaction, unchanged diethyl acetamidomalonate was removed by filtration and xylene was distilled. The residual oil was distilled to yield 21.9 g. (66.5%) of a light yellow oil, b.p. 143–145° (0.01 mm.). Redistillation gave an almost colorless oil, b.p. 143° (0.01 mm.), $n^{23}D$ 1.4790.

Anal. Calcd. for $C_{13}H_{22}N_2O_6$: C, 51.64; H, 7.34; N, 9.27. Found: C, 51.83; H, 7.37; N, 9.27.

3-Acetamido-1,5-dimethyl-2,4-dioxopyrrolidine (V).—Cyclization of II was carried out as for the preparation of III. A solution of 0.93 g. (0.040 g.-atom) of sodium and 11.5 ml. of absolute ethanol in 22.4 ml. of dry benzene was treated with a solution of 12.2 g. (0.040 mole) of N-(α-acetamido-α-ethoxycarbonylacetyl)-N-methylalanine ethyl ester in 36.6 ml. of dry benzene. The crude product of V amounted to 6.5 g. Recrystallization from absolute ethanol yielded 4.7 g. (66.2%) of colorless needles, m.p. 186–187°. It gave an intense blue coloration with ferric chloride solution; ν_{max}^{KBr} 3285, 1674, 1630, 1433, 1401, and 1357 cm.$^{-1}$; $\lambda_{max}^{H_2O}$ 268 mμ (log ε 3.76).

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21; mol. wt., 184.19. Found: C, 52.47; H, 6.47; N, 15.32; mol. wt., 221.8.

The 2,4-dinitrophenylhydrazone of V, as orange-red prisms, had m.p. 265–267° dec.

Anal. Calcd. for $C_{14}H_{16}N_6O_6$: C, 46.15; H, 4.43; N, 23.07. Found: C, 46.50; H, 4.21; N, 22.85.

3-Acetamido-1,5-dimethyl-4-methoxy-2-oxo-3-pyrroline.—This was prepared from 500 mg. of V to give 300 mg. of a crystalline product, m.p. 125–145°. Recrystallization from carbon tetrachloride yielded colorless prisms, m.p. 144–145°.

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.35; H, 6.95; N, 14.29.

3-Acetamido-5-carbethoxy-4-hydroxy-1-methyl-2-pyrrolidone (VI, VI').—A solution of 500 mg. (0.00206 mole) of III in 50 ml. of 50% ethanol was shaken with 2.0 g. of Raney nickel at 70° in a hydrogen stream at 1500 lb./in.$^{-2}$ in an autoclave for 1 hr. After cooling, the reaction mixture was diluted with absolute ethanol to 400 ml. and filtered while hot from Raney nickel. The filtrate was evaporated to dryness under reduced pressure. The crystalline residue amounted to 450 mg. and melted at 150–185°. By fractional crystallization from absolute alcohol, 110 mg. of pure white needles (VI), m.p. 215–216°, was obtained; ν_{max}^{KBr} 3315, 1742, 1691, 1638, and 1196 cm.$^{-1}$.

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(8) J. Timmermans and T. J. F. Mattaar, *Bull. soc. chim. Belges*, **30**, 218 (1921).

(9) A. H. Cook and S. F. Cox, *J. Chem. Soc.*, 2336 (1949).

Anal. Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.17; H, 6.60; N, 11.47. Found: C, 48.77; H, 6.81; N, 11.30.

The residue from the combined mother liquor, which amounted to 320 mg., was further fractionally crystallized from chloroform. From a slightly soluble portion, 90 mg. more of VI was obtained. An insoluble portion which mainly consisted of the hydrolyzed product (VII) of VI was not purified. The remaining 170 mg. of a very soluble substance was submitted to fractional crystallization from tetrahydrofuran, which yielded 10 mg. of VI and 100 mg. of its diastereoisomer (VI'), m.p. 208–209°, depressed to 185–195° on admixture with the isomer of m.p. 215–216°; ν_{max}^{KBr} 3315, 1734, 1700, 1640, and 1205 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.17; H, 6.60; N, 11.47. Found: C, 49.28; H, 6.85; N, 11.28.

The total yield of VI was 210 mg. and that of VI' was 100 mg. Thin layer chromatography of VI and VI' on silica gel was carried out with ethanol–chloroform (1:1 v./v.) as the solvent. The chromatograms were chlorinated by the action of chlorine gas and detected with starch–iodide reagent as violet spots which appeared near each other.

3-Acetamido-4-hydroxy-1-methyl-2-oxo-5-pyrrolidinecarboxylic Acid (VII).—To a suspension of 200 mg. (0.00082 mole) of VI in 0.5 ml. of ethanol, 0.4 ml. of 2 *N* potassium hydroxide solution was added dropwise with agitation. After leaving the solution for 1 day at room temperature, the reaction mixture was diluted with water to 5 ml. and the solution was passed through a column of 10 ml. of Dowex-50 (X2). The column was washed with water until the washings were neutral. The effluent was collected while it was acid. This solution was evaporated to dryness under reduced pressure, leaving 170 mg. of a white crystalline mass. Recrystallization from acetone yielded 100 mg. (47.9%) of colorless plates, m.p. 203–204° dec.

Anal. Calcd. for $C_8H_{12}N_2O_5 \cdot H_2O$: C, 41.02; H, 6.03; N, 11.96. Found: C, 41.37; H, 5.92; N, 12.04.

The anhydrous substance was a hygroscopic solid.

Anal. Calcd. for $C_8H_{12}N_2O_5$: N, 12.96. Found: N, 12.84.

α-Amino-α′-methylamino-β-hydroxyglutaric Acid (VIII).—A solution of 150 mg. of VII in 5 ml. of 6 *N* hydrochloric acid was refluxed for 4 hr. After cooling, the reaction mixture was evaporated to dryness under reduced pressure, leaving a white crystalline mass. The yield, almost quantitative, amounted to 130 mg. By adding excess ethanol to a saturated solution in water and allowing it to stand in a refrigerator, colorless plates, m.p. 228–230° dec., crystallized slowly. Thin-layer chromatography of the derivative on silica gel was carried out with water saturated with phenol as the solvent. The reddish purple spot appeared near the spot of serine with ninhydrin reagent and the reddish orange positive coloration with the Nessler reagent for hydroxyamino acids. These results indicate that the product is a β-hydroxyamino acid.

Anal. Calcd. for $C_6H_{12}N_2O_5 \cdot H_2O$: C, 34.28; H, 6.71; N, 13.33. Found: C, 34.62; H, 6.29; N, 13.03.

The anhydrous substance is hygroscopic.

Anal. Calcd. for $C_6H_{12}N_2O_5$: N, 14.58. Found: N, 14.70.

Reduction of VIII to Glutaric Acid.—A mixture of 140 mg. of VIII and 5 ml. of hydriodic acid (sp. gr. 1.7) was heated at 200–220° in a sealed tube for 4 hr. After cooling, the reaction mixture was diluted with water to 25 ml. The solution was extracted twice with 50 ml. of ether. The ether layer was shaken with a minimum amount of a saturated solution of sodium thiosulfate to remove the dissolved iodine and then washed several times with a small amount of water until the pH of the last washing was about 3. The ether solution was dried over sodium sulfate and evaporated to dryness; the residue was dissolved in a minimum amount of absolute ether. On addition of petroleum ether (b.p. 40–60°) resinous products separated. The decanted solution was evaporated to dryness and the residue was recrystallized from petroleum ether. The yield of the reduction product, m.p. 97–98°, amounted to 5 mg. The melting point of this derivative was not depressed by admixture with authentic glutaric acid. The infrared spectra (KBr) of the two substances were identical and exhibited characteristic peaks at 1702, 1308, and 1210 cm.$^{-1}$.

Acknowledgment.—The author wishes to thank Mrs. Muneo Hiura for the elemental analyses.

Spectral Solvent Shifts. Substituent Effects

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A number of workers have observed that polar solvents cause shifts of the ultraviolet absorption maxima of aromatic molecules as compared to nonpolar solvents. This effect has been explained on the basis of various solute–solvent interactions in both the ground state and the excited state. Ungnade,[2] Nagakura and Baba,[3] and Baba and Suzuki[4] have emphasized hydrogen bonding and dipole–dipole interactions of the ground state. Bayliss and McRae[5] have considered the importance of dipole moment transitions of the solute molecule in going from ground to excited state, along with orientations of the solvent cage in the ground state and the excited state. Schubert and coworkers[6] also believe that solvation of ground state and excited states is important. They believe red shifts to be caused by greater solvation of excited states than ground states with a resultant increase in dipole moments of the solute molecule. Blue shifts would be caused by highly solvated ground states which tend to hinder excitation. Ungnade[2] has proposed a similar type of solvation to explain these shifts. McRae,[7] Semba,[8] and others have attempted to relate solvent shifts to dielectric constant and index of refraction. However, some solvents, especially dioxane, do not fit the proposed equations.

The present study is an attempt to relate the solvent shifts of substituted benzenes to known proprerties of the solute molecule, in order to evaluate the importance of hydrogen bonding and polarization effects. We have studied a series of *ortho*-, *meta*-, and *para*-substituted nitrobenzenes and have observed the effect of the substituent on the solvent shifts for the ^1L_a and ^1L_b[9] bands of nitrobenzene (primary and secondary bands of Doub and Vandenbelt),[10] when polar solvents are compared to cyclohexane. The polar solvents chosen on the basis of their proton donor–acceptor properties and dielectric constants were dioxane, a proton acceptor of low dielectric constant (2.209); methanol, a proton donor of high dielectric constant (37.5); and 2-propanol, a proton donor of intermediate dielectric constant (15.7). Of the two alcohols, methanol is the stronger acid[11] and hence the stronger proton donor. Substituent groups were chosen on the basis of their potential hydrogen-bonding properties. For the nitrobenzenes, the ^1L_a and ^1L_b bands were found to be symmetrical about the peak and band shapes did

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(9) J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949).
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TABLE I

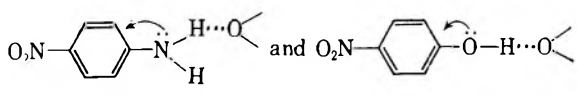
X	σ_p	Cyclohexane[a]	Dioxane[a]	ΔE, kcal./mole	Methanol[a]	ΔE, kcal./mole	2-Propanol[a]	ΔE, kcal./mole
NH_2	−0.66	324 (4.34)	354 (4.12)	−7.48	370 (4.12)	−10.98	379 (4.29)	−12.81
$N(CH_3)_2$	−0.83	356 (4.36)	382 (4.32)	−5.46	390.5 (4.25)	−7.1	390.0 (4.25)	−7.0
OH	−0.36	287 (4.09)	306 (3.96)	−6.19	313 (3.92)	−8.28	313 (3.92)	−8.28
$NHCOCH_3$	0	300 (3.74)	315 (4.15)	−4.54	314 (4.11)	−4.25	314 (4.21)	−4.25
OCH_3	−0.27	294 (4.09)	305 (4.20)	−3.50	305.5 (3.98)	−3.66	305.0 (4.12)	−3.51
CH_3	−0.17	266 (4.02)	274.5 (3.99)	−3.34	274.5 (4.00)	−3.34	273.5 (4.01)	−2.95
H	0	253 (3.94)	260 (3.95)	−3.04	260.5 (3.89)	−3.26	258 (3.82)	−2.19
Br	+0.23	270.5 (4.15)	276.5 (4.22)	−2.30	275.7 (3.98)	−2.00	274.5 (4.12)	−1.55
COOH	+0.41	253 (3.69)	257 (3.70)	−1.76	263.5 (3.83)	−4.51	259.5 (4.15)	−2.83
COOEt	+0.45	254.5 (4.25)	258.5 (4.33)	−1.74	259 (4.31)	−1.95	258.5 (4.16)	−1.74
HC=O	...	260.5 (4.10)	264 (4.08)	−1.45	265 (4.01)	−1.86	263.5 (4.13)	−1.25

[a] Wave lengths in mμ (log ε).

not vary with solvent except for a slight decrease in intensity in going from cyclohexane to polar solvent. In line with accepted practice the absorption maximum was taken as the band position.[5,6]

The results for the solvent shifts of the ^1L_a band for a series of *para*-substituted nitrobenzenes (Table I) show a decrease in excitation energy (red shift) in going from cyclohexane to polar solvents. This energy lowering decreases as the electron donor properties of the group *para* to the nitro decrease. Hammett σ-constants were chosen as a measure of the electron donor–acceptor properties of the groups. The values used are those compiled by McDaniel and Brown[12] taken from ionization constants of benzoic acids. A plot of ΔE *vs.* σ_p (Fig. 1 and 2) shows the substituents to fall into two separate groups, those which contain hydrogen attached to nitrogen or oxygen (NH_2, OH, and $NHCOCH_3$), and those which do not [$N(CH_3)_2$, OCH_3, CH_3, Br, and COOEt], the position of the carboxyl group being solvent dependent. Identical correlations were obtained using σ_p^+-constants of Brown and Okamoto.[13]

The red shifts observed for nonproton-donor groups in the case of the *para* isomers are in line with the suggestions of Bayliss and McRae[5] and Schubert[6] that polar solvent molecules are oriented to polar sites on the solute molecule in the ground state. On excitation the solvent molecules are then in a position to solvate more strongly the more polar excited state, thus stabilizing the excited state with respect to the ground state. These shifts are directly related to the ability of the group *para* to the nitro to release electrons in the excited state under the influence of the electron demand of the nitro group, and to become more positive. The ability of the solvent oxygen to solvate this positive site is reflected in the linear relationship of the excitation energy lowering and σ_p. When substituents are capable of hydrogen bonding with the solvent oxygen, ground state polarization is probably enhanced by forms such as



which would build up electron densities on the substituent atom and assist electron migration toward the NO_2 group on excitation. Solvation of the oxygens

(12) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(13) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

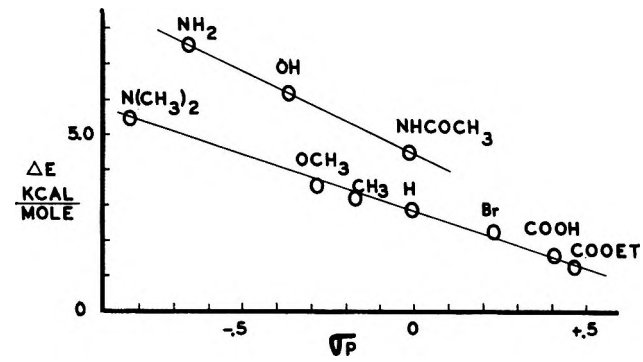


Fig. 1.—Plot of ΔE *vs.* σ_p for dioxane compared to cyclohexane for a series of *para*-substituted nitrobenzenes.

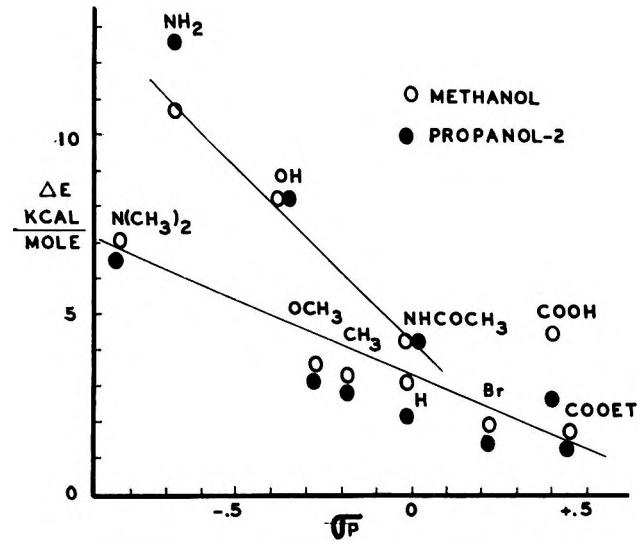


Fig. 2.—Plot of ΔE *vs.* σ_p for methanol and 2-propanol compared to cyclohexane for *para*-substituted nitrobenzenes.

of the nitro group in both the ground and excited states by the alcohols must also be considered[8] and may account, in part, for the slightly larger red shifts observed in methanol for nonproton-donor groups. The abnormally large red shift of *p*-nitrobenzoic acid in methanol suggests some hydrogen-bonded form of the excited state involving the protons of both the carboxyl group and the alcohol.

The solvent shifts for the *meta* isomers (Table II) do not show a linear relationship with Hammett's σ_m-constants. However, the results for the ^1L_a band in dioxane show a high degree of linearity for ΔE values

TABLE II

	Cyclohexane		Dioxane			Methanol			2-Propanol		
X	σ_I	^1L_a[a]	^1L_b[a]	^1L_a[a]	ΔE	^1L_b[a]	^1L_a[a]	ΔE	^1L_b[a]	^1L_a[a]	ΔE	^1L_b[a]	ΔE
CH_3	−0.05	257 (3.85)		264.5 (3.91)	−3.16		264 (3.89)	−2.95		263.5 (3.90)	−2.75		
OH	+0.25	250 (4.03)	315 (3.40)	269.5 (3.77)	−3.88	330 (3.32)	269.5 (3.77)	−3.88	332 (3.46)	269.5 (3.77)	−3.88	334 (3.40)	−5.19
NH_2	+0.10	229 (4.20)	348 (3.38)	234.5 (4.06)	−2.93	370 (3.02)	234.5 (4.08)	−2.93	376 (3.06)	234.5 (4.07)	−2.93	378 (3.08)	−6.52
$NHCOCH_3$	+0.28	236 (3.94)	316 (2.83)	241.5 (3.92)	−2.76	328 (2.75)	242 (4.06)	−3.00	328 (2.74)	242 (4.04)	−3.00	330 (2.70)	−3.85
OCH_3	+0.25	263 (3.85)	319.5 (3.32)	269 (3.67)	−2.42	330.5 (3.30)	267 (3.48)	−1.62	325 (3.06)	267 (3.45)	−1.62	321 (3.05)	−0.42
COOH		250 (3.78)		255 (3.92)	−2.25		257 (3.80)	−3.12		256 (3.86)	−2.68		
COOET	+0.32	250.5 (3.92)		255.5 (3.87)	−2.20		255.5 (3.86)	−2.20		254 (3.93)	−1.60		
Br	+0.45	254.5 (3.77)		259.5 (3.81)	−2.16		258.5 (3.73)	−1.74		259 (3.74)	−1.95		

[a] Wave lengths in mμ (log ε).

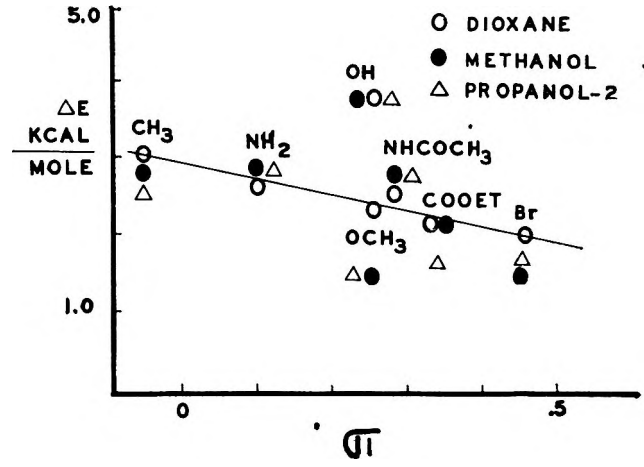
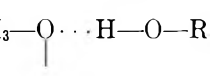
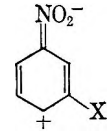


Fig. 3.—Plot of ΔE *vs.* σ_I for dioxane, methanol, and 2-propanol compared to cyclohexane for a series of *meta*-substituted nitrobenzenes.

vs. the inductive σ-constants (σ_I) of Taft[14] (Fig. 3), with only hydroxyl showing an abnormally large red shift due to hydrogen bonding with the solvent. Methanol and 2-propanol give considerable scattering, probably due to solvent–solute interactions, especially in the case of methoxyl, in which hydrogen-bonding forms of this type may be important in ground state solvation.



A correlation of ΔE values for dioxane with σ_m^+ gave linear results except for the methyl group which shows a larger electron donor effect on excitation than would be expected from its σ_m^+ value. The two alcohols gave scattered results here also. The linear relationship of the solvent shifts for dioxane with σ_I for the *meta* substituents is in line with the supposition that groups *meta* to one another are not directly conjugated. Therefore, it would be expected that inductive and field effects, of which σ_I is a measure, would be more important at the *meta* position for the ^1L_a band in which excited state forms of this type may be important.



ortho-Substituted nitrobenzenes are more difficult to interpret because of steric and internal hydrogen-bonding effects which can occur at the *ortho* position. The red shifts in dioxane (Table III) are in the order $OCH_3 > NH_2 > CH_3 > OH > NHCOCH_3$. The low values for the hydroxyl and acetamido groups can probably be accounted for by internal hydrogen bonding with the nitro group, thus preventing interaction with the solvent. In methanol, the order $OCH_3 > CH_3 > NH_2 > OH > NHCOCH_3$, in which a blue shift is obtained with *o*-nitroacetanilide, suggests that methanol is bonding with the unshared pair of electrons on the nitrogen of NH_2 and $NHCOCH_3$.

In the case of both the *ortho* and the *meta* isomers, the ^1L_b band, when present, undergoes larger red shifts than the ^1L_a band, and follows the mesomeric order

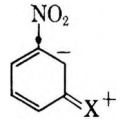
(14) R. W. Taft and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959).

TABLE III

	Cyclohexanol		Dioxane			Methanol			
	^1L_a[a]	^1L_b[a]	^1L_a[a]	ΔE	^1L_b[a]	ΔE	^1L_a[a]	ΔE	^1L_b[a]	ΔE
NH_2	270 (3.44)	379 (3.54)	276 (3.27)	−2.31	400 (3.28)	−3.96	275 (3.43)	−1.93	398 (3.44)	−3.60
OCH_3	250 (3.67)	305.5 (3.53)	255.5 (3.75)	−2.47	320 (3.55)	−4.24	257 (3.73)	−3.12	321 (3.50)	−4.53
CH_3	250 (3.84)		254 (3.73)	−1.80			255 (3.69)	−2.24		
OH	273 (4.30)	348 (3.76)	276 (4.25)	−1.14	351 (3.96)	−0.70	274 (4.07)	−0.38	351 (3.80)	−0.70
$NHCOCH_3$	275 (3.90)	354 (3.80)	276 (3.89)	−0.38	355 (3.78)	−0.23	270	+1.92	340 (3.73)	−3.33

[a] Wave lengths in mμ (log ε).

rather than the inductive order as for the ^1L_a band. This may be due to greater solvation of excited state forms such as



in which the charge appears on the bond[9] and would contribute more to the low intensity ^1L_b band.

Experimental

Absorption spectra in the region 220–400 mμ were obtained using a Bausch and Lomb automatic recording ultraviolet spectrophotometer, Model 505, with a constant 5-Å. band width and 1-cm. matched silica cells. The spectra were run in Spectroquality solvents (Matheson Coleman and Bell), using concentrations of 1.1×10^{-5} to 7.2×10^{-5} mole/l. and a scan time of 10 min. For those compounds which could undergo association in cyclohexane (*i.e.*, the nitrobenzoic acids), determinations were carried out at concentrations below which no change in the absorption maxima was observed (usually absorbancy values of 0.2 to 0.3). After each series of determinations the instrument was calibrated against the 253.7- and 313.1-mμ lines of mercury.

The nitrobenzenes were purchased as the highest purity compounds available and in some cases were further purified by recrystallization or distillation until the physical constants agreed with literature values. Each compound was then dried for a period of 3–24 hr. in an Abderhalden apparatus. Those compounds not available commercially (*p*-nitro-N,N-dimethylaniline, ethyl *p*-nitrobenzoate, and ethyl *m*-nitrobenzoate) were synthesized by methods listed in "Organic Syntheses" or "Beilstein."

Acknowledgment.—The work of Mr. Jorge Olguin was supported in part by a National Science Foundation Undergraduate Research Participation grant.

Exchange Reaction of Isocyanic Acid Esters and Isothiocyanic Acid Esters

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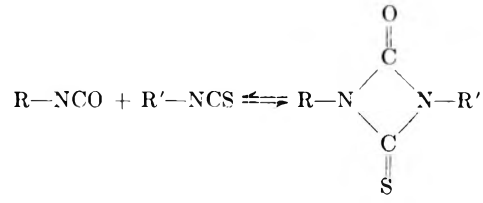
Isocyanic acid esters and isothiocyanic acid esters have been found[1] to undergo an exchange reaction when simply heated together at temperatures in the range of 190–230°. This exchange reaction has been taken

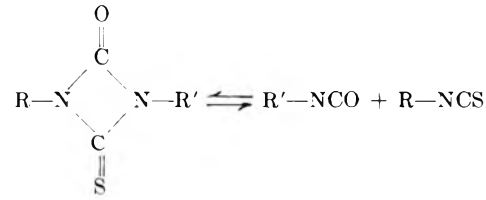
$$R—NCO + R'—NCS \rightleftharpoons R'—NCO + R—NCS \quad (1)$$

advantage of to prepare isocyanates from isothiocyanates. Since isocyanates boil appreciably lower than corresponding isothiocyanates, separation of the desired isocyanates conveniently was achieved by conducting the reaction in the stillpot of a fractionating column. In this manner *n*-hexyl isocyanate was prepared from *n*-hexyl isothiocyanate and *m*-chlorophenyl isocyanate in 61% yield. Allyl isocyanate was obtained in yields of 22.5 and 23% from allyl isothiocyanate and toluene diisocyanate (80% 2,4-; 20% 2,6-) and *o*-chlorophenyl isocyanate, respectively. Similarly, 2-methylallyl isocyanate was obtained in 31% yield from 2-methylallyl isothiocyanate and toluene diisocyanate.

Case proposed that this exchange reaction proceeds through the intermediate formation of uretidinethione ketones.



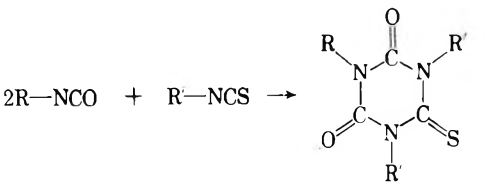
(2)



(3)

The marked difference in yield between the allylic isocyanates and the alkyl isocyanates points to competitive reactions. Vinyl polymerization of the allyl groups is not believed to be a significant factor, owing to the nearly identical yields of allyl isocyanate in exchange with toluene diisocyanate and with *m*-chlorophenyl isocyanate, in spite of the markedly different reaction times (2 hr. *vs.* 26.5 hr.).

Trimerization reactions leading to essentially irreversible formation of thio- and dithioisocyanurates are believed to be the major competitive reactions.



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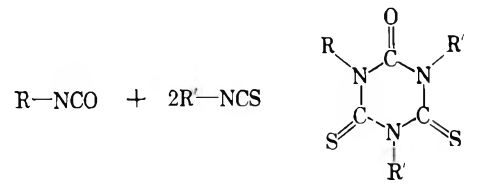

(5)

(1) L. C. Case, *Nature*, **183**, 675 (1959).

Experimental[2]

n-**Hexyl Isocyanate.**—A mixture of 135 g. of *n*-hexyl isothiocyanate (0.94 mole) and 460.5 g. of *m*-chlorophenyl isocyanate (3 moles) was heated together in a 1-l. single-necked flask provided with a thermometer well. A short, glass-helices-packed fractionating column was used to separate the product isocyanate.

In 15 min., the reaction mixture reached 213°. In 45 min. a head temperature of initially 169° was recorded. The fractionated column was operated at total reflux until a constant temperature of 161° was reached (lit.[3] 162–163°). The product distilled over a 10-hr. period at 163–164°. The reaction temperature meanwhile increased to 230°. A total of 77.5 g. of *n*-hexyl isocyanate was obtained for a 61% yield.

The product showed a strong –NCO infrared absorption peak at 4.4 and secondary peaks at 6.9 and 7.45 μ. The charge stock, *m*-chlorophenyl isocyanate, had peaks at 4.45 and at 6.33 μ. The charge stock, *n*-hexyl isothiocyanate, had a very pronounced –NCS peak at 4.79 and a secondary peak at 4.59 μ.

Allyl Isocyanate. A.—A 99-g. sample of allyl isothiocyanate (1 mole) and 365 g. of *o*-chlorophenyl isocyanate (3 moles) were treated similarly. The initial reaction temperature was 189°. The column was operated at total reflux for 20 hr.; then 18.7 g. of allyl isocyanate was distilled at 84–86° over 6.5 hr. At the end of this time, reflux had become negligible and the reaction temperature had reached 247° to yield 22.5%, lit.[4] b.p. 82°. The reaction bottoms were then vacuum stripped and found to be free of unchanged allyl isothiocyanate. After distillation of 12 g. of *m*-chlorophenyl isocyanate, the residual bottoms were submitted for infrared analysis. The spectrogram clearly revealed absorption bands at 4.73–4.87 μ, corresponding to *m*-chlorophenyl isothiocyanate. No bands corresponding to uretidine diketones were observed. A distinct and typical trimer (isocyanurate) band at 5.81 μ was obtained. Similar bands were obtained at 6.25–6.35 μ, which are probably attributable to thioisocyanurate groups.

B.—A 99-g. sample of allyl isothiocyanate (1 mole) and 261 g. of toluene diisocyanate (3 equiv.) were treated similarly. After 1-hr. reflux, the product was distilled at 84–86° over 2 hr. to yield 19.1 g. (23%). A polymeric mass remained in the reaction flask.

2-Methylallyl Isocyanate.—A mixture of 113 g. of 2-methylallyl isothiocyanate (1 mole) and 3 equiv. of toluene diisocyanate were used. A total of 31 g. of 2-methylallyl isocyanate (31%) was obtained at a boiling range of 107–109°.[5] Infrared spectrum revealed a very strong peak at 4.4 μ corresponding to –NCO.

(2) Boiling points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer dual beam Infracord.

(3) G. Schroeter, *Ber.*, **42**, 3358 (1909).

(4) A. Cahours and A. W. Hoffmann, *Ann.*, **102**, 297; Beilstein, IV, p. 214.

(5) J. W. Eastes and T. F. Cooke, U. S. Patent 2,699,440 (Jan. 11, 1955).

Solvolysis of Iso- and Neoisopinocampheyl Sulfonate Esters. Stereochemical Considerations

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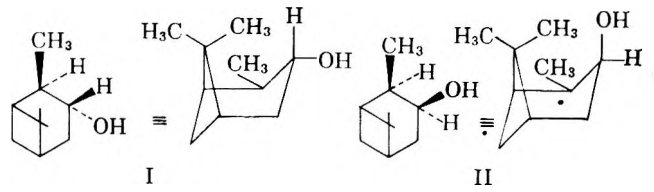
Received February 17, 1964

Recently, Schmidt's[2] configurational assignment of isopinocampheol (I) has been challenged.[3,4] It was proposed that the alcohol belongs to the *cis*-pinane series, but the hydroxyl and the methyl group are in a *cis* relationship (II). The arguments were based on conformational analysis,[3] and on the fact that the



I II

tosylate solvolyzed extremely fast, pointing to considerable assistance to ionization.[4] Unfortunately, the authors failed to extend the study to neoisopinocampheyl tosylate, to which Schmidt assigned the extreme *cis* configuration (II). An extreme *cis* configuration for the isopinocampheol is in contradiction to the configuration deduced from the hydroboration of α-pinene with diborane.[5] It has been shown that hydroboration of α-pinene occurs *cis* and from the less hindered side of the molecule. Since oxidation of the organoborane occurs with retention of configuration, the alcohol obtained should have the hydroxyl and the methyl group in a *trans* relationship (I).

In view of these facts it appeared desirable to synthesize neoisopinocampheol and compare the rate of solvolysis of its sulfonate ester with that of isopinocampheol. The neoisopinocampheol (II) was prepared by oxidation of isopinocampheol to isopinocamphone, followed by reduction of the ketone with lithium trimethoxyaluminohydride.[5] The physical constants of the neoisopinocampheol obtained agreed with those reported by Schmidt.[2]

The methanesulfonate esters of the two alcohols were solvolyzed in methanol at 25°. The results are summarized in Table I.

TABLE I

RATES OF SOLVOLYSIS OF CYCLOPENTYL-, ISO-, AND NEOISOPINOCAMPHEYL SULFONATE ESTERS

Compound	Solvent	$k_{25} \times 10^6$, sec.$^{-1}$	Relative rate
Cyclopentyl methanesulfonate	Methanol	5.58	1
Cyclopentyl tosylate	Ethanol	4.96[a,b]	
Isopinocampheyl methanesulfonate	Methanol	20.2	3.6
Isopinocampheyl tosylate	Ethanol	12.6[a,c]	
Neoisopinocampheyl methanesulfonate	Methanol	58.5	10.0

[a] The rate was determined at 30°. [b] W. Hückel, *et al.*, *Ann.*, 624, 142 (1959). [c] See ref. 4.

The results obtained indicate that isopinocampheyl methanesulfonate solvolyzes 3.6 times faster than the cyclopentyl ester. Moreover, the neoisopinocampheyl ester solvolyzes 2.5 times faster compared with the isopinocampheyl derivative.

Consequently, if the rate of solvolysis reflects the spatial relationship between the methyl and the hydroxyl group, the data in Table I support the contention that the hydroxyl and the methyl group have a *cis* relationship in neoisopinocampheol, and a *trans* relationship in isopinocampheol.

Experimental

Isopinocampheyl Methanesulfonate.—To 25 ml. of pyridine was added 2.84 g. of isopinocampheol[5] [20 mmoles, m.p. 55–57°, $[\alpha]^{20}$ –32.8° (*c* 10, benzene)]. The solution was cooled to 0° and 2.29 g. of methanesulfonyl chloride (20 mmoles) was added.

(1) Chemistry Department, University of California, Davis, Calif.

(2) H. Schmidt, *Ber.*, **77**, 544 (1944).

(3) K. Bose, *J. Org. Chem.*, **20**, 1003 (1955).

(4) W. Hückel and D. S. Nag, *Ann.*, **646**, 101 (1961).

(5) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).

The reaction mixture was maintained at 0° for 24 hr., then poured into a mixture of equal volumes of 6 *N* hydrochloric acid and ether. The sulfonate ester was extracted with ether and the ether extract was washed with ice-cold 6 *N* hydrochloric acid. In order to remove traces of pyridine the ether extract was washed once with 10% cadmium chloride solution and dried over anhydrous magnesium sulfate. The ether was removed and the residue crystallized from a mixture of pentane–ether (10:1) at −70°. The isopinocampheyl methanesulfonate had m.p. ~10°. The compound was stable when kept below 0° for a long period of time.

Anal. Calcd. for $C_{11}H_{20}SO_3$: C, 56.90; H, 8.65. Found: C, 56.79; H, 8.73.

Neoisopinocampheyl Methanesulfonate.—Under similar experimental conditions as described above, 0.71 g. of neoisopinocampheol[5] [(5 mmoles, m.p. 45–47°, $[\alpha]^{20}$ +36° (*c* 3, benzene)] was converted to the neoisopinocampheyl methanesulfonate, m.p. ~0°. The compound is less stable as compared to the isopinocampheyl derivative.

Anal. Calcd. for $C_{11}H_{20}SO_3$: C, 56.90; H, 8.65. Found: C, 56.41; H, 8.07.

Rate Studies.—The reaction rates were followed by conventional titrimetric procedures. The first-order reaction constants obtained are summarized in Table I.

Organoboron Compounds. XVI. An Improved Method for the Preparation of Trialkylboroxines[1,2]

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The reaction of boric oxide with trialkylboranes was reported earlier[3] to provide a more convenient method for the preparation of trialkylboroxines than the previously used dehydration of alkylboronic acids. Because of the high temperatures and long heating times required, this reaction was restricted to the preparation of primary trialkylboroxines, since thermal isomerization[4] of secondary or tertiary alkyl groups to primary groups occurred during reaction and, as more recently observed,[1] partial conversion of primary alkyl groups to secondary alkyl groups also took place. Furthermore it was found on continued use of this reaction that it was difficult to obtain or prepare samples of anhydrous boric oxide with reproducible reaction characteristics. Incompletely dehydrated boric oxide causes some hydrolysis of trialkylboranes, and boric oxide thoroughly dehydrated at high temperature was found to be very unreactive, resulting in heating times as long as 60 hr. in some instances.

A modification of the method, involving the use of trimethoxyboroxine as a source of reactive boric oxide, with resultant decrease of time of reaction, lower reaction temperatures, and decreased thermal isomerization is reported in the present paper.

Trimethoxyboroxine, obtainable from the reaction of boric oxide with trimethoxyborane (and also available commercially from the Callery Company) is dissociated on attempted distillation[5–7] into boric oxide and trimethoxyborane.

Under controlled conditions it has been found that heating of mixtures of primary trialkylboranes and trimethoxyboroxine as low as 131° and for periods as short as 2 hr. results in 60–77% yields of isomer-pure, sharp-boiling trialkylboroxines. An essential feature of the reaction conditions is that the trimethoxyborane formed by decomposition of trimethoxyboroxine must be distilled as rapidly as it is formed. If the mixture is heated without rapid removal of the trimethoxyborane, the reaction products consist mostly of dialkylmethoxyboranes and alkyldimethoxyboranes resulting from the reaction of trimethoxyborane with trialkylboranes.[8]

In order to determine whether any of the alkyldimethoxyborane, obtained as a by-product in the preparative reaction, resulted from direct reaction between trimethoxyborane and trialkylboroxine, this possible reaction was attempted under the same conditions as used for the preparative reaction. It was found that under these conditions only a 6% yield of alkyldimethoxyborane was obtained.

Of the three reactions involved in the process, the most rapid is apparently the thermal decomposition of trimethoxyboroxine. This follows from the observation that trimethoxyborane can be removed from the reaction mixture in almost quantitative yield by distillation. This requires that reaction of trimethoxyborane with trialkylborane and reaction of boric oxide with trialkylborane be relatively slow. Of the latter two reactions, the trimethoxyborane–trialkylborane reaction appears to be the more rapid since the yield of esters is higher than the yield of trialkylboroxine when the trimethoxyborane is left in the reaction mixture.

The rapid formation of trialkylboroxines at relatively low temperature led to the expectation that isomer-pure secondary trialkylboroxines could be obtained by this method. This expectation was realized in the case of the preparation of tri-*sec*-butylboroxine although it was found that during the preparative reaction some isomerization of secondary to primary groups occurred. From the reaction mixture there was obtained a 35% yield of isomer-pure tri-*sec*-butylboroxine. The total yield of tributylboroxine was 69%. In the case of the treatment of triisopropylborane with trimethoxyboroxine heating for 1 hr. in the same temperature range as for tri-*sec*-butylborane and removal of trimethoxyborane resulted in the precipitation of solid boric oxide but no formation of tripropylboroxine. Heating of the reaction mixture for an additional hour resulted in dissolution of the boric oxide and formation of tripropylboroxine which consisted of an inseparable mixture of normal and isopropylboroxines. It appears that direct reaction of triisopropylborane with trimethoxyboroxine does not occur, while direct reaction of tri-*sec*-butylborane with trimethoxyboroxine does take place under essentially the same conditions. The reason for this difference in behavior is not immediately evident.

(1) Previous paper: P. A. McCusker, F. M. Rossi, J. H. Bright, and G. F. Hennion, *J. Org. Chem.*, **28**, 2889 (1963).

(2) Contribution from the Radiation Laboratory operated by the University of Notre Dame under contract with the Atomic Energy Commission.

(3) G. F. Hennion, P. A. McCusker, E. C. Ashby, and A. J. Rutkowski, *J. Am. Chem. Soc.*, **79**, 5179 (1957).

(4) G. F. Hennion, P. A. McCusker, E. C. Ashby, and A. J. Rutkowski, *ibid.*, **79**, 5190 (1957).

(5) J. Goubeau and H. Keller, *Z. Anorg. Allgem. Chem.*, **267**, 1 (1951).

(6) G. L. O'Connor and H. R. Nace, *J. Am. Chem. Soc.*, **77**, 1578 (1955).

(7) M. F. Lappert, *J. Chem. Soc.*, 2790 (1958).

(8) R. Koster, *Angew. Chem.*, **71**, 31 (1959).

From the purified trialkylboroxines, alkylboronic acids may be prepared in high purity by simple addition of water.

Experimental

All operations were carried out in an atmosphere of dry nitrogen.

Preparation of Triisobutylboroxine from Triisobutylborane and Trimethoxyboroxine.—The preparation of triisobutylboroxine will be detailed as typical of the procedure used for all the boroxine preparations. Trimethoxyboroxine (78 g., 0.42 mole), obtained from Callery Chemical Co., was heated with triisobutylborane (76 g., 0.42 mole) at atmospheric pressure, and the resulting trimethoxyborane was removed as rapidly as it was formed by distillation through a 28-theoretical-plate, spinning-band column. Complete removal of the trimethoxyborane (0.39 mole) required 2.5 hr., during which time the temperature of the reaction mixture rose from 131 to 207°. Distillation of the remaining reaction mixture gave a few grams of a forerun containing isobutyldimethoxyborane and unchanged triisobutylborane, and 77 g. of crude triisobutylboroxine. Unchanged boric oxide (7.0 g.) remained as a residue. Redistillation of the crude material gave 68 g. (64% yield) of pure triisobutylboroxine, b.p. 90.1° at 3.6 mm., $n^{25}D$ 1.4117, d^{25} 0.8558; MR_D calcd.,[9] 73.13; MR_D obsd., 72.89.

In a separate experiment trimethoxyboroxine (47 g., 0.27 mole) was heated with triisobutylborane (59 g., 0.32 mole) except that the resulting trimethoxyborane was removed slowly over a period of 5 hr. Distillation of the resulting mixture gave the following spectrum of crude products: 0.05 mole of diisobutylmethoxyborane, 0.15 mole of triisobutylboroxine, 0.22 mole of unchanged triisobutylborane, and 0.06 mole of boric oxide.

Other Trialkylboroxines Containing Primary Alkyl Groups.—By entirely similar procedures tri-*n*-propylboroxine, tri-*n*-butylboroxine, and tri-*n*-amylboroxine were prepared in yields above 60%. Close boiling fractions, with physical properties in agreement with those previously reported,[10] were obtained.

Attempted Preparation of Triisopropylboroxine.—Trimethoxyboroxine (28 g., 0.16 mole) was heated with isomer-pure triisopropylborane at 133–210° and 0.14 mole of trimethoxyborane was rapidly removed by distillation over a period of 1 hr. During removal of the trimethoxyborane large amounts of white solid formed in the reaction mixture. Distillation resulted in the recovery of starting materials only. No triisopropylboroxine was obtained.

In a second experiment trimethoxyboroxine (17 g., 0.10 mole) was heated with triisopropylborane (18 g., 0.09 mole) in a temperature range of 138–191° over a 2-hr. period with removal of trimethoxyborane. After about 1 hr. the formation of a white solid was noted but continued heating resulted in the disappearance of the solid. After a total of 2 hr., distillation of the reaction mixture gave 20 g. of a fraction containing a mixture of tripropylboroxines, b.p. 57–67° at 4 mm.

Anal. Calcd. for $C_{19}H_{21}B_3O_3$: B, 15.45. Found: B, 15.15.

By oxidation and gas–liquid chromatography of the resulting alcohols, the mixture was found to contain *n*-propyl groups and isopropyl groups in a 57:43 ratio. The yield of mixed tripropylboroxines was essentially quantitative.

Preparation of Tri-*sec*-butylboroxine from Tri-*sec*-butylborane and Trimethoxyboroxine.—Trimethoxyboroxine (24 g., 0.14 mole) was heated with isomer-pure tri-*sec*-butylborane (24 g., 0.13 mole) with rapid removal of 0.14 mole of trimethoxyborane. The temperature of the reaction mixture ranged from 149 to 197° and the reaction was complete in 1 hr. Distillation resulted in two principal fractions. The first, 17 g., had the following properties: b.p. 70.5–75.1° at 1.35 mm., $n^{25}D$ 1.4159, d^{25} 0.8705.

Anal. Calcd. for $C_{12}H_{27}B_3O_3$: B, 12.9. Found: B, 12.9.

By g.l.c. the ratio of *sec*-butyl to *n*-butyl groups was 94:6. The second fraction (7 g.) had the following properties: b.p. 75.1–93.0° at 1.4 mm., $n^{25}D$ 1.4174, d^{25} 0.8717. (*Anal.* Found: B, 12.8.) The *sec*-butyl–*n*-butyl group ratio was 65:35. The combined yield of tributylboroxine was 69%. Redistillation of the lower boiling fraction gave 0.05 mole (35% yield) of pure tri-*sec*-butylboroxine, b.p. 59.1° at 0.6 mm.

Anal. Calcd. for C_4H_9BO: C, 57.2; H, 10.8; B, 12.9. Found: C, 55.6; H, 11.1; B, 12.8.

Preparation of Trimethoxyboroxine.—Metaboric acid (23 g., 0.52 mole), obtained from Fisher Scientific Co., was heated at 168° and 1 mm. for 12 hr. in a vacuum oven. Trimethoxyborane (42 g., 0.40 mole) was added to the resulting boric oxide and the mixture refluxed over a period of 6 hr. in the temperature range of 229–117°. Half of the excess trimethoxyborane was distilled and the resulting material was treated with tri-*n*-butylborane as in the above preparations. Tri-*n*-butylboroxine was obtained in yields comparable to those obtained when commercial trimethoxyboroxine was used.

Treatment of Trimethoxyborane with Tri-*n*-butylboroxine.—To tri-*n*-butylboroxine (28 g., 0.11 mole) at reflux temperature was added over a period of 3.5 hr. 25 g. (0.24 mole) of trimethoxyborane. During the addition, the reaction temperature dropped from 189 to 134°. Heating was continued for an additional 2 hr. Distillation of the reaction mixture resulted in the recovery of 0.20 mole of unchanged trimethoxyborane, 0.10 mole of unchanged tri-*n*-butylboroxine, and 4 g. of a material collected in a cold trap. From the trap material there was obtained on hydrolysis 0.02 mole of *n*-butylboronic acid. The estimated yield of *n*-butyldimethoxyborane was 6%.

(9) R. G. Gillis, *Rev. Pure Appl. Chem.*, **10**, 1 (1960).

(10) P. A. McCusker, E. C. Ashby, and H. S. Makowski, *J. Am. Chem. Soc.* **79**, 5179 (1957).

Organoboron Compounds. XVII. Preparation and Hydrolytic Properties of Some Substituted Borazines Containing Fluorescent Groups[1]

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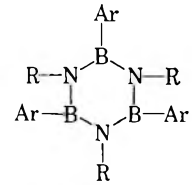
For the detection of neutrons by means of scintillation counters, compounds which have both high neutron cross sections and are strongly fluorescent are desirable. Interesting examples of such types of compounds can be obtained by introducing polyphenyl groups into the borazine molecule. In the present paper the preparation of four such compounds, B-tris(diphenylyl)-N-trimethylborazine (I), B-tris(diphenylyl)-N-triphenylborazine (II), B-tris(α-naphthyl)-N-trimethylborazine (III), and B-tris(*p*-terphenylyl)-N-trimethylborazine (IV), is described and their rates of hydrolysis are compared. The structural formulation of the compounds is given in Chart I.

CHART I



I, Ar = $C_6H_5C_6H_4$; R = CH_3
II, Ar = $C_6H_5C_6H_4$; R = C_6H_5
III, Ar = α-$C_{10}H_7$; R = CH_3
IV, Ar = *p*-$C_6H_5C_6H_4C_6H_4$; R = CH_3

Among the several methods reported for the preparation of borazine derivatives,[4] the more generally

(1) Previous paper: P. A. McCusker and J. H. Bright, *J. Org. Chem.*, **29**, 2093 (1964).

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(3) The Radiation Laboratory of the University of Notre Dame is operated under contract with the U. S. Atomic Energy Commission.

(4) J. C. Sheldon and B. C. Smith, *Quart. Rev.* (London), **14**, 201 (1960).

used are the method of Ruigh[5] which involves the reaction of organodichloroboranes with amines and the method of Harris, Ryschkewitsch, and Sisler[6] and Groszos and Stafiej[7] which consist of the reaction of Grignard reagents with substituted B-trichloroborazines. The availability of a convenient method for the preparation of the required B-trichloro-N-substituted borazines dictated our choice of the latter method for the preparation of the desired compounds.

Three of the four compounds to be prepared contain methyl groups attached to nitrogen and compounds of this type have been reported[7] to be readily hydrolyzed in contact with water. Completely anhydrous procedures were therefore used. It was found that much better results were obtained when lithium aryls were used rather than Grignard reagents. The yield of I was increased from 33 to 61% by using lithium aryl rather than Grignard reagent. In the case of IV the required Grignard is obtainable only with difficulty, while the lithium aryl was prepared conveniently by halogen exchange. The principal advantage of lithium aryls over Grignard reagents in these preparations lies in the relative ease of separation of lithium chloride from ether solutions compared to the separation of magnesium salts. The elimination of lithium chloride or its etherate from the residue, obtained by removal of most of the ether by distillation, was readily accomplished by successive treatments with dry benzene at reflux temperature, removal of ether by distillation, and separation of precipitated lithium chloride by filtration under anhydrous conditions.

No significant differences in the rates of reaction of the N-trimethyltrichloroborazine with the three different lithium aryls was observed, indicating that steric effects arising from the size of the aryl group did not seriously affect the reaction. The variation in the yields obtained is probably due to differences in the losses during crystallizations.

The products, obtained by recrystallization from a variety of solvents, were in the form of small white needles. Their identification was based on the reactions used and on elemental analysis. The infrared spectra all showed strong absorption in the B–N ring stretching region (1370–1410 $cm.^{-1}$) as well as the characteristic frequencies corresponding to the aryl groups.

The substituted borazines prepared in this work, although less sensitive to moisture than borazine itself, were found to undergo significant hydrolysis on storage as the result of occasional exposure to normal atmosphere. Elemental analysis of samples, stored for several months with occasional short exposure to the atmosphere, gave evidence of about 5% hydrolytic decomposition in the case of III and IV, and of about 15% decomposition in the case of I, accompanied by loss of volatile amine.

On contact with liquid water, there was extensive hydrolysis in a period of 30 min. in the case of B-tris-(diphenylyl)-N-trimethylborazine (I), while the corresponding N-phenylborazine was only slightly hydrolyzed in the same period. This observation is in agreement with that of Groszos and Stafiej[7] on the relative rates of hydrolysis of N-methyl- and N-phenyl-substituted borazines. Two of the N-methyl-substituted borazines prepared in this work, III and IV, however, did not exhibit the property of ready hydrolysis on contact with liquid water. These latter two compounds were quite resistant to hydrolytic attack by liquid water and were comparable in this respect to the N-phenyl compound. It would appear that the large α-naphthyl and p-terphenylyl groups on the boron exert a steric effect which slows the attack by water.

More quantitative studies on relative hydrolysis rates were carried out on solutions containing 1.12 mg./ml. of the compounds in 22.5 wt. % dioxane in water. The rates of hydrolysis were followed by measurements of the conductivity of the solutions *vs.* time. The required relationships between conductivity and concentrations were obtained by measurements of the conductivities of various solutions of methylamine–phenylboronic acid in dioxane–water and of similar solutions of aniline–phenylboronic acid. Within a period of 2 min. at 25° I underwent 82% hydrolysis, while, in a 3-min. period, II was only 11% hydrolyzed. Slow hydrolysis of II proceeded, however, and reached 34% in about 18.5 hr. The data obtained on the rates of hydrolysis could not be fitted to any simple rate law. Since I and II have the same groups on boron and different groups on nitrogen, it would appear that, in this case, the nature of the group attached to nitrogen is a controlling factor in the rate of hydrolysis. The reduced rate of hydrolysis of an N-methylborazine when a diphenylyl group on boron is replaced by an α-naphthyl group, however, indicates that steric protection of boron can also reduce the rate of hydrolysis.

Experimental

Preparation of the Substituted Borazines.—The procedures used for the preparation of the several substituted borazines were, in general, quite similar. One of the preparations will be described in detail as typical of the general method used.

All operations, including filtrations, were carried out without exposure to air or moisture. Closed apparatus, using dry-nitrogen pressure, or a dry-nitrogen filled drybox was used. All solvents were thoroughly dried.

Preparation of B-Tris(diphenylyl)-N-trimethylborazine (I).—B-Trichloro-N-trimethylborazine was prepared by the method of Brown and Laubengayer.[8] A solution of 4.65 g. of B-trichloro-N-trimethylborazine in 100 ml. of dry ether was added dropwise with stirring to 90 ml. of a 0.685 M solution of diphenyllithium[9] in ethyl ether. A rapid exothermic reaction occurred and a white precipitate separated. The addition was complete in 20 min. and stirring and refluxing were continued for an additional hour. The ether was distilled off until a thick paste remained. Dry benzene (200 ml.) was then added and the solvent was distilled to near dryness. Additional benzene was added and the resulting suspension was filtered while hot and washed with hot benzene. These operations were repeated until a filtrate free of chloride was obtained. The solid remaining after evaporation of benzene was recrystallized from ethyl ether solution (saturated at reflux temperature and slowly cooled to −78°) giving 7.2 g. of crude product (yield, 61%), m.p. 214–219°. Several additional recrystallizations from ethyl ether gave white needles, m.p. 222–223°.

(5) W. L. Ruigh, Research on Boron Polymers, WADC Report 55-26, part I–III (1955–1956).

(6) J. J. Harris, C. E. Ryschkewitsch, and H. H. Sisler, Abstracts, 132nd National Meeting of the American Chemical Society, New York, N. Y., Sept., 1957, 9S; *J. Am. Chem. Soc.*, **80**, 4515 (1958).

(7) S. J. Groszos and S. F. Stafiej, Abstracts, 131st National Meeting of the American Chemical Society, Miami, Fla., April, 1957, 53-O; *J. Am. Chem. Soc.*, **80**, 1359 (1958).

(8) C. A. Brown and A. W. Laubengayer, *ibid.*, **77**, 3699 (1955).

(9) H. Gilman, E. H. Zoellner, and W. M. Selby, *ibid.*, **54**, 1957 (1932).

Anal. Calcd. for $C_{39}H_{36}B_3N_3$: C, 80.81; H, 6.21; B, 5.61; N, 7.21. Found: C, 78.11; H, 6.41; B, 5.81; N, 7.31.

Preparation of B-Tris(diphenylyl)-N-triphenylborazine (II).—Following the general procedure described above, 44 g. of B-trichloro-N-triphenylborazine[7] reacted with 450 ml. of 0.725 *M* diphenyllithium in ethyl ether to give 38.2 g. of crude product (47% yield), m.p. 292–298°. The product was purified by several recrystallizations from a 1:6 by volume mixture of benzene and petroleum ether (b.p. 35–55°), saturating at reflux temperature and slowly cooling to −30°. The purified product was in the form of white needles, m.p. 222–223°.

Anal. Calcd. for $C_{51}H_{42}B_3N_3$: C, 84.7; H, 5.5; B, 4.2; N, 5.5. Found: C, 84.8; H, 5.6; B, 4.7; N, 5.4.

Preparation of B-Tris(α-naphthyl)-N-trimethylborazine (III).—B-Trichloro-N-trimethylborazine (22.5 g.) reacted with 215 ml. of 1.41 *M* α-naphthylmagnesium bromide in ethyl ether. The combined crude products from three crystallizations from benzene totaled 28.1 g. (66% yield), m.p. 290–292°. Recrystallizations from a 1:5 by volume mixture of benzene and petroleum ether gave white crystals, m.p. 291–292.

Anal. Calcd. for $C_{33}H_{30}B_3N_3$: C, 79.1; H, 6.0; B, 6.5; N, 8.4. Found: C, 80.6; H, 5.9; B, 6.1; N, 7.7.

Preparation of B-Tris(*p*-terphenylyl)-N-trimethylborazine (IV).—Attempts to prepare *p*-terphenyllithium by direct reaction of *p*-terphenyl bromide with lithium gave very low yields. Better results were obtained when the *p*-terphenyllithium was prepared by a displacement reaction between *n*-butyllithium and *p*-terphenyl bromide.

B-Trichloro-N-trimethylborazine (22.7 g.) reacted as above with 0.3 mole of *p*-terphenyllithium. An 11-g. yield of crude product was obtained (15% yield based on *p*-terphenyl bromide), m.p. 245–250°. Recrystallizations from a 1:4 by volume mixture of benzene and petroleum ether gave a product, m.p. 255–256°.

Anal. Calcd. for $C_{57}H_{48}B_3N_3$: C, 84.8; H, 6.0; B, 4.0; N, 5.2. Found: C, 82.8; H, 5.9; B, 3.9; N, 5.0.

Hydrolysis Studies.—For the qualitative hydrolysis experiments, weighed samples (50–100 mg.) were treated with 20 ml. of water in a small flask at room temperature and in one case at reflux temperature. After various time intervals, the suspensions were filtered through sintered glass crucibles and the insoluble materials dried under vacuum, weighed, and their identity checked by melting point. The filtrates were analyzed for boron. The results of these experiments are given in Table I. In addition, samples of I and II were treated for several hours with hot concentrated KOH and hydrolysis was found to be complete. Similar treatment of III resulted in only 30% hydrolysis.

TABLE I

HYDROLYSIS OF SUBSTITUTED BORAZINES

Compound	Time, hr.	% recovery	B analysis of filtrate	M.p., °C., of recovered solid
I	0.5	52	Pos.	199–202
II	0.5	95	Neg.	Unchanged
II	0.5[a]	91	Pos.	Unchanged
III	24	95	Neg.	Unchanged

[a] At reflux temperature.

The data obtained on the rates of hydrolysis of I and II in dioxane–water solutions are listed in Table II. Less complete studies on the hydrolysis of III under comparable conditions indicated that the rate of hydrolysis of III was roughly comparable to that of II.

TABLE II

RATES OF HYDROLYSIS IN DIOXANE–WATER SOLUTIONS AT 25°

Compound I		Compound II	
Time, min.	% hydrolysis	Time, min.	% hydrolysis
2	82	3	11
8	87	5	13
27	90	15	16
157	93	53	20
1013	97	83	22
		1112	34

Decarboxylative Deamination of Amino Acids

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Reactions of aliphatic α-amino acids with isoamyl nitrite (γ-methylbutyl nitrite) in various solvents have been studied and the volatile hydrocarbon products have been analyzed by v.p.c. (Table I). In addition to these volatile hydrocarbon components, nitrogen, carbon dioxide, nitrous oxide, and nitric oxide are products of the reactions. The yield of nitrogen is apparently quantitative based on initial amino acid, but, since these inorganic gases also arise from thermal decomposition of isoamyl nitrite,[1] their yields are not necessarily meaningful. The hydrocarbon fraction constitutes less than 1% of the total amino acid consumed in the reaction. Preliminary studies of the nonvolatile products indicate that several products are formed (see Experimental). These have not been characterized. Control reactions have definitely established that the volatile hydrocarbon products do not arise from thermal decomposition of isoamyl nitrite, nor are they formed when isoamyl nitrite is not present in the reaction mixture.

TABLE I

VOLATILE HYDROCARBON PRODUCTS FROM REACTION OF ISOAMYL NITRITE AND α-AMINO ACIDS[a]

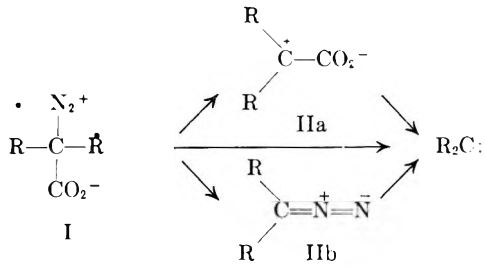
Hydrocarbons[d]	Valine–dioxane	Valine–DMF[b]	Valine–EtOH–H_2O[c]	α-Amino-butyric acid–dioxane	Alanine–DMF[b]
Methane	—[e]	—	—	2	3
Ethylene	—	—	3	3	94
Ethane	—	—	—	—	—
Propylene	5	1	—	87	3
Propane	—	—	—	—	0
Cyclopropane	—	0	—	5	—
Isobutane	—	—	—	—	0
Isobutene[f] + 1-butene	76	88	82	2	*g*
trans-2-Butene	6	6	15	1	*g*
Methylcyclopropane	12	2	0	0	*g*
cis-2-Butene	≈1	3	0	0	*g*

[a] At 63°; values for products given in per cent. [b] Dimethylformamide. [c] 70% ethyl alcohol–water; room temperature. [d] Given in per cent of the total volatile ($<C_5$) hydrocarbon fraction ($<1\%$ of initial amino acid). [e] — indicates trace amount observed. [f] Not separated under the experimental conditions (see Experimental). [g] The presence of these components was not checked.

This study was originally undertaken to ascertain whether diazotization of α-amino acids under aprotic conditions[2] would lead to the formation of carbenoid species by simultaneous or stepwise loss of nitrogen and carbon dioxide from I. The extremely low yields (*vide supra*) of hydrocarbon products in these reactions, which might be derived from such a reaction, certainly negate any preparatory value.

(1) D. H. Szulczewski and T. Higuchi, *Anal. Chem.*, **29**, 1541 (1957); see also N. Kornblum and E. P. Oliveto, *J. Am. Chem. Soc.*, **71**, 226 (1949).

(2) L. Friedman and F. M. Logullo, *ibid.*, **85**, 1549 (1963).



Although, the formation of cyclopropanes in these reactions might be due to carbene intermediates, formation of *cis*- and *trans*-2-butene from valine requires at least the simultaneous occurrence of an ionic path.[3] This might involve methyl or hydrogen migration in IIa to yield a carbonium ion β to the carboxylate group and subsequent decarboxylation to yield olefins. Alternatively, it has been suggested that protonation of IIb by unchanged amino acid or other reaction products could yield an alkyl diazonium ion.[4] Loss of nitrogen from the diazonium ion and subsequent established reactions of the resultant alkyl carbonium ion could account for the product distribution including the cyclopropanes.[5] If methylcyclopropane arises from carbenoid intermediates, its absence in the ethyl alcohol–water experiment might be explained by rapid trapping reactions. On the other hand this result could imply that only IIa is formed under these conditions and that it undergoes ionic rearrangements exclusively and then decarboxylation.[6]

Experimental

The amino acids used were optically inactive reagent grade materials (Matheson Coleman and Bell). Dimethylformamide was shaken with potassium hydroxide pellets and lump calcium oxide, and distilled from molecular sieves. *p*-Dioxane was shaken with potassium hydroxide pellets, refluxed for 50 hr. over sodium metal, and distilled. Isoamyl nitrite (Matheson Coleman and Bell) was used as commercially obtained.

Diazotization Reaction Conditions.—The method will be described for a typical reaction with valine. A heterogeneous mixture consisting of 0.1 g. (8.5×10^{-4} mole) of *dl*-valine, 1 ml. (7.5×10^{-3} mole) of isoamyl nitrite, and 25 ml. of anhydrous dioxane was heated with stirring under an atmosphere of prepurified nitrogen at 63° until gas evolution ceased (6–10 hr.). The reaction time is apparently a function of the rate of solution of amino acid in the solvent, since rates are strongly dependent on particle size. Approximately 25 ml. of gas was evolved and this was collected over mercury in a gas buret. The gas was analyzed by vapor phase chromatography yielding the composition: nitrogen[7] (82%), carbon dioxide (12%), nitrous oxide (5%), and hydrocarbon fraction (<1%). The presence of nitric oxide is inferred by the formation of traces of solid on the surface of the mercury in the gas buret, and the appearance of the characteristic nitrogen dioxide coloration (and solids) when the product gases were allowed to bubble through a mercury bubbler into the atmosphere in a separate experiment.

V.p.c. Analyses.—The hydrocarbon content of each gas sample was quantitatively analyzed using a 10 ft. × 0.125 in. 20% silicone SF-96 (60/80 firebrick) column (0°, nitrogen flow 20 ml./min.) in conjunction with an Aerograph (Wilkens Instrument Co.) electrometer and flame ionization detector. Retention times for the hydrocarbon gases under these conditions are methane (88 sec.), ethylene (111 sec.), ethane (125 sec.), propylene (227 sec.), propane (240 sec.), cyclopropane (375 sec.), isobutane (455 sec.), isobutene and 1-butene (600 sec.), *trans*-2-butene (745 sec.), methylcyclopropane (825 sec.), and *cis*-2-butene (865 sec.). The inorganic gases were identified using a 15 ft. × 0.25 in. silicone column in conjunction with an Aerograph A-90-C chromatograph equipped with a thermal conductivity detector. Proper and reproducible temperature was obtained in this latter instrument by placing Dry Ice in the oven.

Preliminary Analysis of Nonvolatile Products.—A reaction mixture from decomposition of valine in dioxane was distilled not quite to dryness and an infrared spectrum was taken of the liquid residue (reference pure dioxane). Bands were observed at 3420 (s), 1800 (w), 1780–1720 (s), 1640 (s), 1590 (sh), and 1555 cm.$^{-1}$ (s). The strong hydroxyl absorption is probably due to water and isoamyl alcohol, both anticipated reaction products. The infrared spectrum can also accomodate the presence of various esters and acids which might be expected and isovaleraldehyde (from isoamyl nitrite decomposition). An infrared spectrum of the distillate showed strong bands at 3420, 1640, and 1590 cm.$^{-1}$ (sh). The first is probably due to water, and the latter two are tentatively assigned to unchanged isoamyl nitrite.

Acknowledgment.—The invaluable assistance of Dr. Jerry A. Bell with the v.p.c. analyses is gratefully acknowledged. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.[8]

(3) Rearrangement reactions of isobutylidene apparently do not yield *cis*- or *trans*-2-butene [L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959).

(4) L. Friedman, private communication.

(5) M. S. Silver, *J. Am. Chem. Soc.*, **82**, 2971 (1960); P. S. Skell, *et al.*, *ibid.*, **82**, 2971 (1960); **84**, 3962, 3963 (1962).

(6) We have no strong preference for the zwitterion IIa over an α-lactone intermediate. However, the diazonium ion origin of the intermediate implies that it would be more ionic than α-lactone intermediates which arise in nucleophilic substitution reactions of α-halocarboxylic acid salts.

(7) Corrected for the initial nitrogen present in the system.

(8) After these studies were completed, it was learned that Dr. Lester Friedman had obtained similar results with other amino acids. Helpful discussions with him are gratefully acknowledged.

A Convenient Spectrophotometric Method for Following the Reactions of Arenesulfonates[1]

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A convenient spectrophotometric method has been developed for following the reactions of methyl *p*-toluenesulfonate (tosylate). This should be of general interest in view of the widespread use of arenesulfonates for studies of organic reactions. The absorptions of methyl tosylate and tosylate anion are sufficiently different so that the reactions can be followed spectrophotometrically; at 261 mμ (in water) methyl tosylate has ϵ 671 and tosylate anion has ϵ 344. For reactions in transparent solvents, rate measurements are made by simply measuring the decrease in optical density (absorbance) with time. First-order rate constants determined by this method for the reactions of methyl tosylate in the presence of a large excess of various nucleophiles (conditions which preclude the use of titrimetric or conductometric methods) in methanol[2] were reproducible to 0.5 to 3%. The first-order rate constant for the hydrolysis of methyl tosylate in water at 25.00° of 7.98 ± 0.05 (average deviation from mean of three trials) × 10^{-6} sec.$^{-1}$, as determined by this

(1) Supported in part by the Atomic Energy Commission under Contract No. AT(30-1)-905 and by N.S.F. and N.I.H. predoctoral fellowships.

(2) C. G. Swain and W. D. Burrows, unpublished results

method,[3] may be compared with that of 7.78×10^{-6} sec.$^{-1}$ at 24.85°, determined by conductivity.[4]

By suitable extraction techniques, this method may be used also for reactions in solvents that absorb in this region. Thus, reactions of methyl tosylate in benzene can be followed by extracting aliquots of the reaction mixture with water, back-extracting with cyclohexane, and measuring the absorbance of the water layer. In a number of runs in water, methyl tosylate was determined in cyclohexane after extraction. Similarly, extraction techniques may also be devised for following the reactions of an ester whose absorption is the same as that of the anion produced.

Experimental

The procedure used for the reactions in water is described below using the hydrolysis of methyl tosylate as a typical example.

Water was laboratory distilled water redistilled from sodium hydroxide–potassium permanganate in an all-Pyrex apparatus. It was degassed by bubbling carbon dioxide-free nitrogen through it for at least 20 min.

Methyl tosylate, Eastman White Label grade, was recrystallized from reagent grade cyclohexane–ether and dried in a desiccator over phosphorus pentoxide at 22° (1 mm.) for 3 days. The ester was allowed to melt, cooled, and a seed crystal was introduced. When approximately 75% of the material had crystallized, the solid ester was collected on a filter and then dried as before for 24 hr. The methyl tosylate, m.p. 28.4–29.4° (uncor.) lit.[5] m.p. 28–29°, was stored in a desiccator over Drierite (calcium sulfate).

Kinetics.—Temperature control was ± 0.02°. The temperature was determined using a thermometer calibrated by the National Bureau of Standards.

A 50-ml. volumetric flask was filled to the mark with water under an atmosphere of carbon dioxide-free nitrogen. Approximately 10 μl. of methyl tosylate was added and the resulting mixture was shaken vigorously to give the reaction solution, which was placed in the constant-temperature bath at 25°. After 10 min. (zero point), and at suitable times thereafter, a sample of reaction solution was transferred to a glass-stoppered 1-cm. silica cell and its absorbance was determined at 261 mμ at a slit width of 0.4 mm. using a Beckman DU spectrophotometer. A Beer's law plot (absorbance *vs.* fraction sodium tosylate) was linear for the change from methyl tosylate to tosylate anion. The concentration of methyl tosylate present initially was calculated from the infinity point, which was taken after the solution had been in the bath for 10 half-lives.

First-order rate constants were obtained from a plot of per cent unchanged methyl tosylate *vs.* time on semilogarithmic paper by dividing 0.693 by the half-life. Data for a typical run are shown in Table I.

TABLE I
HYDROLYSIS OF 1.22×10^{-3} *M* METHYL TOSYLATE IN WATER AT 25°

Time, hr.	Absorbance	% unchanged
0.0	0.791	100.0
5.0	0.746	87.9
9.0	0.709	77.9
18.0	0.645	60.6
24.0	0.611	51.5
32.0	0.570	40.4
44.0	0.526	28.6
55.0	0.498	21.0
67.0	0.471	13.7
290.0	0.420	0.0

$k_1 = 7.91 \times 10^{-6}$ sec.$^{-1}$

(3) C. R. Morgan, Ph.D. thesis in Organic Chemistry, Massachusetts Institute of Technology, May, 1963, p. 49.
(4) R. E. Robertson, *Can. J. Chem.*, **33**, 1536 (1955).
(5) F. Drahowzal and D. Klamann, *Monatsh.*, **82**, 460 (1951).

α-Pinene Oxide Reaction with Acetic Acid–Sodium Acetate

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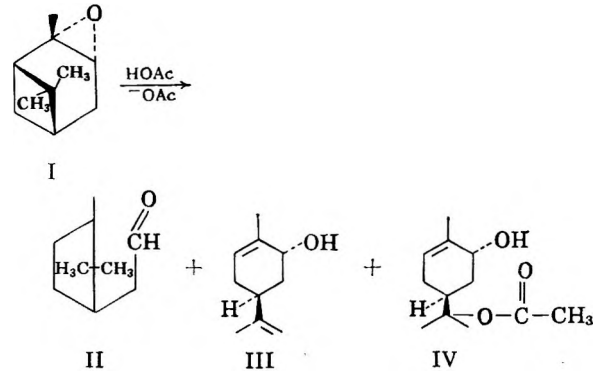
Received December 26, 1963

In a previous study,[3] the reaction of α-pinene oxide (I) with glacial acetic acid was reported to give campholenaldehyde (II) and a high boiling fraction which was apparently a crude hydroxyacetate. Arbuzow and Mikhailow[4] have reported the formation of a glycol monoacetate on treatment of α-pinene with peracetic acid in chloroform solution, and that a similar product was obtained on treatment of α-pinene oxide with acetic acid.

We have reinvestigated the reaction of *dl*-α-pinene oxide with a solution of sodium acetate in glacial acetic acid and found it to afford 39% campholenaldehyde, 19% *dl-trans*-carveol (III), and 23% *dl-trans*-8-acetoxy-6-hydroxy-1-*p*-menthene (IV). Identity of the latter product was established by saponification to *dl-trans*-sobrerol, and by pyrolysis to yield *dl-trans*-carveol (III) as the only product.

Inasmuch as the conversion of α-pinene oxide in this and previously reported work[4-7] to sobrerol or its derivatives has invariably afforded the *trans* isomers,[8] the stereochemistry of the epoxide must be as shown in I, the influence of steric hindrance playing a role similar to that observed for pinol.[9]

In view of the present results, the theoretical arguments of Brewster,[10] and the hydrogenation of the higher rotating carvotanacetol to the carvomenthols having the hydroxyl *trans* to the isopropyl group,[11] we must conclude that the generally accepted con-



(1) Research Associate, Newport Industries Division, Heyden Newport Chemical Corp., Pensacola, Fla.
(2) National Defense Education Act Fellow, 1960–1963.
(3) E. E. Royals and L. L. Harrell, Jr., *J. Am. Chem. Soc.*, **77**, 3405 (1955); L. C. King and H. Farber, *J. Org. Chem.*, **26**, 326 (1961).
(4) B. A. Arbuzow and B. M. Mikhailow, *J. prakt. Chem.*, **127**, 1 (1930).
(5) N. Prileschaev and V. Vershuk, *J. Russ. Phys. Chem. Soc.*, **61**, 473 (1929).
(6) A. J. Durbetaki and S. M. Linder, U. S. Patent 2,949,489 (1960); *Chem. Abstr.*, **55**, 608 (1961).
(7) E. A. Klein, U. S. Patent 2,815,378 (1957).
(8) H. Schmidt, *Ber.*, **86**, 1437 (1953).
(9) K. Piatkowski and H. Kuczynski, *Roczniki Chem.*, **35**, 1579 (1961).
(10) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5493 (1959), and references therein.
(11) R. L. Kenney and G. S. Fisher, *J. Org. Chem.*, **28**, 3509 (1963).

figurational assignments for the carveols are correct, and that the reassignments suggested by Farges and Kergomard[12] are invalid.

Experimental

Melting points were taken in capillaries on a Mel-Temp melting point apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 21 recording spectrophotometer. Gas–liquid chromatography separations were effected on a Wilkins Aerograph Master Model A-100 equipped with a 10-ft., 0.25-in., Carbowax 20 M column. Analyses were by G. Weiler and F. B. Strauss, Oxford, England.

Reaction of *dl*-α-Pinene Oxide with a Sodium Acetate–Glacial Acetic Acid Solution.—Freshly distilled *dl*-α-pinene oxide (136 g.), b.p. 63–65° (10 mm.), $n^{25}D$ 1.4670, was slowly added to a slurry of sodium acetate (123 g.) in glacial acetic acid (600 g.) over a period of 2.5 hr. The reaction temperature rose to approximately 40°. The reaction was stirred for 72 hr., during which time the temperature dropped to 27°. The reaction mixture was poured into 1000 ml. of water, the oil layer separated, and the aqueous phase extracted with three 100-ml. portions of ether. The organic phases were combined, neutralized with a saturated sodium bicarbonate solution, and washed with three 75-ml. portions of water. The ethereal phase was dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the product distilled over a 3-ft. spinning band column to give three fractions. The first fraction (53 g.) was campholenaldehyde (39%), b.p. 80° (10 mm.), $n^{25}D$ 1.4630, which gave a yellow 2,4-DNP, m.p. 110–111°, and semicarbazone, m.p. 138.5–140° (lit.[3] m.p. 139.5–140.5°).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.61; H, 10.63.

The second component (26 g.), b.p. 76° (4 mm.), $n^{25}D$ 1.4949, was identified as *dl-trans*-carveol (19.1%) by g.l.c. and infrared comparison with an authentic sample of *d-trans*-carveol. This alcohol formed a 3,5-dinitrobenzoate, m.p. 118–118.5° (lit.[13] $n^{19}D$ 1.4956, 3,5-dinitrobenzoate m.p. 119°).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.48; H, 10.55.

The third component (43.5 g.), b.p. 128–133° (4 mm.), $n^{25}D$ 1.4813, was subsequently identified as the monoacetate of sobrerol (*dl-trans*-8-acetoxy-6-hydroxy-1-*p*-menthene, 22.9%), which gave a 3,5-dinitrobenzoate, m.p. 130.5–132°.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.24; H, 9.72.

Saponification of the hydroxyacetate (0.4 g.) with a solution of 4 ml. of 50% potassium hydroxide in 10 ml. of a 20% ethanol solution afforded *dl-trans*-sobrerol, m.p. 128–129°, whose melting point was undepressed on admixture with an authentic sample.[6]

Pyrolysis of *dl-trans*-8-Acetoxy-6-hydroxy-1-*p*-menthene.—The sobrerol monoacetate (6.0 g.), produced above, was pyrolyzed at 370°. The pyrolysis product was taken up in ether, neutralized with a sodium bicarbonate solution, washed with water, and dried over anhydrous sodium sulfate. After removal of the solvent, the crude product (4.24 g.), identified by g.l.c. to be greater than 90% *trans*-carveol, was distilled on a modified Hickman still to give *dl-trans*-carveol (3.78 g.), $n^{25}D$ 1.4959, 3,5-dinitrobenzoate m.p. 119°. This alcohol gave an infrared spectrum identical with an authentic sample.

(12) G. Farges and A. Kergomard, *Bull. soc. chim. France*, 51 (1963).

(13) E. Guenther and D. Althausen, "The Essential Oils," Vol. II, D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 203.

An Improved Synthesis of Peroxybenzoic Acid

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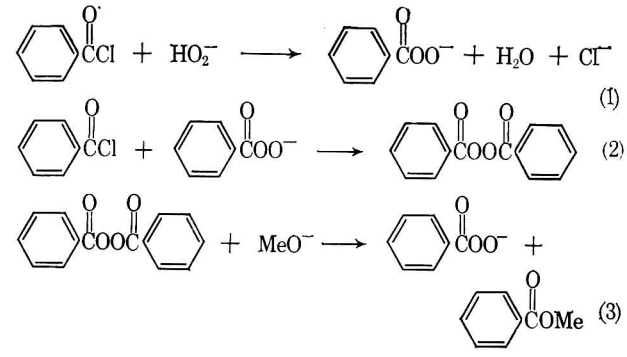
Peroxybenzoic acid is commonly prepared by a two-step process. In the first step, benzoyl chloride reacts with aqueous sodium peroxide. Because benzoyl chloride is immiscible with the solution, the reaction with the hydroperoxide ion (eq. 1) takes place at the surface of the droplets. The peroxybenzoate anion is less reactive toward benzoyl chloride than is HO_2^-, but reacts preferentially (eq. 2) because it is in contact. Several experimental procedures have been given.[1-3]

In the second step, benzoyl peroxide is cleaved by sodium methoxide (eq. 3). The procedure described by Braun[4] has been modified by later workers.[5,6]



Kergomard and Bigou[7,8] and Vilkas[9] have reported a method which avoids the formation of benzoyl peroxide. Sodium peroxide, or equivalent amounts of hydrogen peroxide and sodium hydroxide, is dissolved in a mixed solvent system in which benzoyl chloride is also soluble. In such a system, the peroxybenzoate ion and the hydroperoxide ion can compete as nucleophiles for benzoyl chloride. Very little benzoyl peroxide is formed. Peroxybenzoic acid can be recovered from the reaction mixture as soon as the addition of benzoyl chloride is complete.

This method is quicker, gives better yields, and is much safer in that neither benzoyl peroxide nor sodium metal is involved. It has the disadvantage of requiring a reaction temperature of −5° or lower.

We have had occasion to repeat many times this last method. We consistently obtain better yields using sodium peroxide rather than hydrogen peroxide and sodium hydroxide. Purification of the sodium peroxide by recrystallization as $Na_2O_2 \cdot 8H_2O$ gives further improvements in yield. This indicates that catalytic decomposition is occurring.

In commercial bleaching operations, the catalytic effect of traces of metal ions is inhibited by adding a small amount of magnesium sulfate.[10] We have found that the addition of a little magnesium sulfate to the reaction mixture allows the reaction to be run at room

(1) C. C. Price and E. Krebs, *Org. Syn.*, **23**, 65 (1943).

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(3) J. D'Ans, J. Mattner, and W. Busse, *Angew. Chem.*, **65**, 57 (1953).

(4) G. Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431.

(5) I. M. Kolthoff, T. S. Lee, and M. A. Mairs, *J. Polymer Sci.*, **2**, 199 (1947).

(6) C. G. Overberger and R. W. Cummins, *J. Am. Chem. Soc.*, **75**, 4250 (1953).

(7) A. Kergomard and J. Bigou, *Bull. soc. chim. France*, 486 (1956).

(8) A. Kergomard and J. Bigou, *ibid.*, 334 (1958).

(9) M. Vilkas, *ibid.*, 1501, (1959); French Patent 1,177,466 (1958).

(10) L. A. Beeman and J. S. Reichert, "The Bleaching of Pulp," R. S. Hatch, Ed., Technical Association of the Pulp and Paper Industry, New York, N. Y., 1953, p. 228.

temperature with yields equal to those obtained at −5° without the addition of magnesium sulfate.

Experimental

A solution of 8.0 g. (0.102 mole) of sodium peroxide in 135 ml. of water is prepared with cooling so that the temperature does not exceed 20°. The solution is filtered through a "fine" porosity fritted disk to remove the yellow suspended solids. The filtrate is placed in a 1000-ml. beaker and stirred magnetically while 175 ml. of denatured ethanol and a solution of 0.5 g. of $MgSO_4 \cdot 7H_2O$ in 15 ml. of water are added. Heat liberated during the addition of ethanol raises the temperature of the solution about 8°.

When the solution is again at room temperature, 11.6 ml. (0.100 mole) of benzoyl chloride is added dropwise while the solution is stirred magnetically. The addition should take 10 to 12 min. The mixture is filtered to remove any benzoyl peroxide. The filtrate is acidified[11] with 20% sulfuric acid and extracted with carbon tetrachloride, chloroform, or benzene. Six extractions using about 75-ml. portions give 0.075 mole of peroxybenzoic acid. The entire procedure takes about 1.5 hr.

If ethanol is incompatible with subsequent reactants, methanol may be substituted. About 25 ml. of ethanol is extracted into the organic phase. Methanol is not extracted, but yields are about 60% *vs.* the 75% obtained using ethanol.

(11) Vilkas[9] reports better yields when the solution of sodium peroxybenzoate is added to the sulfuric acid rather than the converse.

β-Ylangene, a New Sesquiterpene Hydrocarbon from Orange Oil

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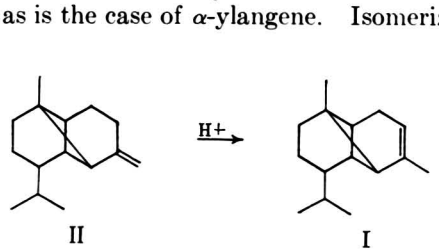
Previous work in this laboratory[1] showed that ylangene (I), hereafter called α-ylangene, was a stereoisomer of copaene. Copaene has recently been shown to contain a cyclobutane ring[2] in place of the cyclopropyl group which had previously been proposed.[3,4] In the present work the authors have isolated a new sesquiterpene hydrocarbon from Valencia orange oil which when reduced with PtO_2–H_2 at low pressure gave ylangane. This sesquiterpene hydrocarbon (II), hereafter called β-ylangene, therefore has the same stereochemistry as α-ylangene (I) and differs only in that it contains an exocyclic terminal double bond at position six instead of the endocyclic double bond at this position as is the case of α-ylangene. Isomerization of



II I

(1) G. L. K. Hunter and W. B. Brogden, Jr., *J. Org. Chem.*, **29**, 982 (1964).
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(3) L. H. Briggs and W. I. Taylor, *J. Chem. Soc.*, 1338 (1947).
(4) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, London, 1952, p. 88.

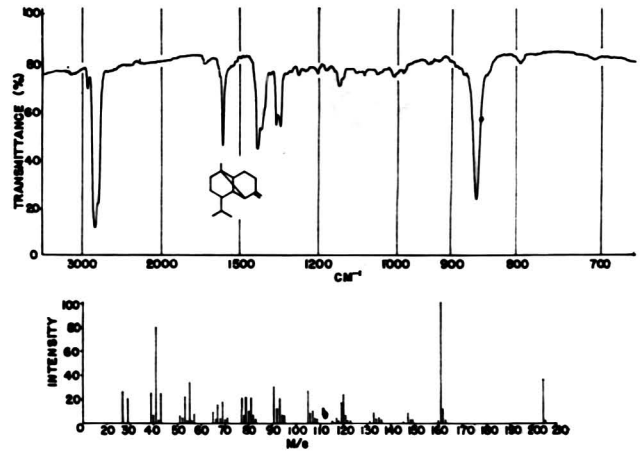

Fig. 1.—Infrared and mass spectra of β-ylangene.

β-ylangene in the presence of sulfuric acid gave α-ylangene.

Experimental

Isolation of β-Ylangene.—Seven pounds of cold pressed Valencia orange oil was rapidly stripped of terpenes and low boiling oxygenated materials in an Arthur F. Smith 2-in. Rota-Film molecular still at 85° (1 mm.). The residue (200 g.) was redistilled in the same still, and 12 g. (0.3% of the total oil) boiling in the sesquiterpene range (100–110° at 0.25 mm.) was collected. The oxygenated compounds were removed from this fraction by elution with *n*-hexane through a 0.75 × 18 in. column containing basic alumina to give 1.7 g. (0.04% of the total oil) upon removal of the solvent *in vacuo*. This material was placed in a 0.75 × 36 in. column containing basic alumina and the first four fractions containing 3 ml. each were combined. Gas chromatographic[5] and infrared analyses of the residue upon removal of the solvent indicated the presence of α-copaene, α-ylangene, β-ylangene, and Δ-cadinene. The material having a retention time of 80 min., representing one of the major sesquiterpene constituents (0.008% of the total oil) was collected to give the infrared and mass spectra shown in Fig. 1. Absorptions at 1640 and 875 cm.$^{-1}$ showed the presence of a terminal double bond and those at 1387 and 1370 cm.$^{-1}$ indicated the presence of a *gem*-dimethyl group.[6] The principal peak at *m/e* 161 indicates the loss of the isopropyl fragment. β-Ylangene has a boiling point of 121–122° (10 mm.) by the method of Garcia[7] and a refractive index of $n^{20}D$ 1.5000.

Reduction of β-Ylangene to Ylangane.—Five microliters of β-ylangene was placed in a Parr apparatus with a catalytic amount of PtO_2 and allowed to shake for 4 hr. at room temperature under a hydrogen pressure of 70 lb./in.^{2} to give a quantitative yield of ylangane. The infrared spectrum obtained on the material, following filtration of the catalyst, was identical in every respect with ylangane.[8] The molecular weight showed an increase of two in the *m/e* value by mass spectroscopy upon reduction of β-ylangene. The mass spectral cracking patterns after reduction of both β-ylangene and α-ylangene were identical.

Isomerization of β-Ylangene to α-Ylangene.—Five microliters of β-ylangene was placed in a vial containing a milliliter of 50% H_2SO_4 and shaken for 30 min. The emulsion was extracted with ether and gas chromatographed.[5] The material corresponding to the large peak, approximately 4 μl. of material and having the same retention time as α-ylangene, was collected. Infrared and mass spectra of this material were identical in all respects with the corresponding spectra of α-ylangene.[9]

(5) Column: 0.25-in. × 16-ft. containing 25% Carbowax 30M on Chromosorb P; flow rate, 60 ml./min.; temperature, programmed from 150–200° at 1.1°/min.
(6) N. Horak and J. Pliva, *Collection Czech. Chem. Commun.*, **25**, 1679 (1960).
(7) C. R. Garcia, *Ind. Eng. Chem. Anal. Ed.*, **15**, 648 (1943).
(8) J. Pliva, M. Horak, V. Herout, and F. Sorm in "Die Terpene. I. Sesquiterpene," Akademie, Verlag, Berlin, 1960, p. 220.
(9) Ref. 8, p. 221.

The Isolation of Dihydromexicanin E from *Helenium autumnale L.*

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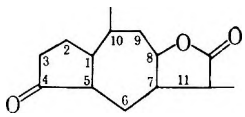
Recently we had occasion to extract a batch of *Helenium autumnale* L. seeking a supply of the sesquiterpene lactone, helenalin, for use in chemical studies.[1] The plants were obtained in late summer, 1963, in the vicinity of Chapel Hill, North Carolina.[2] They were air-dried and 7 kg. of finely ground leaves and stems was extracted in the usual way with methylene chloride.[3] After treatment of an alcoholic solution of the crude extract with aqueous lead acetate, the clarified aqueous alcoholic solution was partially evaporated and extracted with methylene chloride. When attempted crystallization of the dried extract from benzene failed to produce helenalin, as expected, the material was subjected to chromatography in benzene on II–III Activity Woelm neutral alumina. Repeated chromatography of the benzene eluates yielded 14.9 g. of a product which crystallized from ethyl acetate. Repeated crystallization from the same solvent afforded colorless rods, m.p. 133–135°, $[\alpha]^{25}D$ −188° ($CHCl_3$), λ_{max}^{EtOH} 222 mμ (ε 10,400), λ_{max}^{NaOH} 242 mμ; ν^{Nujol} 1760 (γ-lactone), 1700, and 1586 (cyclopentenone) cm.$^{-1}$.

The n.m.r. spectrum,[4] τ 7.80 dd (H-2), 6.25 dd (H-3), 4.60 c (H-8), and 1.23 d and 1.13 d (C-10 and C-11 methyl), suggested a norsesquiterpenoid structure.

Anal. Calcd. for $C_{14}H_{18}O_3$; C, 71.77; H, 7.74. Found: C, 71.79; H, 7.84.

Finally, comparison of published data for dihydromexicanin E[5] pointed to the identification of our substance.



Dihydromexicanin E

Through the courtesy of Dr. J. Romo, University of Mexico, Mexico City, Mexico, a sample of dihydromexicanin E was obtained for direct comparison and proved to be identical by the usual criteria. As far as we know, this represents the first isolation of this substance from plant material. It is interesting that no helenalin could be isolated from this sample of *Helenium autumnale* L. inasmuch as it is usually the principal sesquiterpene component.[6]

(1) R. A. Lucas, S. Rovinski, R. J. Kiesel, L. Dorfman, and H. B. MacPhillamy, *J. Org. Chem.*, **29**, 1549 (1964).

(2) The plant material was collected and identified by H. E. Ahles, Botany Department, University of North Carolina, Chapel Hill, N. C., to whom our thanks are due.

(3) E. P. Clark, *J. Am. Chem. Soc.*, **58**, 1982 (1936).

(4) This was run in deuteriochloroform solution on a Varian A-60 n.m.r. spectrometer using tetramethylsilane as internal reference; multiplets are described: d, doublet; dd, doublet of doublets; c, complex band whose center is given.

(5) A. Romo de Vivar and J. Romo, *J. Am. Chem. Soc.*, **83**, 2326 (1961); J. Romo, A. Romo de Vivar, and W. Herz, *Tetrahedron*, **19**, 2317 (1963).

(6) E. P. Clark, *J. Am. Chem. Soc.*, **58**, 1982 (1936); **61**, 1836 (1939); **62**, 597 (1940).

Bromination of 6-Benzoyl-2,5-diphenyl-2-phenylglyoxoyl-3,4-dihydro-2H-pyran

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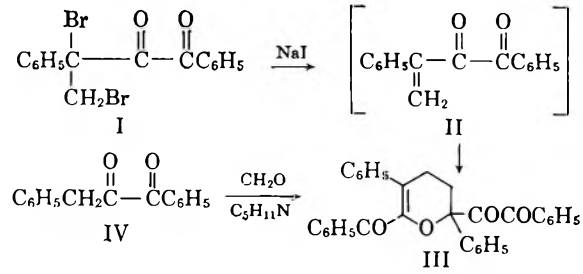
Received October 14, 1963

Treatment of 3,4-dibromo-1,3-diphenyl-1,2-butanedione (I) with sodium iodide in acetone previously[2] was reported to produce a dimeric substance which was formulated as 6-benzoyl-2,5-diphenyl-2-phenylglyoxoyl-3,4-dihydro-2H-pyran (III). The structural assignment was based primarily on the elemental analysis,[3] molecular weight of the material, and the analogy to other dimers of similar and proven structure.[3] Presumably III arose *via* the dimerization of 1,3-diphenyl-3-butene-1,2-dione (II) although II could not be isolated. Additional support for this view was obtained by the production of III from the reaction of 1,3-diphenyl-1,2-propanedione (IV) with formaldehyde in the presence of a catalytic amount of piperidine.



Treatment of III with 1 equiv. of bromine in dry carbon tetrachloride provided hydrogen bromide and a yellow solid (V, $C_{32}H_{22}O_4$) in 74.6% yield. The same substance could be generated from III using excess bromine or N-bromosuccinimide.

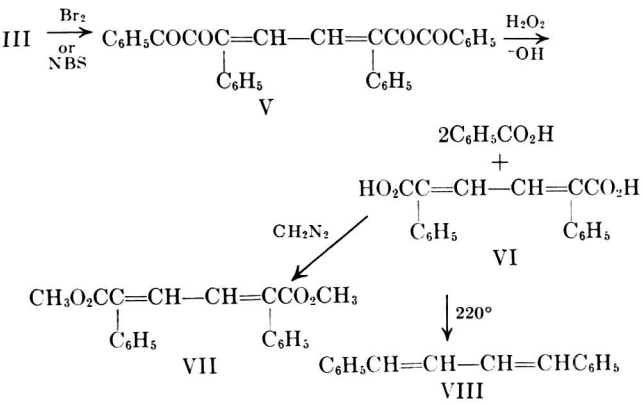
The ultraviolet spectrum of V, λ_{max} 250 mμ (ε 30,550), 357 (16,500), indicated considerable unsaturation; however, no tractable hydrogenation product could be obtained. Although oxidation of V with periodic acid or ozone provided no information as to the nature of V, treatment of the substance with alkaline hydrogen peroxide provided 2 equiv. of benzoic acid and a high melting acid (VI, $C_{18}H_{14}O_4$).

The dibasic nature of VI was confirmed by the formation of a dimethyl ester (VII) when VI was treated with excess diazomethane. Hydrogenation of VII provided a mixture of diastereoisomers. Decarboxylation of VI was accomplished smoothly using a copper–quinoline catalyst at 220°. Chromatography of the product provided *trans*-1,4-diphenyl-1,3-butadiene (VIII), identical in all respects with an authentic sample. On the basis of these conversions, the bromination product (V) can be formulated as 1,3,6,8-tetraphenylocta-3,5-diene-1,2,7,8-tetraone.

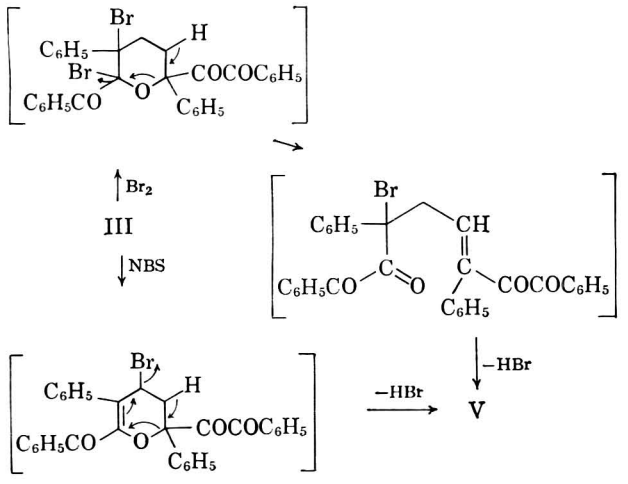
(1) Abstracted in part from a dissertation by R. L. Smith submitted to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, June, 1962.

(2) C. L. Stevens and R. G. Hiskey, *J. Org. Chem.*, **24**, 32 (1959).

(3) K. Alder and E. Ruden, *Ber.*, **74**, 920 (1941); C. Mannich, *ibid.*, **74**, 557 (1941); H. Fiesselmann and F. Meisel, *ibid.*, **89**, 657 (1956).



The formation of V from III may be rationalized by several pathways. One possibility would involve the following scheme. The isolation of V from III provides definite evidence for the previous assignment of III.



Experimental[4]

Preparation of 6-Benzoyl-2,5-diphenyl-2-phenylglyoxoyl-3,4-dihydro-2H-pyran (III).—To 18.2 g. (0.081 mole) of 1,3-diphenyl-1,2-propanedione[5] in 80 ml. of methanol was added 25 ml. (0.29 mole) of 37% formalin solution. The mixture was heated to reflux and 0.5 ml. of piperidine in 10 ml. of methanol was added in 5 min. The solution was refluxed 3 hr., poured into water, and extracted with methylene chloride. The organic extract was washed with successive portions of dilute sulfuric acid, 5% sodium bicarbonate solution, and water. Removal of the solvent provided a yellow oil which was heated 10 hr. at 95°. The oil was then triturated with methanol and yielded a yellow solid which was recrystallized from a benzene-*n*-heptane mixture to afford 2.1 g. (11.5%) of dense yellow prisms, m.p. 132–134°. A mixture melting with a sample of III obtained[2] from I melted at 132–134°.

Bromination of 6-Benzoyl-2,5-diphenyl-2-phenylglyoxoyl-3,4-dihydro-2H-pyran (III).—Treatment of 2.0 g. (4.2 mmoles) of III in 100 ml. of refluxing dry carbon tetrachloride with 1.0 g. (6.25 mmoles) of bromine in 50 ml. of carbon tetrachloride provided 1.47 g. (74.6%) of yellow needles, m.p. 166–167° after recrystallization from a benzene–*n*-heptane mixture, lit.[2] m.p. 162–163°.

Anal. Calcd. for $C_{32}H_{22}O_4$: C, 81.68; H, 4.71. Found: C, 81.51; H, 4.62.

When 0.60 g. (1.28 mmoles) of III was treated with a solution of 0.23 g. (1.28 mmoles) of N-bromosuccinimide in carbon tetrachloride containing a trace of benzoyl peroxide, hydrogen bromide was evolved copiously. Purification of the resulting solid provided 0.42 g. (70.0%) of V.

Oxidation of V with Alkaline Hydrogen Peroxide.—A solution of 2.0 g. (4.3 mmoles) of V in 35 ml. of purified dioxane was treated with 5 ml. of 30% hydrogen peroxide. To this solution was added 2.3 ml. of 20% sodium hydroxide solution. The addition was carried out drop-wise over a 30-min. period. The solution was stirred overnight, the solvent removed, and the residue was dissolved in water. Acidification of the aqueous solution provided 1.87 g. (85%) of acidic material. Sublimation of the resulting solid afforded 0.97 g. of benzoic acid and 0.90 g. of an acid melting above 300°. The high melting acid (VI) exhibited a maximum at 316 mμ (ε 20,250).

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.45; H, 4.79. Found: C, 73.28; H, 4.61.

A 0.90-g. (0.30 mmole) sample of VI was suspended in 25 ml. of dry ether and treated with excess diazomethane solution. Filtration and removal of the solvent afforded 0.85 g. (88.1%) of solid ester. Recrystallization from a benzene–petroleum ether mixture gave VII as needles, m.p. 178–179°; λ_{max} 321 mμ (ε 18,750).

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.47; H, 5.64

Hydrogenation of 1,4-Dicarbomethoxy-1,4-diphenyl-1,3-butadiene (VII).—A solution containing 0.15 g. (0.47 mmole) of VII in 30 ml. of ethyl acetate consumed 23.0 ml. of hydrogen when stirred at room temperature and atmospheric pressure with 0.10 g. of 10% palladium-on-charcoal catalyst. Recrystallization of the resulting solid from *n*-heptane provided dense prisms melting indefinitely from 95–112°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.59; H, 6.80. Found: C, 73.88; H, 6.67.

Decarboxylation of 1,4-Dicarboxy-1,4-diphenyl-1,3-butadiene (V).—To 0.60 g. (2.05 mmole) of V was added 0.125 g.-atom of copper powder and 5 ml. of quinoline. The mixture was heated at 220° for 6 hr., diluted with ether, and filtered; the quinoline was removed by extraction with dilute hydrochloric acid. The ether extract was washed with sodium bicarbonate and water. Removal of the solvent provided a yellow oil which was dissolved in petroleum ether and chromatographed on neutral alumina. Elution with petroleum ether provided 0.275 g. of colorless solid, m.p. 145–149°. Recrystallization from benzene–ethanol afforded colorless crystals of VIII, m.p. 152–153°. A mixture melting point with an authentic sample[6] of VIII was not depressed.

(4) Melting points are uncorrected. Elemental analysis were by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Micro-Tech Laboratories, Skokie, Ill.

(5) H. Fiesselmann and J. Ribka, *Ber.*, **89**, 27 (1956).

(6) B. B. Corson, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 229.

Overreduction of Naphthalenic Diethers

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Received December 26, 1963

The Birch reaction is a standard method for converting aromatic ethers into unsaturated alicyclic ketones.[1] The reduction of di- and tetrahydronaphthalenic *monoethers* is a basic step in many schemes for the total synthesis of terpenes and steroids. In contrast, the conversion of naphthalenic *diethers* into bicyclic ketones has been almost ignored; to date only 2,6-dimethoxynaphthalene, 2,6-diethoxynaphthalene, and 1,5-dimethoxynaphthalene are known to be reducible in sodium–liquid ammonia solution in the presence of ethanol.[2] Both 2,6-diethers afford the expected 2,6-dialkoxy-1,4,5,8-tetrahydronaphthalenes

(1) For a comprehensive review of this entire field, see H. Smith, "Organic Reactions in Liquid Ammonia," John Wiley and Sons, Inc., New York, N. Y., 1963, pp. 245–279.

(2) M. Kocor and W. Kotlarek, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.*, **9**, 507 (1961).

which on hydrolysis give 2,6-diketo-1,2,3,4.5,6,7,8-octahydronaphthalene. The 1,5-diether is reduced with the loss of a methoxy group to 1-methoxy-5,8-dihydronaphthalene.

Reduction in sodium–liquid ammonia in the absence of alcohol of the model compounds 1- and 2-naphthyl methyl ether involves both hydrogenation of the aromatic nucleus and reductive cleavage of the methoxy group.[3] The first ether produces a mixture containing α-tetralone, naphthalene, and 1,4-dihydronaphthalene. In contrast, the second ether is converted into a mixture of tetralin and 2-methoxy-5,8-dihydronaphthalene. Similar cases that involve the loss of methoxy during the reduction of a variety of alkyl aryl ethers are known; thus, sodium and ethanol in liquid ammonia convert pyrogallol trimethyl ether into 2,5-dihydroresorcinol dimethyl ether,[4] veratric acid into 3-methoxy-2-cyclohexene-1-carboxylic acid,[5] 3,4,5-trimethoxybenzoic acid into 1,4-dihydro-3,5-dimethoxybenzoic acid,[6] 3,4,5-trimethoxybenzamide and a series of N-alkylated analogs into the corresponding 1,4-dihydro-3,5-dimethoxybenzamides,[6] and 1- and 3-methoxy-2-naphthoic acid into 1,2,3,4,5,8-hexahydro-2-naphthoic acid.[7] Finally, 6-methoxytetralin apparently yields only one product, 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene, by reduction with sodium or lithium and ethanol in liquid ammonia.[8–10]

These observations are recapitulated here since our results show similar loss of the methoxy group. Briefly, 2,7-dimethoxynaphthalene was treated with excess lithium–liquid ammonia in the initial absence of alcohol in the hope of obtaining 2,7-dimethoxy-1,4,5,8-tetrahydronaphthalene. The crude product consisted of *two* substances as demonstrated by thin layer and gas chromatographic data. The mixture was subjected to acid hydrolysis in order to convert the expected enol ether into $\Delta^{1,9}$-octalin-2,7-dione. On work-up, the yellow oil was found to contain *three* products. The ultraviolet spectrum of the mixture showed typical aromatic absorption bands while the infrared spectrum exhibited both conjugated and unconjugated carbonyl maxima.

This mixture was chromatographed to give two main fractions; the first was identified as 6-methoxy-1,2,3,4-tetrahydronaphthalene, while the second was characterized as $\Delta^{1,9}$-octalone-2. The latter material, on the basis of infrared and thin layer evidence, was admixed with a small amount of the unconjugated β,γ-ketone. Clearly, the reduction of 2,7-dimethoxynaphthalene by lithium–liquid ammonia in the initial absence of alcohol did not afford 2,7-dimethoxy-1,4,5,8-tetrahydronaphthalene; instead, the product was a mixture consisting mainly of 2-methoxy-1,4,5,6,7,8-hexahydronaphthalene. Acid hydrolysis of this material then produced both the conjugated and unconjugated ketones. The methoxytetralin was unaffected by the acid and was found again in the characterization of the crude product. This reductive chain can be explained by invoking the sequence 2,7-dimethoxynaphthalene → 2,7-dimethoxy-1,4-dihydronaphthalene → 2,7-dimethoxy-3,4-dihydronaphthalene → 6-methoxytetralin → 2-methoxy-1,4,5,6,7,8-hexahydronaphthalene. Alternatively, allylic cleavage or 1,4-addition of hydrogen to 2,7-dimethoxy-1,2-dihydronaphthalene would yield the same set of products.

In a separate experiment 2-methoxynaphthalene was reduced by excess lithium–liquid ammonia in the presence of methanol. Vapor phase chromatography (DEGS) separated the product into three fractions: hydrocarbon (70%), 6-methoxytetralin (5%), and 2-methoxy-1,4,5,6,7,8-hexahydronaphthalene (25%). Further gas chromatographic examination (CDMS) disclosed that the hydrocarbon fraction contained three components: tetralin (6%), 1,4,5,6,7,8-hexahydronaphthalene (87%), and decalin (7%). The variety of reduced systems encountered here indicated that hydrogenolysis of a methoxy group proceeded in an orderly manner under *forcing* conditions.

It would appear that the variety of compounds observed in our reductions must be due to two types of reductions which take place in the same reaction; first, a metal–ammonia reduction undoubtedly gives certain new products (*e.g.*, demethoxylated and partially reduced compounds); and second, the addition of alcohol to the blue solution yields a metal–alcohol–ammonia combination that further reduces the intermediates derived from the metal–ammonia reduction. Naturally, the exact product or products seen in such a Birch reduction sequence will depend on solvent, alkali metal, molar ratios, proton donor liquids, and reaction time. All of these factors tend to hinder the easy prediction of structure and quantity of overreduced reaction products in specialized situations.

Experimental[11]

Methylation of Naphthols.—The literature procedure[12] employing a basic aqueous solution of the naphthol to which was added dimethyl sulfate produced 2,7-dimethoxynaphthalene [m.p. 136–137°, $\lambda_{max}^{ethanol}$ 235 mμ (log ϵ 4.99), lit.[10] m.p. 138°] and 2-methoxynaphthalene [m.p. 72–73°, $\lambda_{max}^{ethanol}$ 226.5 mμ (log ϵ 4.98), lit.[12] m.p. 72°].

Reduction of 2,7-Dimethoxynaphthalene. A.—To a blue solution of 7.0 g. of lithium (1.01 g.-atoms) in 500 ml. of ammonia, 4.66 g. (0.025 mole) of 2,7-dimethoxynaphthalene was added with stirring over a period of 30 min. After stirring further for 1 hr. at −30°, 20 ml. of reagent grade methanol was introduced dropwise to the blue solution to produce a colorless medium. After the ammonia had evaporated overnight at room temperature, water (250 ml.) was added to the residual gray slurry. The aqueous solution was extracted with three 175-ml. portions of ether and the combined ether extracts were washed with water (1 l.) and saturated salt solution. After drying with anhydrous magnesium sulfate, the ether was removed under reduced pressure on the rotary evaporator, providing 3.96 g. of a yellow oil (*ca.* 85%). Distillation of the sample (75–85° at 1 mm.) afforded a colorless liquid containing two components, 6-methoxytetralin and 2-methoxy-1,4,5,6,7,8-hexhydronaphthalene. Analytical v.p.c. on a diethylene glycol succinate (DEGS) column (2 m., on Chromosorb P at 145°, 15 lb. of N_2 pressure) revealed the two substances in almost equal amounts at 3.0 and 4.8 min. Thin-layer chromatography (ether–hexane, 1:1) showed one spot (R_f 0.70), while hexane as an eluent produced two connected spots (R_f 0.71 and 0.65). In neither instance did a retention time or an R_f value correspond to the starting material.

(3) W. Hückel and E. Vevera, *Chem. Ber.*, **89**, 2105 (1956).
(4) A. J. Birch, *J. Chem. Soc.*, 102 (1947).
(5) A. J. Birch, J. Cymerman-Craig, and M. Slaytor, *Australian J. Chem.*, **8**, 512 (1955).
(6) M. E. Kuehne and B. F. Lambert, *J. Am. Chem. Soc.*, **81**, 4278 (1959).
(7) E. L. Eliel and T. E. Hoover, *J. Org. Chem.*, **24**, 938 (1959).
(8) A. J. Birch, *J. Chem. Soc.*, 430 (1944).
(9) A. J. Birch, A. R. Murray, and H. Smith, *ibid.*, 1945 (1951).
(10) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.* **75**, 5360 (1953).
(11) Melting points and boiling points are uncorrected.
(12) O. Fischer and W. Kern, *J. prakt. Chem.* **94**, 34 (1916).

B.—The procedure of A was exactly repeated using 2.50 g. (0.013 mole) of 2,7-dimethoxynaphthalene and 6.0 g. (0.86 g.-atom) of lithium in 500 ml. of liquid ammonia. After the addition of 55 ml. of methanol and evaporation of the ammonia, the ether extraction afforded 3.1 g. of a yellow oil. The distilled colorless liquid (b.p. 90–91° at 2.5 mm.) seemed homogeneous using both t.l.c. (ether–hexane 1:1, R_f 0.70) and v.p.c. (3.0 min., with 5% at 4.8 min.) methods; $\lambda_{max}^{ethanol}$ 280 mμ (log ε 2.53) and 288 mμ (log ε 2.49). The n.m.r. spectrum (in $CDCl_3$) of this slightly impure compound integrated for three methoxy protons (δ 3.55) and slightly more than six saturated protons (δ 1–2).

Acid Hydrolysis of the Reduced Materials. A.—From the reduction A (above) 2.75 g. of the mixture was added with stirring to 250 ml. of methanol, 15 ml. of water, and 2 ml. of hydrochloric acid. After standing 2 hr. at room temperature, 500 ml. of water was added and the aqueous material was extracted with three 250-ml. portions of ether. The combined ethereal extracts were washed in turn with dilute sodium carbonate solution, water, and saturated salt solution. After drying with magnesium sulfate and removing the ether on the rotary evaporator, there remained a yellow oil (2.20 g., 91%). Analysis by v.p.c. (DEGS, 145°, 15 lb.) indicated the presence of three components: 3.8 min. (<10%), 4.8 min. (35%), and 10.6 min. (55%); t.l.c. (ether–hexane, 1:1) revealed three components (R_f values: 0.70, 0.50, and 0.35). The infrared spectrum showed carbonyl absorption at 6.0 μ (with a shoulder at 5.85 μ) and an intense aromatic C=C stretch at 6.25 μ. The ultraviolet spectrum exhibited three maxima: 280 mμ (log ε 3.04), mol. wt. = 192; 288 mμ (log ε 3.01), mol. wt. = 192; and 232 mμ (log ε 3.94), mol. wt. = 150.

This mixture (2.15 g.) was placed directly on a column of 100 g. of silica (L. Light Co.) previously packed in hexane. Using continuous gradient elution, 25-ml. portions were taken with the following results: fractions 1–19, 0.175 g., yellow, eluted with hexane–benzene; fractions 20–34, 0.470 g., colorless, benzene; fractions 35–48, 0.220 g., colorless, benzene–ether (9:1); fractions 49–64, 1.265 g., colorless, benzene–ether (1:1); fractions 65–79, 0.020 g., yellow, ether. The colorless liquid, $n^{25}D$ 1.5420, b.p. 77–78° (0.9 mm.), obtained from the second set of fractions appeared homogeneous by v.p.c. (DEGS, 145°, 15 lb., 4.8 min.) and on t.l.c. (ether–hexane, 1:1) as one spot (R_f 0.72). The infrared spectrum had an intense C=C stretch absorption at 6.25 μ, while the ultraviolet spectrum contained only two maxima: 279.5 mμ (log ε 3.31) and 288 mμ (log ε 2.25). The n.m.r. spectrum (in $CDCl_3$) integrated for three aromatic protons (δ 6.55–7.10), three methoxy protons (δ 3.72), four benzilic protons (δ 2.69), and four saturated protons (δ 1.56–1.95). This data fitted a structure assignment for 6-methoxy-1,2,3,4-tetrahydronaphthalene.[13]

Material from the fourth set of fractions appeared homogeneous by v.p.c. [DEGS, 145°, 15 lbs., 10.6 min.; phenyldiethanolamine succinate (PDEAS), 180°, 25 lb., 17.5 min.], but on t.l.c. (ether–hexane, 1:1) two components were evident (R_f 0.35 and 0.50). The liquid, $n^{28}D$ 1.5215, b.p., 81–82° (0.6 mm.), possessed a carbonyl absorption in the infrared spectrum at 6.00 μ with a weak shoulder at 5.85 μ; in the ultraviolet spectrum there were maxima at 307 mμ (log ε 1.77) and 2.38 mμ (log ε 4.18). Two derivatives were made: the semicarbazone, m.p. 204.0–204.5°, $\lambda_{max}^{ethanol}$ 268 mμ (log ε 4.52); and the 2,4-dinitrophenylhydrazone, m.p. 173.0–173.2°, $\lambda_{max}^{chloroform}$ 390 mμ (log ε 4.46).

This information was in accord with the corresponding literature values for $\Delta^{1,9}$-octalone-2 and its derivatives (plus the contaminant, β,γ-unsaturated ketone).[14] In addition, a comparison of our α,β-unsaturated ketone with an authentic sample of the $\Delta^{1,9}$-octalone-2 containing some β,γ-ketone produced identical R_f values in three solvent systems (ether, ether–hexane, benzene–acetone) and the same retention times on two different vapor phase chromatographic columns (DEGS and PDEAS). A mixture melting point of the dinitrophenylhydrazones from the two sources showed no depression.

B.—The procedure of acid hydrolysis in A (above) was applied to 132 mg. of the liquid obtained in the B reduction. The yield of yellow oil was 94 mg. (78%) which by v.p.c. (DEGS, 155°, 15 lbs.) showed three components: 3.1 min. (6%), 3.9 min. (12%), and 7.7 min. (82%); t.l.c. showed three spots (R_f values: 0.75, 0.45, and 0.35; ether–hexane 1:1). The ultraviolet spectrum revealed the presence of 6-methoxytetralin and of the α,β-unsaturated ketone. The 2,4-dinitrophenylhydrazone gave no depression with that prepared in A (above). The infrared spectra of the ketone and the dinitrophenylhydrazone were virtually superimposable with those obtained in A (above).

Reduction of 2-Methoxynaphthalene.—Using conditions similar to those mentioned above, 2.51 g. (0.016 mole) of 2-methoxynaphthalene in 200 ml. of liquid ammonia was treated with 3.0 g. (0.43 g.-atom) of lithium and gave, after addition of 30 ml. of methanol and evaporation of the ammonia overnight, a white slurry. The usual work-up afforded 2.55 g. of a yellow oil (*ca.* 99%) which by t.l.c. (ether–hexane, 1:1) appeared to contain two major components (R_f 1.0 and 0.70); however, v.p.c. (DEGS, 140°, 15 lb.) showed three components: 1.2 min. (70%), 3.8 min. (25%), and 6.2 min. (5%). The second and third components were shown to be identical by v.p.c. comparison to 2-methoxyhexahydronaphthalene and 2-methoxytetralin, respectively. Also, on acid hydrolysis with aqueous methanol (mineral acid) and addition of 2,4-dinitrophenylhydrazine solution, a dinitrophenylhydrazone was formed which proved identical with those prepared above by mixture melting point and by comparison of infrared spectra.

A sample of distilled material (102–104° at 16 mm.) was chromatographed preparatively through a cyclohexanedimethanol succinate (CDMS) column (on Chromosorb W at 145° with helium flow rate of 60 ml./min.). Three hydrocarbon fractions were isolated at 6.6 min. (7%), 14.6 min. (87%), and 18.9 min. (6%). The first of these was proved to be decalin (retention time on DEGS and infrared spectrum in chloroform), while the last was tetralin (retention time on DEGS and ultraviolet spectrum in ethanol). The second and largest component, $n^{28}D$ 1.5110, possessed a molecular weight of 134 (by mass spectroscopy) showed *cis* protons in the infrared spectrum (out-of-plane bending, 658 $cm.^{-1}$), and was transparent in the ultraviolet down to 220 mμ. The n.m.r. spectrum exhibited three types of protons: vinyl (δ 5.72), doubly allylic (δ 2.53), and saturated and allylic (δ 1.5–2.2); this data agreed with the literature data for 1,4,5,6,7,8-hexahydronaphthalene.[3]

Anal. Calcd. for $C_{10}H_{14}$: C, 89.5; H, 10.5. Found: C, 89.8; H, 10.6.

(13) A. J. Birch, E. M. A. Shoukry, and P. Stansfield, *J. Chem. Soc.*, 5376 (1961).

(14) (a) H. H. Zeiss and W. B. Martin, Jr., *J. Am. Chem. Soc.*, **75**, 5935 (1953); (b) D. J. Baisted and J. S. Whitehurst, *J. Chem. Soc.*, 4089 (1961).

Copper Salts Induced Addition of Ethyl Trichloroacetate to Olefins

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Peroxide-induced addition of alkyl polyhalides to olefins is well known.[1] Recently addition of carbon tetrachloride and chloroform to olefins using catalytic amounts of metallic salts was reported and the oxidation–reduction mechanism was suggested for this kind of addition.[2]

Experiments reported in this note show that ethyl trichloroacetate can also be added to olefins in the presence of a catalytic amount of copper salts. From acrylonitrile, ethyl acrylate, 1-octene, and norbornene, good yields of 1:1 adducts, ethyl 2,2,4-trichlorocarboxylates, have been obtained.

When acrylonitrile (0.1 mole) and ethyl trichloroacetate (0.1 mole) were heated under reflux in ethanol for 20 hr. in the presence of 0.002 mole of cuprous oxide, ethyl 4-cyano-2,2,4-trichlorobutyrate (I) was obtained in a yield of 37%. In the same manner, diethyl 2,2,4-

(1) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 247.

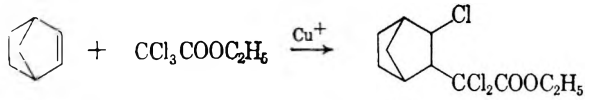
(2) (a) F. Minisci and R. Galli, *Tetrahedron Letters*, 533 (1962); (b) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 2261 (1961); *Chem. Ind.* (London), 209 (1963); M. Asscher, E. Levy, H. Rosin, and D. Vofsi, *Ind. Eng. Chem., Prod. Res. Develop.*, **2**, 121 (1963).

trichloroglutarate (II, 32%) and ethyl 2,2,4-trichlorodecanoate (III, 13–29%) were obtained from ethyl acrylate and 1-octene, respectively, using cuprous chloride as a catalyst.

$$R{-}CH{=}CH_2 + CCl_3COOC_2H_5 \xrightarrow{Cu^+} R{-}CHClCH_2CCl_2COOC_2H_5$$

I, R = CN
II, R = $COOC_2H_5$
III, R = C_6H_{13}

Norbornene also gave a good yield (63%) of 1:1 adduct, ethyl α,α,3-trichloronorbornane-2-acetate (IV), when treated at slightly elevated temperature (120°); however, no effort was made to determine the stereochemistry of IV.



IV

In the reaction of acrylonitrile with ethyl trichloroacetate, cuprous and cupric chloride were also effective as the catalysts, but ferrous, ferric, and cobaltous chloride were ineffective to induce such addition. Addition of hydroquinone to the reaction mixture had no influence on these reactions and this may indicate that a usual radical chain process might be unlikely. These facts could be explained by an oxidation–reduction mechanism, in the same manner as suggested previously.[2]

$$Cu^+ + CCl_3COOC_2H_5 \longrightarrow CuCl^+ + \cdot CCl_2COOC_2H_5 \quad (1)$$

$$R{-}CH{=}CH_2 + \cdot CCl_2COOC_2H_5 \longrightarrow R{-}\dot{C}HCH_2CCl_2COOC_2H_5 \quad (2)$$

$$R{-}\dot{C}HCH_2CCl_2COOC_2H_5 + CuCl^+ \longrightarrow R{-}CHClCH_2CCl_2COOC_2H_5 + Cu^+ \quad (3)$$

Because of the high efficiency of step 3, the telomer formation has been suppressed and 1:1 adducts were obtained exclusively in the copper salts catalyzed addition.

Experimental

Reaction of Acrylonitrile with Ethyl Trichloroacetate.—A mixture of 5.4 g. (0.1 mole) of acrylonitrile, 19.1 g. (0.1 mole) of ethyl trichloroacetate, 0.28 g. (0.002 mole) of cuprous oxide, and 50 ml. of anhydrous ethanol was refluxed for 20 hr. Solvent and unchanged materials were removed by distillation under reduced pressure and precipitated inorganic materials were removed by filtration. The residual oil was distilled to give 9.0 g. (37%) of a colorless oil boiling at 124–126° (6 mm.), which had infrared absorptions at 1726, 1730 (C=O), and 2250 (C≡N) cm.$^{-1}$. This product was identified as ethyl 4-cyano-2,2,4-trichlorobutyrate (I) by further treatment as described below.

Anal. Calcd. for $C_7H_8Cl_3NO_2$: C, 34.38; H, 3.30. Found: C, 34.79; H, 3.28.

Reduction of 2.0 g. of I by heating under reflux with 15 g. of zinc powder in 30 ml. of 95% ethanol for 10 hr. gave 0.3 g. of ethyl 4-cyanobutyrate boiling at 60–80° (6–10 mm.). This was then hydrolyzed by heating under reflux with 15 ml. of concentrated hydrochloric acid for 10 hr. After removal of the water by distillation under reduced pressure, the residual product was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. Removal of ether at aspirator pressure left 0.3 g. of white crystalline solid which, after recrystallization from benzene, formed colorless needles, m.p. 96–97°, undepressed on admixture with authentic glutaric acid.

Anal. Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10. Found: C, 45.50; H, 6.39.

When cuprous chloride (0.002 mole) was used instead of cuprous oxide in the reaction of acrylonitrile and ethyl trichloroacetate, I was obtained in a yield of 20%. The addition of hydroquinone (5.5 g., 0.05 mole) to the reaction mixture had no influence on the reaction.

Cupric chloride (0.002 mole) was also able to give I in a yield of 10%.

When ferrous chloride tetrahydrate (0.002 mole) was used as a catalyst, about half the amount of acrylonitrile used was polymerized under the same conditions and no 1:1 adduct was obtained.

Ferric and cobaltous chloride (0.002 mole) were unable to induce addition and the starting materials were almost completely recovered in these experiments.

Reaction of Ethyl Acrylate with Ethyl Trichloroacetate.—A mixture of 11.0 g. (0.1 mole) of ethyl acrylate, 19.1 g. (0.1 mole) of ethyl trichloroacetate, 0.2 g. (0.002 mole) of cuprous chloride, and 40 ml. of anhydrous ethanol was heated under reflux for 20 hr. By treating the reaction mixture as described above, 6.3 g. (32%) of diethyl 2,2,4-trichloroglutarate (II) was obtained, b.p. 101–105° (3 mm.).

Anal. Calcd. for $C_9H_{13}Cl_3O_4$: C, 37.07; H, 4.49. Found: C, 37.35; H, 4.62

By reduction with zinc powder and 95% ethanol followed by hydrolysis with concentrated hydrochloric acid in the same manner as described above, II gave glutaric acid, m.p. 96–97°, undepressed on admixture with an authentic sample.

Anal. Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10. Found: C, 45.54; H, 5.92.

Reaction of 1-Octene with Ethyl Trichloroacetate.—A mixture of 5.6 g. (0.05 mole) of 1-octene, 9.5 g. (0.05 mole) of ethyl trichloroacetate, 0.1 g. (0.001 mole) of cuprous chloride, and 25 ml. of anhydrous ethanol was heated under reflux for 20 hr. By treating the reaction mixture as described above, 2.0 g. (13%) of ethyl 2,2,4-trichlorodecanoate (III) was obtained, b.p. 103–104° (0.5 mm.). This product has strong infrared absorptions at 1730 (C=O) and 2870 (—CH_2—) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{21}Cl_3O_2$: C, 47.46; H, 6.97. Found: C, 47.32; H, 7.02.

Reduction of III with zinc powder and 95% ethanol gave ethyl decanoate which was identified by gas chromatography on a 550 cm. silicone column at 188°.

The yield of III was raised to 29% when reaction was carried out at 120°, for 10 hr., in a 50-ml. glass tube placed in a 60-ml. stainless steel bomb.

Reaction of Norbornene with Ethyl Trichloroacetate.—A mixture of 9.2 g. (0.06 mole) of norbornene, 11.5 g. (0.06 mole) of ethyl trichloroacetate, 15 ml. of acetonitrile, and 0.2 g. (0.002 mole) of cuprous chloride in a 50-ml. glass tube was placed in a 60-ml. stainless steel bomb and heated in an oil bath at 120° for 16 hr. By treating the reaction mixture as described above 13 g. (63%) of ethyl α,α,3-trichloronorbornane-2-acetate (IV) was obtained, b.p. 95–101° (0.4 mm.). (In some other experiments this fraction was contaminated with a small amount of white crystals, less than 0.1 g., which was easily separated from the 1:1 adduct by filtration and was recrystallized from hexane, m.p. 140.5–141.5°. This compound was not treated further.) The 1:1 adduct (IV) was redistilled at 96–98° (0.4 mm.), infrared 1730 (C=O) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{15}Cl_3O_2$: C, 46.26; H, 5.29; Cl, 37.24. Found: C, 46.13; H, 5.21; Cl, 36.36.

Acknowledgment—The authors are grateful to Dr. Yoshinobu Odaira for his helpful suggestions.

The Lithium Aluminum Hydride Reduction of 3-Acetoxy-6-methanesulfonoxytropane[1]

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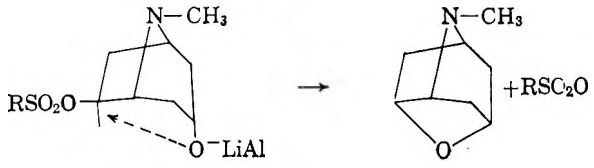
In an attempt to convert scopolamine into tromine, 3-acetoxy-6-methanesulfonoxytropane was prepared from the naturally occurring alkaloid. When this com-

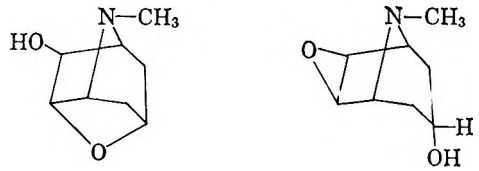
pound was reduced with lithium aluminum hydride a basic compound, whose infrared spectrum was similar but not identical with that of tropine, was isolated. The picrate of this compound possessed a melting point almost identical with that of tropine picrate. Its infrared spectrum, however, was not identical with that of an authentic sample of tropine picrate. Lithium aluminum hydride reduction of impure samples of 6-hydroxyhyoscyamine ditosylate and 6-hydroxyhyoscyamine dimesylate gave rise to the identical basic compound as well as to 2-phenyl-1-propanol.

It appeared that this product might be 3,6-epoxytropane and that it might result from the attack of lithium aluminum hydride on the acetoxy group to form the intermediate I, followed by nucleophilic displacement of the sulfonate group by the alkoxide ion to yield 3,6-epoxytropane II. A somewhat similar



I II

rearrangement has been reported by Fodor[3] who performed a lithium aluminum hydride reduction on scopolamine. Scopoline III rather than the expected scopine IV was isolated. Fodor suggested that this product



III IV

might arise by a backside nucleophilic attack of the lithium aluminum alkoxide complex on the epoxide ring.

In order to verify the structure of the unknown basic product resulting from the lithium aluminum hydride reduction of 3-acetoxy-6-methanesulfonoxytropane, an authentic sample of 3,6-epoxytropane was prepared by the dehydration of 3,6-tropanediol with phosphorus oxychloride, following the procedure of Fodor.[4] The infrared spectra of this sample of 3,6-epoxytropane and that of its picrate were identical with those of the rearranged product and that of its picrate.

Experimental[5]

3-Acetoxy-6-methanesulfonyloxytropane Picrate.—To a solution of 1.0 g. (5.0 mmoles) of 3-acetoxy-6-propanol[4] in 10 ml. of dry pyridine was added 0.6 g. (5.25 mmoles) of methanesulfonyl chloride, and the mixture was warmed on a steam bath for 3 hr. The pyridine was removed *in vacuo*, and the brown residue was dissolved in 20 ml. of water. The aqueous solution was saturated with anhydrous potassium carbonate and then extracted with six 25-ml. portions of chloroform. The chloroform extracts were washed with two 25-ml. portions of water and dried over anhydrous sodium sulfate. The chloroform was removed to afford 1.29 g. (93%) of a viscous brown sirup. This sirup was treated with picric acid in the usual manner to yield the picrate which, after recrystallization from ethanol, melted at 216–217° dec.

Anal. Calcd. for $C_{17}H_{22}N_4O_{12}S$: C, 40.32; H, 4.38; N, 11.06. Found: C, 40.59; H, 4.12; N, 11.00.

Lithium Aluminum Hydride Reduction of 3-Acetoxy-6-methanesulfonyloxytropane.—To a suspension of 3 g. of lithium aluminum hydride in 75 ml. of freshly distilled tetrahydrofuran was added dropwise with mechanical stirring a solution of 1.2 g. (4.3 mmoles) of 3-acetoxy-6-methanesulfonyloxytropane in 50 ml. of freshly distilled tetrahydrofuran, and the mixture was then refluxed with continued stirring for 5 hr. The solution was cooled in an ice bath and the excess lithium aluminum hydride was decomposed by addition of 6 ml. of water and 6 ml. of 10% sodium hydroxide solution. The crystalline lithium aluminate was removed by filtration and the filter cake was washed with three 20-ml. portions of hot tetrahydrofuran. The combined tetrahydrofuran filtrates were then evaporated *in vacuo*. The residue was dissolved in 20 ml. of 20% sodium hydroxide and the aqueous solution was continuously extracted with ether for 15 hr. The ether extract was dried over anhydrous sodium sulfate and then evaporated to yield 0.4 g. of a light yellow oil.

The picrate of this oil melted at 284–286° dec. after recrystallization from a mixture of equal parts of ethanol and acetone.

Anal. Calcd. for $C_{14}H_{16}N_4O_8$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.22; H, 4.38; N, 15.15.

3,6-Epoxytropane.—One gram (64 mmoles) of 3,6-tropanediol was gently refluxed with 10 ml. of phosphorus oxychloride for 1 hr. The excess phosphorus oxychloride was removed *in vacuo* and the dark brown residue was poured over 10 g. of ice. The aqueous solution was saturated with potassium carbonate and extracted with three 15-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated to yield 0.53 g. (59.6%) of a light green oil of 3,6-epoxytropane, which was converted to the picrate in the usual manner, m.p. 285–287° dec. after recrystallization from absolute ethanol–acetone.

The hydrobromide salt, prepared by reacting 3,6-epoxytropane with anhydrous hydrogen bromide, melted at 278–280° after recrystallization from ethanol–ether, lit.[4] m.p. 280°.

Anal. Calcd. for $C_8H_{14}BrNO$: C, 43.66; H, 6.41; Br, 36.31; N, 6.36. Found: C, 43.39; H, 6.42; Br, 36.20; N, 6.40.

Conversion of 6-Hydroxyhyoscyamine to 3,6-Epoxytropane.—To a solution of 2.28 g. (7.5 mmoles) of 6-hydroxyhyoscyamine in 15 ml. of dry pyridine was added 3.0 g. (15.2 mmoles) of *p*-toluenesulfonyl chloride, and the mixture was warmed on a steam bath for 3 hr. The pyridine was removed *in vacuo* and the brown residue was dissolved in 20 ml. of water. The aqueous solution was saturated with anhydrous potassium carbonate and then extracted with six 25-ml. portions of chloroform. The chloroform extracts were combined, washed with water, and dried over anhydrous sodium sulfate. The chloroform was removed by distillation to yield 2.69 g. (59%) of a viscous brown sirup. While it was not possible to obtain this compound in a pure form, its infrared spectrum indicated that it was the ditosyl derivative of 6-hydroxyhyoscyamine.

When 2.62 g. (4.3 mmoles) of the crude ditosyl derivative of 6-hydroxyhyoscyamine was reduced with 5 g. of lithium aluminum hydride following the procedure described for the reduction of 3-acetoxy-6-methanesulfonyloxytropane, and the products were separated by extraction with dilute hydrochloric acid, 0.58 g. (48%) of 2-phenyl-1-propanol and 0.53 g. (60%) of 3,6-epoxytropane were obtained. The 2-phenyl-1-propanol possessed an infrared spectrum identical with that of an authentic sample. The 3,6-epoxytropane was identified as its picrate, m.p. 285–287°.

(1) Abstracted from a thesis submitted by F. A. Turner to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) National Science Foundation Cooperative Graduate Fellow, 1959–1961.

(3) G. Fodor and O. Kovacs, *J. Chem. Soc.*, 2341 (1953).

(4) D. Bobo, G. Fodor, *et. al.*, *ibid.*, 3461 (1959).

(5) All melting points were obtained by the capillary tube method and are corrected. Microanalyses were performed by Weiler and Strauss Microanalytical Laboratories, Oxford, England.

Nuclear Magnetic Resonance Determination of Substituent Methyls in Fatty Acids[1]

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In spite of the plethora of applications of n.m.r. spectroscopy to elucidation of structural problems, there appears to be a paucity of data on application of this tool in the field of branched-chain fatty acids, perhaps on account of the limited availability of the necessary compounds. Since a wide variety of branched-chain acids has been synthesized in this laboratory,[3] appropriate compounds have been examined in order that the quantitative and qualitative applications of n.m.r. spectroscopy might be ascertained. Data on the more interesting compounds are presented here.

Quantitative determination of the number of methyl groups in branched-chain acids has been proposed, by comparison of the area of the band due to methyl hydrogens with that due to methylene and methinyl hydrogens.[4] We have found this method to be hopelessly inaccurate on account of overlap of the two bands, which is extensive for multibranched acids. Any error in extrapolation becomes multiplied by two since the overlapping bands are those whose ratio is being examined. This pyramiding of error is avoided, however, if the methyl ester is used for the determination, and the point of reference is established as the area of the unsplit, isolated band (about τ 6.35) attributed to the signal from the three protons in methoxyl (*cf.* Fig. 1).

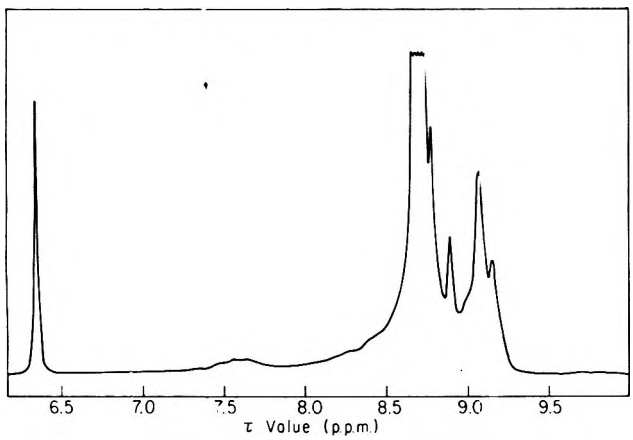

Fig. 1.—Tracing of n.m.r. spectrum of methyl 2,4,6-trimethylhexacosanoate (27 mg./0.4 ml. of carbon tetrachloride).

Data assembled in Table I illustrate that this method gives reliable results for substituent methyl groups until the number of such groups reaches four. For four or more methyl groups, the extrapolated area for the methyl band is consistently too large, an effect which has been noted in analysis of hydrocarbons in petroleum.[5]

TABLE I

QUANTITATIVE DETERMINATION OF METHYL GROUPS IN BRANCHED-CHAIN FATTY ACIDS

Methyl ester	No. of methyl groups	Area of methyl groups[a] / Area of methoxyl group
Stearate	1	1.13
Tetracosanoate	1	1.10
2-Methylheptadecanoate[b]	2	2.19 (1.00)
3-Methyloctadecanoate[b]	2	1.96
4-Methyloctadecanoate[b]	2	2.00
17-Methyloctadecanoate[b]	2	2.31
2-Ethyloctadecanoate	2	3.00
2,4-Dimethyldocosanoate	3	(1.83, 1.85)
2,5-Dimethylheptadecanoate[b]	3	3.00 (1.90)
4,8,12-Trimethyloctadecanoate	4	4.95
2,3,4-Trimethylhexadecanoate	4	(3.96)
2,4,6-Trimethyldocosanoate[c]	4	(3.80)
2,4,6-Trimethylhexacosanoate[d]	4	(4.12, 3.86)

[a] Values in parentheses were determined with exclusion of the area of the 2-methyl doublet, which is embedded in the edge of the methylene band (*e.g.*, *cf.* Fig. 1). Areas were determined with a planimeter on the resultant bands after the overlapping bands had been extrapolated to their theoretical shape if alone. [b] *Cf.* Fig. 2. [c] *Cf.* J. Cason, P. Tavs, and A. Weiss, *Tetrahedron*, **18**, 437 (1962). [d] *Cf.* Fig. 1, also J. Cason, G. L. Lange, W. T. Miller, and A. Weiss, *Tetrahedron*, **20**, 91 (1964).

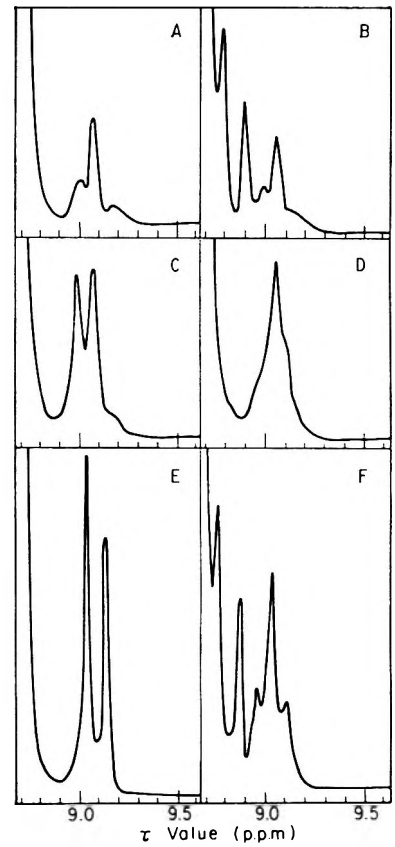

Fig. 2.—Methyl region of the n.m.r. spectra of the methyl esters of branched-chain acids: A, stearate; B, 2-methylheptadecanoate; C, 3-methyloctadecanoate; D, 4-methyloctadecanoate; E, 17-methyloctadecanoate; F, 2,5-dimethylheptadecanoate.

Even for the larger numbers of methyls, however, results are reproducible, and the number of substituent methyls in an unknown structure may be established by comparison with known compounds. In the case o

(1) This investigation was supported in part by a grant (No. EF-136) from the National Institutes of Health, U. S. Public Health Service.

(2) Recipient of a Monsanto Chemical Co. Research Fellowship, summer of 1960, and of a Woodrow Wilson Foundation Fellowship, 1961 and 1962.

(3) For paper XXXVI in the series "Branched-Chain Fatty Acids," see J. Cason and D. J. McLeod, *J. Org. Chem.*, **23**, 1497 (1958).

(4) M. Sonneveld, P. Laverkamp-Begemann, G. J. van Beers, R. Keunig, and J. C. M. Schogt, *J. Lipid Res.*, **3**, 351 (1962).

(5) B. J. Mair, N. C. Krouskop, and T. J. Mayer [*J. Chem. Eng. Data* **7**, 420 (1962)] used electronic integration of the signal and also ascribed the error to band overlap.

a 2-ethyl substituent, the methyl band is similar in shape to that from a normal acid,[6] but there is more overlap, and the error is surprisingly large (*cf.* Table I). This appears to be a persistent difficulty with branches larger than methyl. In the case of methyl 4-butyl-4-ethylnonanoate, the overlap of the methyl and methylene bands was so extensive that extrapolation was not attempted.

The location of a methyl group at the 2- or 3-position appears reliable. The 2-methyl doublet (J = 6 c.p.s.) appears downfield from the other methyl protons, never quite buried in the huge methylene band (Fig. 1, 2B, 2F). In addition, the multiplet for the single proton in the 2-position is centered at about τ 7.62 (*cf.* Fig. 1), whereas the triplet for a 2-methylene group is centered in the region τ 7.70–7.75. In the case of 2,2-dimethyloctadecanoate, the unsplit band for the two α-methyls is shifted downfield to τ 8.83.

In the case of the 3-methyl substituent, the 2-methylene band is an unsymmetrical doublet, with the major peak (the upfield one, as expected) at τ 7.87. The doublet for the 3-methyl substituent (Fig. 2C) is shifted significantly downfield and lies on the band from the terminal methyl so as to give the appearance of one split band. It is readily distinguished from the split band from the terminal isopropyl group (Fig. 2E), for the latter has sharper peaks, is somewhat upfield, and shows the expected greater intensity for the lower-field segment.

A methyl substituent more remote from carboxyl than the 3-position results in a combined methyl band of rather ill-defined appearance (Fig. 2D), and nothing can be learned of the location. The tracing from 6-methyloctadecanoate is nearly identical with that from 4-methyloctadecanoate.

Determination of spectra was accomplished on a Varian A-60 instrument, operating at 60 Mc./sec., with 6–8% solutions of the esters in carbon tetrachloride. Tetramethylsilane was used as external standard.

(6) The unsymmetrical triplet for the terminal methyl, of the same form as in *n*-alkanes, has previously been noted; *e.g.*, *cf.* C. R. Smith, Jr., T. L. Wilson, R. B. Bates, and C. R. Scholfield, *J. Org. Chem.*, **27**, 3112 (1962).

Phenylation of Dinitroalkanes

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Received January 16, 1964

Publication by Kornblum and Taylor[1] of the method of phenylating nitroalkanes using Beringer's[2] diphenyliodonium salts prompts us to add a note on phenylation of dinitroalkanes. Using diphenyliodonium tosylate in *t*-butyl alcohol as solvent, phenyl derivatives of 1,1-dinitropropane and 1,1-dinitroethane were obtained from the potassium salts of the dinitroalkanes in 67 and 68% yields, respectively. Yields were less than 5% in N,N-dimethylformamide at room temperature in contrast to Kornblum's findings with mononitroalkanes.

We were unable to phenylate the potassium salts of phenylnitromethane and phenyldinitromethane in either solvent.

Experimental

Potassium 1-Nitropropylnitronate.[3,4]—In a 1-l. three-necked flask equipped with a mechanical stirrer, thermometer, and dropping funnel, and cooled with an ice bath, potassium nitrite (85 g., 1 mole) was dissolved in 140 ml. of water. To this was added a solution of 124 g. (1 mole) of 1-chloro-1-nitropropane in 280 ml. of 95% methanol. The temperature was maintained between 0 and 10° while a cold solution of 1 mole of potassium hydroxide in 150 ml. of 95% methanol was added over a 15 min. period. Stirring was continued for 15 min. after completion of the addition and the reaction mixture was allowed to stand overnight in the refrigerator.

The yellow salt was stirred in 300 ml. of warm water to remove large amounts of potassium chloride, cooled in ice, and collected on a Buchner funnel, yielding 150–160 g. (87–93%). The dry potassium 1-nitropropylnitronate can be detonated but can be safely stored at room temperature for at least 10 years!

The less stable potassium salt of 1,1-dinitroethane[4] was prepared in like manner.

1,1-Dinitro-1-phenylpropane.—Equimolar amounts of potassium 1-nitropropylnitronate (8.00 g., 0.0495 mole) and diphenyliodonium tosylate[1,5] (22.30 g., 0.0495 mole) in 800 ml. of dry *t*-butyl alcohol were refluxed for 6 hr. The precipitated potassium tosylate was removed by filtration and the solvent was removed at ambient temperatures on a rotating evaporator.

The crude oily mixture was run onto a chromatographic column of acid-free alumina. Elution with petroleum ether (b.p. 30–60°) first removed iodobenzene and then 1,1-dinitro-1-phenylpropane as a pale yellow oil. Distillation at reduced pressure gave 7.0 g. (67%) of colorless product, b.p. 136° (4 mm.), n^{25}D 1.5270; d^{25}_4 1.2340.

The infrared spectrum verified the presence of the *gem*-dinitro group with absorption at 7.45 and 7.55 μ.[6] The n.m.r. spectrum verified the presence of one ethyl and one phenyl group in the compound.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.40; H, 4.80; N, 13.34. Found: C, 51.46; H, 4.88; N, 13.69.

1,1-Dinitro-1-phenylethane was prepared in a similar manner in 68% yield, b.p. 82–83° (2 mm.), n^{25}D 1.5320, d^{25}_4 1.2875.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.97; H, 4.11; N, 14.27. Found: C, 49.13; H, 4.29; N, 14.40.

In N,N-dimethylformamide, the reaction took a different course. Nine grams (0.020 mole) of diphenyliodonium tosylate and 3.24 g. (0.020 mole) of potassium 1-nitropropylnitronate was dissolved in 15 ml. of dry N,N-dimethylformamide[7] by mechanical stirring at room temperature. Within 5 min. an exothermic reaction started but the temperature was kept at 25° by efficient cooling and stirring. After standing overnight the reaction mixture was poured into 100 ml. of ice–water and extracted with 250 ml. of ether in five portions. The ether extract was dried over anhydrous sodium sulfate, reduced to small volume by evaporation, and put on a chromatographic column of alumina. Elution with petroleum ether first gave iodobenzene and then 1.77 g. (72%) of nitrobenzene (b.p. 210°). The infrared spectrum of the nitrobenzene showed only a small absorption at the expected position for a *gem*-dinitro group (*vide supra*), estimated to indicate less than 5% phenylation of the dinitroalkane. The ultimate fate of the alkyl carbons, not immediately apparent, is under investigation.

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