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Oxetanes. IX. Structural and Solvent Effects in the Reaction of γ-Bromoalcohols with Base[1,2]

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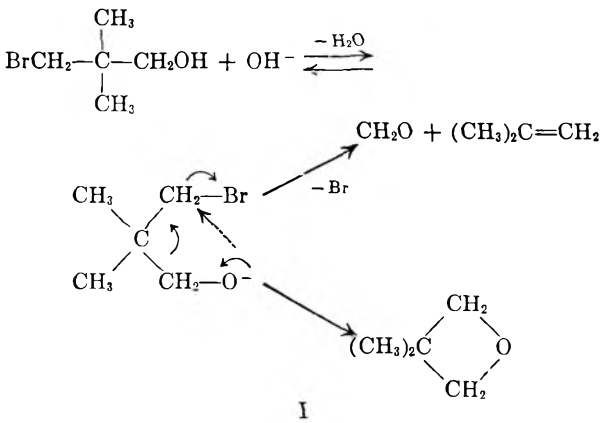
The alkaline decomposition of a series of 3-bromo-1-propanols, having various hydrocarbon substituents on carbon-2, was investigated with respect to influence of C-2 substitution and of the medium on the relative yields of intramolecular substitution and 1,4-elimination products. Elimination is favored by thermodynamic stability of the olefin that can be formed, and it is also favored by a more ionizing media. The results indicate that both the intramolecular substitution process and the 1,4-elimination process have a common intermediate, the γ-bromoalkoxide ion, and that the former process goes by a dissociation mechanism, the latter by a displacement mechanism. Several new oxetanes were prepared in the course of the work.

The yield of 3,3-dimethyloxetane from the reaction of 2,2-dimethyl-3-bromo-1-propanol with alkali is much less than might be expected from a compound which cannot undergo 1,2-elimination of hydrogen bromide as a side reaction. Although this common side reaction in intramolecular Williamson reactions is here blocked, a 1,4-elimination of hydrogen bromide occurs to a considerable extent.[3] This process results in cleavage of a carbon-carbon bond, forming isobutylene and formaldehyde, and may logically be interpreted as due to an inherent instability of the γ-bromoalkoxide ion (I) that is required for the intramolecular Williamson reaction.



I

It is common for alkyl halides to react by substitution and elimination processes simultaneously, but this particular pair of parallel processes seems rather unusual. The substitution process appears to be of the displacement type but is intramolecular and involves the closing of a strained ring. The elimination process is of a type that is not commonly associated with substitution, as it resembles the retrograde aldol condensation, the decomposition of salts of β-bromo acids[3] and similar cleavage reactions.[4,5]

(1) Previous paper in this series: S. Searles, Jr., and E. F. Lutz, *J. Am. Chem. Soc.*, 81, 3674 (1959).

(2) Supported in part by research grants from the Graduate School, Northwestern University, and from the National Science Foundation, for which grateful acknowledgment is given. Most of the material is abstracted from the Ph.D. Dissertation of Richard G. Nickerson, Northwestern University, 1955.

(3) S. Searles, Jr., and M. J. Gortatowski, *J. Am. Chem. Soc.*, 75, 3050 (1953).

(4) S. J. Cristol and W. P. Norris, *J. Am. Chem. Soc.*, 75, 632, 2645 (1953).

(5) Other examples are the alkaline decomposition of β,β-dimethyl-α-tosyloxy-γ-butyrolactone into β,β-dimethylacrylate ion, formaldehyde, and tosylate ion (H. Bretschneider and H. Hass, *Monatsh.*, 81, 945 (1950), and the alkaline decomposition of dimethylaminopivalophenone into isobutylene, benzoic acid and trimethylamine (H. R. Synder and J. H. Brewster, *J. Am. Chem. Soc.*, 71, 1061 (1949)). In each case, the action of base produces an intermediate, bearing a negative charge on oxygen, which can

On account of the importance of this competition in the usual synthesis of oxetanes, a study was made of the effect of solvent and structural changes. The results are also of interest for comparison with the effects of such factors in the ordinary bimolecular substitution and 1,2-elimination competition that has been carefully studied by Hughes, Ingold and co-workers.[6]

For this purpose a series of 3-bromo-1-propanols having various alkyl and/or aryl groups at carbon-2 were prepared in good yield from the corresponding glycols by reaction with hydrobromic acid in acetic acid, the intermediate acetate ester being alcoholized to the bromo alcohol. The bromo alcohols were treated with aqueous potassium hydroxide of two different concentrations under standardized conditions, and the yields of olefins and oxetanes were determined by isolation. Alcoholic base was also used in several instances and aqueous sodium carbonate in one instance. The yield of oxetane provides a measure of the extent of intramolecular substitution occurring, and the yield of olefin was used as a measure of the extent of 1,4-elimination. The results are compiled in Tables I, II, and III. Since duplicate runs were made in most cases, it is felt that the yields recorded are correct within about 3%.

TABLE I

PRODUCTS FROM 3-BROMO-1-PROPANOLS AND 15% POTASSIUM HYDROXIDE

3-Bromo-1-Propanol	Yields, %		Ratio, Oxetane/ Olefin
	Oxetane	Olefin	
2,2-Dimethyl	12	60	0.2
2,2-Diethyl	27	54	0.5
2-Ethyl-2-isopropyl	14	50	0.3
2-Ethyl	23	19[a]	1.2
2-Butyl	21	24	0.9
2-Phenyl	0	26[b]	0.1
2-Methyl-2-phenyl	0	15	0.0
2-Ethyl-2-phenyl	0	47	0.0
2,2-Tetramethylene	8	63	0.13
2,2-Pentamethylene	33	50	0.66

[a] 2-Ethylallyl alcohol, the product of ordinary 1,2-elimination, was isolated in 19% yield. [b] 40% yield of 2-phenyl alcohol also obtained.

TABLE II

PRODUCTS FROM 3-BROMO-1-PROPANOLS AND 50% POTASSIUM HYDROXIDE

Substituents in 3-Bromo-1-propanol	Yields, %		Ratio, Oxetane/ Olefin
	Oxetane	Olefin	
None	15	0	..
2,2-Dimethyl	57	33	1.7
2,2-Diethyl	57	9	6.
2-Ethyl-2-isopropyl	47	6	8.
2-Ethyl	25	5[a]	5.
2-Butyl	30	0[b]	..
2,2-Tetramethylene	48	26	1.8

[a] Also obtained was a 19% yield of 2-ethylallyl alcohol. [b] Also obtained was a 33% yield of 2-butylallyl alcohol.

TABLE III

PRODUCTS FROM 3-BROMO-1-PROPANOLS AND OTHER BASES

3-Bromo-1-propanol	Base	Yields, %	
		Oxetane	Olefin
2,2-Dimethyl	20% $Na_2CO_3(H_2O)$	10[a]	30[a]
2,2-Dimethyl	6% NaOEt(EtOH)	...[b]	18
2,2-Diethyl	6% NaOEt(EtOH)	43	..[b]
2,2-Pentamethylene[c]	10% KOH(EtOH)	68	..
2,2-Dibenzyl[d]	5.7% NaOEt(EtOH)	46.7	17

[a] The yields in this particular case are based on amount of bromoalcohol not recovered; 50% of the starting bromoalcohol was recovered from the distillate. [b] The compound indicated was not isolated in a pure state due to the difficulty of separating it from the ethanol by fractional distillation. [c] Experiment performed by Eugene F. Lutz. [d] Experiment performed by Shogo Nukina.

With the 2,2-disubstituted compounds the difference between the sum of these two yields and 100% is largely due to incomplete reaction, for some bromo alcohol was always carried over in the distillation of the products from the reaction mixture. With compounds monosubstituted at carbon-2, some 1,2-elimination, giving allylic alcohols, and bimolecular substitution, giving diols and hydroxyethers, takes place during the alkali treatment, and of course the olefin and epoxide yields are thereby lowered. These processes, however, were not taken further account of, because they would not involve intermediate formation of the γ-bromoalkoxide ion. The ratio of oxetane to olefin then still gives the relative tendencies of the alkoxide ion to undergo cleavage (1,4-elimination) or cyclization (intramolecular substitution).

It is seen that at either base concentration, substituents at carbon-2 favor the 1,4-elimination process over intramolecular substitution in the order:

$$C_6H_5 \gg CH_3 > C_2H_5, n\text{-}C_4H_9 > H$$

This order appears to parallel the thermodynamic stability of the olefins formed. Comparing isomeric compounds, we see that there is relatively more tendency to form methylpropene, $\Delta H_f^{25°}$ −3343

decompose into an olefin, a carbonyl compound, and an easily formed ion or molecule.

A new example which we wish to report here is the alkaline decomposition of 3-dimethylamino-2,2-dimethylpivaldehyde methiodide (in 25% aqueous potassium hydroxide at about 150°) to form trimethylamine (isolated in 15% yield), isobutylene (20%) and presumably formate ion. The Cannizzaro reaction, reported by E. R. Alexander, *J. Am. Chem. Soc.*, **70**, 2592 (1948), occurs simultaneously, but this elimination process had been overlooked in the earlier work. It is, of course, entirely analogous to the case of Synder and Brewster cited above.

(6) (a) E. D. Hughes, C. K. Ingold, and coworkers, *J. Chem. Soc.*, 157 *et seq.* (1946); (b) *J. Chem. Soc.*, 2038, *et seq.* (1948); (c) E. D. Hughes, *Quart. Rev.*, **5**, 245 (1951).

cal./mole,[7] than 1-butene, $\Delta H_f^{25°}$ 280 cal./mole, from the corresponding bromohydrins. Likewise, formation of 2-ethyl-1-butene, $\Delta H_f^{25°}$ −12920 cal./mole,[6] competes with oxetane formation better than that of 1-hexene, $\Delta H_f^{25°}$ −9960 cal./mole.[6] Particularly striking is the effect of the phenyl group on carbon-2, which results in the elimination reaction occurring so easily that no oxetane formation whatever was observed. This may be ascribed to the stabilizing effect of the phenyl group on the double bond.

For a complete analysis, certainly other factors besides the stability of the possible olefin formed should be considered, such as the relative stability of the possible oxetane formed and the Thorpe-Ingold effect of a *gem*-dialkyl grouping at carbon 2, bringing the oxygen atom into closer proximity to carbon-3.[8] The latter may be a cause of the greater ratio of oxetane to olefin from 2,2-diethyl-3-bromo-1-propanol than that from the dimethyl- and the tetramethylene-substituted bromohydrins. Molecular models suggest that the better yield of oxetane from 2,2-pentamethylene-3-bromo-1-propanol, as compared to that from 2,2-tetramethylene-3-bromo-1-propanol, may be due to interaction of the axial hydrogens on the exocyclic methylenes, thereby forcing them into closer proximity. Operating in the same direction, however, would be the probable greater stability of the double bond in methylenecyclopentane, as compared to methylenecyclohexane.[9]

These substituent effects resemble somewhat those affecting the relative yields of substitution and elimination products in ordinary bimolecular reactions of bases with alkyl halides. The latter have been interpreted, however, on the basis of steric retardation of the substitution process by the β-substituent regulating the relative rates of substitution and elimination.[6] Such a steric factor is unlikely in the present case, due to the cyclic transition state that must be involved in the intramolecular substitution process.

A marked solvent effect was observed on the competition between the intramolecular substitution and the 1,4-elimination processes. Comparison of the results from the use of 15% aqueous potassium hydroxide and of alcoholic base show clearly that the elimination is favored by a more ionizing media. Comparison of the results obtained with 15% and with 50% aqueous potassium hydroxide leads to the same conclusion, since the latter must be a poorer ionizing solvent. With most of the water molecules in 50% potassium hydroxide tied up by solvation of potassium and hydroxide ions, the capacity to solvate new ions must be relatively low.[10] The basicity of the medium does not appear to be a major factor, because the oxetane/olefin ratio was not greatly different when the reaction was carried out in 20% aqueous sodium carbonate solution.

This solvent effect is exactly opposite to that observed in the usual reactions of primary alkyl halides with bases, where elimination is favored over substitution by less ionizing (or solvating) media.[6] The solvent effect found in this investigation is in accord with the 1,4-elimination going by a dissociative mechanism and the substitution process by a displacement mechanism. This confirms that the γ-bromoalkoxide ion, such as I, is a discrete intermediate, which can undergo either solvolysis with concurrent rupture of C=C bonds, or cyclization by an internal displacement process.

Apparently the π-electrons on oxygen in this intermediate are potentially mobile, like those in the double bond in allylic halides, and can facilitate the release of γ-bromide even when the latter is primary, if the β-carbon bears an alkyl or aryl group. This 1,4-elimination process then appears to be a neat example of the nonconcerted mechanism termed by Ingold "E1cb",[11] and is particularly interesting in view of the observation that 1,4-elimination of hydrogen halide from a four-carbon chain is thought to proceed by a concerted mechanism.[12,13]

Some additional experiments were carried out to investigate the possible generality of the 1,4-elimination process, which can be formulated as X—C—C—C—Y. Little olefin formation was observed, however, when 3-dimethylamino-2,2-dimethyl-1-propanol methiodide[14] (X = OH, Y = NMe_3) or 1,1-methylamino-3-bromo-2,2-dimethylpropane[15] (X = $NHCH_3$, Y = Br) were heated with aqueous potassium hydroxide nor when 1,3-di-

(7) Heats of formation from *Properties of Hydrocarbons*, American Petroleum Institute, Project 44, Table 8p.

(8) R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, **107**, 1080 (1915).

(9) H. C. Brown, J. H. Brewster, and H. Schechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(10) An analogy is the observation of G. L. Lucas and L. P. Hammett, *J. Am. Chem. Soc.*, **64**, 1928 (1942), that sodium hydroxide retards the rate of hydrolysis of *tert*-butyl nitrate.

(11) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 467.

(12) S. J. Cristol, W. Barasch, and C. H. Tiemann, *J. Am. Chem. Soc.*, **77**, 583 (1955); S. J. Cristol, Abstracts of Fourteenth National Organic Chemistry Symposium, ACS, 1955, p. 12.

(13) (a) A related 1,4-elimination process, the cleavage of 3-dialkylamino-1,1-diphenylpropanols to 1,1-diphenylethylene and other products when heated in refluxing acetic anhydride, has been reported by D. W. Adamson, *Nature*, **164**, 500 (1949). It, of course, does not proceed *via* a conjugate base, however. (b) A number of other 1,4-eliminations with cleavage are discussed by C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955).

(14) C. Mannich, F. Lesser, and E. Sieten, *Ber.*, **65**, 378 (1932).

(15) C. Mannich and E. Baumgarten, *Ber.*, **70**, 210 (1937).

TABLE IV

LITHIUM ALUMINUM HYDRIDE REDUCTION[a] OF MALONIC ESTERS

Starting Ester	1,3-Propanediol	Yield, %	B.P. ° (mm.) Obs.	Lit.
Ethyl ethylmalonate[b]	2-Ethyl	71	124–127 (16)	83–86 (1–2)[h]
Ethyl ethylisopropylmalonate[b]	2-Ethyl-2-isopropyl[d]	76	72–74 (0.3)	
Ethyl phenylmalonate[b]	2-Phenyl[e]	36	189 (16)	
Ethyl cyclopropane-1,1-dicarboxylate[b]	2,2-Dimethylene	72	70	
Ethyl cyclobutane-1,1-dicarboxylate[c]	2,2-Trimethylene	76[i]	132–140 (22)	147 (20)[j]
Ethyl cyclopentane-1,1-dicarboxylate[c]	2,2-Tetramethylene[g]	81	M.P. 92–92.5	
Ethyl cyclohexane-1,1-dicarboxylate[c]	2,2-Pentamethylene	68	M.P. 93–98	97–97.5[k]
Ethyl dibenzylmalonate	2,2-Dibenzyl	92	M.P. 82–83[l]	

[a] One mol. of lithium aluminum hydride was used for 0.75 mol. of ester in ethyl ether. [b] After hydrolysis the reaction mixture was continuously extracted with ethyl ether for 2–3 days to remove the diol. [c] Reaction mixture decomposed with 20% sodium hydroxide, the ether solution being decanted from the solid salts. [d] *Anal.* Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.04; H, 12.21. [e] *Anal.* Calcd. for $C_9H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 59.15; H, 9.75. [g] Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.55; H, 11.11. [h] H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, **70**, 3121 (1948). [i] By inverse addition; by usual method, yield is about 50% (experiments of E. F. Lutz). [j] N. D. Zelinsky and M. N. Ujedinov, *Ber.*, **46**, 1093 (1913). They reported n_D^{22} 1.4758; the product obtained in our work had n_D^{22} 1.4778. [k] H. J. Backer and H. J. Winter, *Rec. trav. chim.*, **56**, 492 (1937). [l] *Anal.* Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.95; H, 8.05.

bromo-2,2-dimethylpropane[16] was heated with alcoholic potassium hydrogen sulfide. (In the last reaction 3-bromo-2,2-dimethyl-1-propyl mercaptan (X = SH, Y = Br) is presumably an intermediate.) In the last two cases, intermolecular substitution proceeds with greater ease[15,16] than in the case of the corresponding γ-bromoalcohol. Thus, for the 1,4-elimination process, X should be not very nucleophilic and Y should be easily dissociable.

It is interesting to note that β-substitution is not required for the 1,4-elimination process with γ-halogeno alcohols, if the γ-halogen is not primary. Gaylord and co-workers[17] have shown it to occur when 2-chloro-4-hexanol and 1-phenyl-3-chloro-1-butanol are treated with alkali. These workers postulated that the mechanism for the cleavage process was (1) base-catalyzed hydrolysis of oxetane initially formed, giving a 1,3-diol and (2) base-catalyzed cleavage of the latter to olefin and carbonyl compound. The basis for this postulation was some work by Barbot,[18] but inspection of the latter indicates it to be concerned actually with acid-catalyzed cleavage of 1,3-diols. This mechanism is untenable, as it has been shown[19] that 1,3-diols of the type postulated as formed are cleaved by hot alkali to carbonyl compounds and alcohols, not olefins. Furthermore, base-catalyzed hydrolysis of the substituted oxetanes involved, to form 1,3-diols, required more drastic conditions than required for cleavage of the bromohydrins.

(16) H. J. Backer and K. J. Keuning, *Rec. trav. chim.*, **53**, 808 (1934).

(17) N. G. Gaylord, J. H. Crowdle, W. A. Himmler, and H. J. Pepe, *J. Am. Chem. Soc.*, **76**, 59 (1954).

(18) A. Barbot, *Bull. soc. chim.*, (5), **2**, 1438 (1935).

(19) S. Searles, E. L. Ives, and S. Nukino, *J. Org. Chem.*, **24**, 1770 (1959), and Abstracts, 127th Meeting of ACS, Cincinnati, Ohio, April, 1955, p. 24N; K. C. Brannock and G. R. Lappin, *J. Am. Chem. Soc.*, **77**, 6052 (1955).

EXPERIMENTAL

The *1,3-diols* were synthesized by lithium aluminum hydride reduction of the corresponding malonic esters,[20] except 2,2-dimethyl-1,3-propanediol, which was a commercial sample. Each was fractionally distilled or crystallized until the b.p. or m.p. agreed with literature values. Preparative data on those diols which are new to the litera-

TABLE V

3-BROMO-1-PROPANOLS

Substituents	Yield, %	B.P., ° (mm.)	n_D (t°)
2-Ethyl	54	60–65 (4)	
2-Butyl	73	105–110 (9)	1.4806 (20)
2-Phenyl[a]	57	90–93 (0.1)	1.5616 (25)
2,2-Dimethyl	84	76–80 (13)[b]	1.4825 (20)
2,2-Diethyl[c]	90	103 (12)	1.4880 (20)
2-Ethyl-2-isopropyl	76	110–120 (1)	1.4910 (20)
2-Ethyl-2-phenyl	78	124–132 (0.5)	1.5628 (27.5)
2,2-Pentamethylene[d]	50	85–87	1.5181 (25)
2,2-Tetramethylene[e]	70	100–105	1.5105 (25)
2,2-Trimethylene	13	75–78	1.5011 (26)
2,2-Dibenzyl[f]	75	183–185 (0.1)	1.5970 (20)

[a] *Anal.* Calcd. for $C_9H_{11}OBr$: C, 50.25; H, 5.15. Found: C, 50.50; H, 5.25. [b] A. Franke and H. Hinterberger, *Monatash.*, **43**, 655 (1953) report b.p. 73–74° (10 mm.). [c] *Anal.* Calcd. for $C_6H_{15}OBr$: C, 43.08; H, 7.75. Found: C, 43.80; H, 8.10. The allophanate, prepared by passing cyanic acid gas into the bromoalcohol, was obtained as white leaflets, m.p. 110–110.5°, from alcohol. *Anal.* Calcd. for $C_9H_{17}O_3N_2Br$: N, 9.96. Found: N, 9.91. [d] *Anal.* Calcd. for $C_8H_{15}OBr$: C, 46.61; H, 7.34. Found: C, 44.53; H, 7.27. [e] Calcd. for $C_7H_{13}OBr$: C, 43.54; H, 6.79. Found: C, 44.51; H, 7.27. [f] *Anal.* Calcd. for $C_{17}H_{19}OBr$: C, 63.9; H, 6.0. Found: C, 65.0; H, 6.6. This bromohydrin was prepared by alcoholysis of its acetate, which was isolated in this case, and the yield is based on the pure acetate started with. The acetate was isolated by simply removing the solvent under vacuum after the reaction of the diol with hydrogen bromide had proceeded under reflux for 3 hr., giving a tan crystalline residue which was recrystallized from ethanol to give white needles, m.p. 109°. *Anal.* Calcd. for $C_{19}H_{21}O_2Br$: C, 63.16; H, 5.86. Found: C, 63.42; H, 5.79.

(20) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1197 (1947).

TABLE VI

OLEFINIC PRODUCTS[a]

Compound	B.P., ° Obs.	B.P., ° Lit.	n_D (t°) Obs.	n_D (t°) Lit.
Methylpropene[b]	−6 to 0	−6.9		
1-Butene	−4 to 0	−6.3		
2-Ethyl-1-butene[c]	65–70	66.5	1.3918 (20)	1.396 (20)
1-Hexene	60–68	67		
3-Methyl-2-ethyl-1-butene	91–93	88–90	1.4028 (27)	1.407 (25)
Styrene	140–149	146		
α-Methylstyrene	83–90 (40 mm.)	68–69 (27 mm.)[d]	1.5248 (18)	1.5334 (20)
α-Ethylstyrene	179–180	181[e]	1.5329 (25)	1.5264 (25)[e]
Methylenecyclohexane	100–110	106[f]	1.4466 (26)	1.4491 (20)[f]
Methylenecyclopentane	76–81	78–81[g]	1.4325 (26)	1.4335 (19)[g]
2-Methylene-1-butanol	130–135	133[h]		
2-Phenyl-2-propen-1-ol	120–130 (60 mm.)	115 (10 mm.)[i]		
2-Benzyl-3-phenylpropene[j]	95 (0.5 mm.)		1.5851 (20)	

[a] Except when otherwise noted, literature values are taken from F. D. Rossini, *Selected Values of Properties of Hydrocarbons and Related Compounds*, Am. Pet. Inst. Proj. 44, Petrol. Res. Lab., Carnegie Inst. of Technology, Pittsburgh, Pa. [b] The 2,4-dinitrobenzenesulfenyl chloride adduct had m.p. 86–87°, in agreement with the value reported by N. Kharasch and C. M. Buess, *J. Am. Chem. Soc.*, **71**, 2724 (1949). [c] The 2,4-dinitrobenzenesulfonyl chloride adduct was crystallized from dilute alcohol and has m.p. 86–87°. To our knowledge, this derivative has not been reported previously. *Anal.* Calcd. for $C_{12}H_{12}ClN_2O_4S$: C, 45.21; H, 4.74. Found: C, 45.66; H, 4.87. [d] M. Tiffeneau, *Ann. Chim.* [8], **10**, 157 (1907). [e] C. G. Overberger and D. Tanner, *J. Am. Chem. Soc.*, **77**, 369 (1955). [f] O. Wallach, *Ann.*, **359**, 249 (1908). [g] O. Wallach, *Ann.*, **347**, 325 (1906). [h] V. I. Lyubomilov and A. P. Terentev, *J. Gen. Chem.* (*U.S.S.R.*), **21**, 1479 (1951). [i] J. M. Butler, U. S. Patent **2,537,622** (Jan. 9, 1951); *Chem. Abstr.*, **45**, 5723 (1951). [j] *Anal.* Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.01; H, 8.02.

TABLE VII

OXETANE PRODUCTS

Oxetane	B.P., °	n_D (t°)	Empirical Formula	% C Calcd.	% C Found	% H Calcd.	% H Found
3-Ethyl	98.5–99		$C_5H_{10}O$	69.72	70.02	11.70	11.45
3-Butyl	85–85 (85)	1.4180	$C_7H_{14}O$	73.63	72.49[b]	12.36	12.15
3,3-Dimethyl	76–77[a]	1.3907					
3,3-Diethyl	138–140	1.4230	$C_7H_{14}O$	73.63	73.72	12.36	12.46
3-Ethyl-3-isopropyl	155–157	1.4312 (27)	$C_8H_{16}O$	74.94	73.69[b]	12.58	12.59
3,3-Pentamethylene	173 or 69–70 (20)	1.4584 (25)	$C_8H_{14}O$	76.14	75.73	11.18	11.27
3,3-Tetramethylene	149–150	1.4539	$C_7H_{12}O$	74.95	75.27	10.78	10.85
3,3-Dibenzyl	135 (1)	1.5759	$C_{17}H_{18}O$	85.67	86.83	7.61	7.98

[a] S. Searles and M. J. Gortatowski, *J. Am. Chem. Soc.*, **75**, 3030 (1953) reported b.p. 77–79°. [b] Oxetane analyses tend to run low (probably due to the great ease of peroxide formation in air) as observed by G. M. Bennett and W. G. Philip, *J. Chem. Soc.*, 1938 (1928); D. E. Applequist and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 4012 (1956); S. Searles, K. A. Pollart, and E. F. Lutz, *J. Am. Chem. Soc.*, **79**, 948 (1957).

ture or which have not been prepared by this method previously, are listed in Table IV.

The *3-bromo-1-propanols* were obtained by acetylating the corresponding 1,3-diols and cleaving the latter with hydrogen bromide to 3-bromo-1-propyl acetates, which then were subjected to ethanolysis. The general procedure[21] was as follows: To a refluxing solution of 1 mole of the diol and 200 ml. of glacial acetic acid, previously heated under reflux with 5 ml. of 48% hydrobromic acid for 20 min., a solution of 1.1 moles of dry hydrogen bromide in 400 ml. of acetic acid was added dropwise over a period of 8–10 hr. After refluxing an additional 8–10 hr., the acetic acid was removed by distillation under reduced pressure. To the undistilled residue was added 350 ml. of absolute alcohol and 3 ml. of 48% hydrobromic acid, and the ethyl acetate–ethanol azeotrope was removed by distillation through a fractionating column until the odor of ethyl acetate was no longer apparent in the distillate. More alcohol and hydrobromic acid were added if necessary. The bromopropanol was isolated by vacuum distillation and was purified by repeated fractional distillation. It was usually not possible to get good analyses on these products, due to their tendency to darken and decompose somewhat on standing even a few days. Preparative data is given in Table V. 2,2-Dimethylene-1,3-propanediol gave only tars.

The reaction of the 3-bromo-1-propanols with base was carried out by a standard procedure, illustrated by the following case: To 120 ml. of 15% potassium hydroxide solution in water, heated to 95° by an oil bath and stirred, was added 30 g. of 2,2-diethyl-3-bromo-1-propanol over a period of 1 hr. Distillate was carried off through a condenser into a trap cooled with solid carbon dioxide. With continued stirring, the temperature was maintained at 100° for an additional hour. Water that distilled over was replaced. Most of the products were collected by this time, but to drive over the last, the temperature was finally raised to 150–180°. The two layers of distillate were separated and the organic materials in the water layer salted out with potassium carbonate.

(21) A modification of the method of M. Beyaert and M. Hansens, *Natuurk. Tidschr.* (*Ghent*), 22, 249 (1940) for conversion of pentaerythritol to 2,2-bis(bromomethyl)-1,3-propanediol.

The combined organic layers, weighing 12.4 g., were dried over potassium carbonate and distilled to give 7 g. (55%) of 2-ethyl-1-butene, b.p. 65–70°, and 4.5 g. (26%) of 3,3-diethyloxetane, b.p. 135–140°. The identity of the products in each case was established by means of the properties given in Tables VI and VII and their infrared spectra.

The reactions with alcoholic base were carried out at about 20° lower temperature except for the final baking.

No products were isolated from the reaction of base with 2,2-trimethylene-3-bromo-1-propanol.

MANHATTAN, KAN.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY]

Stereochemistry of the Cycloheptane Ring. Synthesis and Deamination of *cis* and *trans*-2-Aminocycloheptanol

J. W. HUFFMAN AND J. E. ENGLE

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Cis and *trans*-2-aminocycloheptanol have been prepared by the route: cycloheptene oxide → *trans*-2-aminocycloheptanol → *trans*-2-(*p*-nitrobenzoylamino)cycloheptanol → *cis*-2-*p*-nitrophenyl-4,5-cycloheptanoöxazoline → *cis*-2-aminocycloheptanol. Deamination of the *trans* isomer with nitrous acid gives cyclohexylmethanal, whereas the *cis* isomer affords a mixture of cyclohexylmethanal and cycloheptanone. These results are compared with those obtained from *cis*- and *trans*-2-aminocyclohexanol and are interpreted in terms of the rate of reaction versus the rate of conformational change.

Although a great deal of work has been done on the steric relationships of cyclohexane compounds,[1] comparatively little systematic work has been done on the steric effects operative in seven membered ring systems. Several isolated aspects of the stereochemistry of cycloheptanes have been discussed recently, and a few earlier workers attempted a systematic study of the stereochemistry of medium sized rings.

Ayres and Raphael[2] have recently prepared *trans*-cycloheptane 1,2-dicarboxylic acid, and found that this compound readily forms a *trans* fused cyclic anhydride, in contrast to the behavior of *trans*-cyclohexane-1,2-dicarboxylic acid. The ease of formation of a *trans* anhydride may be explained on the basis that the cycloheptane ring is considerably more flexible than that of cyclohexane. The greater flexibility of the seven-membered ring may also be invoked to explain the formation from both *cis* and *trans* cycloheptane-1,2-diol of a cyclic ketal, under the same conditions, and to rationalize the observation that both *cis* and *trans*-1,2-cycloheptanediol increase the conductivity of boric acid solutions, while neither of the cyclohexane-1,2-diols will do so.[3]

We felt that the application to cycloheptane compounds of a reaction, the steric requirements of which are well defined, would shed additional light on the preferred conformation of cycloheptane derivatives. Such a reaction appeared to be the deamination of *cis* and *trans*-2-aminocycloheptanol. The steric requirements of the reaction of amino alcohols with nitrous acid has been studied thoroughly,[4] and the reaction has been applied to, and its steric implications interpreted for *cis* and *trans*-2-aminocyclohexanol.[5]

Trans-2-aminocycloheptanol (I) was prepared by the reaction of aqueous ammonia with cycloheptene oxide.[6] Of the possible synthetic routes available for the preparation of *cis*-2-aminocycloheptanol, that which appeared best was the general method employed for the conversion of *trans*-2-aminocyclohexanol to the *cis*-isomer.[7]

Trans-2-aminocycloheptanol was converted smoothly to *trans*-2-(*p*-nitrobenzoylamino)cycloheptanol (II), by the action of *p*-nitrobenzoyl chloride and aqueous base. Treatment of this amide with thionyl chloride afforded *cis*-2-*p*-nitrophenyl-4,5-cycloheptanoöxazoline (III). Prolonged boiling of (III) with aqueous hydrochloric acid yielded *cis*-2-aminocycloheptanol (IV) which with *p*-nitrobenzoyl chloride and base gave *cis*-2-(*p*-nitrobenzoylamino)cycloheptanol (V).

Trans-2-aminocycloheptanol was deaminated with sodium nitrite in acetic acid to afford as the only isolable product hexahydrobenzaldehyde (VI), identical in all respects to a sample prepared from cyclohexylmagnesium bromide and triethyl orthoformate.[8] The infrared spectrum of the crude de-

(1) a. W. Klyne, *Progress in Stereochemistry*, Vol. I, Butterworths, London, 1954, pp. 36–90. b. W. G. Dauben and K. S. Pitzer in M. J. Newman, *Steric Effects in Organic Chemistry*, J. Wiley and Sons, New York, 1954, pp. 1–60. (c) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 1 (1956).

(2) D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 3151 (1958). We are indebted to Prof. Raphael for communicating his results to us prior to their publication.

(3) a. P. H. Hermans and C. J. Maan, *Rec. trav. chem.*, **57**, 643 (1938). b. J. Boeseken, *Rec. trav. chem.*, **58**, 856 (1939).

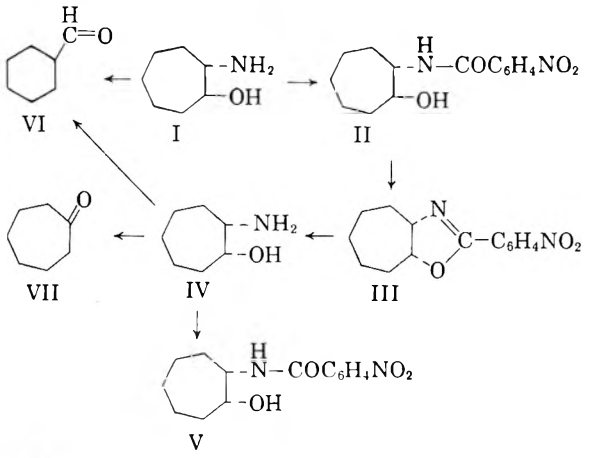
(4) P. I. Pollak and D. Y. Curtin, *J. Am. Chem. Soc.*, **72**, 961 (1950).

(5) G. E. McCasland, *J. Am. Chem. Soc.*, **73**, 2294 (1951).

(6) a. M. Mousseron and R. Granger, *Bull. soc. chim.*, 850 (1947). b. P. B. Talukdar and P. E. Fanta, *J. Org. Chem.*, **24**, 555 (1959).

(7) G. E. McCasland and D. A. Smith, *J. Am. Chem. Soc.*, **72**, 2194 (1950).

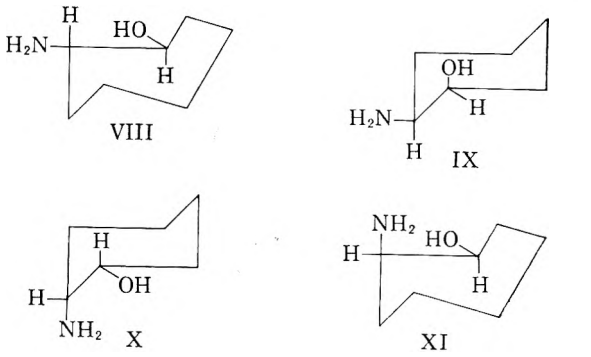
(8) C. E. Wood and M. C. Comley, *J. Soc. Chem. Ind.*, **42**, 429T (1923).



amination showed only one carbonyl band, at 5.81 μ. The 2,4-dinitrophenylhydrazone crystallized readily and was easily purified, giving additional evidence for the homogeneity of the product. Although the product from the *cis*-amino alcohol under the same conditions gave cycloheptanone-2,4-dinitrophenylhydrazone on treatment with dinitrophenylhydrazine, this derivative required several recrystallizations to reach the melting point of an authentic sample. The infrared spectrum of the crude product showed in addition to the ketone band at 5.89 μ, a shoulder at 5.81 μ. Isolation of the total aldehyde fraction by means of dimedone solution indicated that 18% of the crude product was hexahydrobenzaldehyde, while infrared measurements for two runs showed 20.4 ± 1% of aldehyde. The balance of the product was assumed to be cycloheptanone.

According to the well known steric requirements for group migration in the nitrous acid deaminations of amino alcohols,[1,4,5] the amino group must be located antiparallel to the bond which migrates. On this basis, a study of molecular models of *trans*-2-aminocycloheptanol indicates that the amino group, and consequently the hydroxyl group, must occupy a position analogous to the equatorial position in cyclohexane compounds. We obtained in our deaminations of *trans*-2-aminocycloheptanol no detectable amount of cycloheptene oxide, which would arise if the functional groups on the cycloheptane ring had a conformation similar to the 1,2-diaxial position for cyclohexanes. Of the several possible conformations, (VIII) seems to best fulfill these requirements. These results are in accord with those obtained in the cyclohexane series, where *trans*-2-aminocyclohexanol gives cyclopentylmethanal upon treatment with nitrous acid.

The formation of a large amount of cycloheptanone from the deamination of *cis*-2-aminocycloheptanol is in direct contrast to the products obtained from the deamination of *cis*-2-aminocyclohexanol.[6] In the cyclohexane series, deamination of the *cis* compound proceeds to give about 70% cyclopentylmethanal. If it be assumed, as is probable, that the amino group is somewhat larger than the hydroxyl group, then the conformation of *cis*-2-aminocyclohexanol which would predominate at equilibrium would be that where the amino group is equatorial and the hydroxyl group is axial (IX). Deamination of a compound of this conformation will proceed with ring contraction to give the aldehyde, whereas the slightly less favorable conformation (X), would give cyclohexanone.



The production of cycloheptanone as the principal product in the deamination of *cis*-2-aminocycloheptanol demands that at the time of reaction the amino group be in an axial conformation, and antiparallel to a hydrogen atom (XI). As we have already seen as a result of the deamination of *cis*-2-aminocyclohexanol that the amino group tends to assume an equatorial position in six membered rings, and as a result of the deamination of *trans*-2-aminocycloheptanol, that bulky groups occupy a quasi-equatorial position in seven-membered rings, we would be led to predict that, on purely conformational grounds, the deamination of *cis*-2-aminocyclohexanol and *cis*-2-aminocycloheptanol should give nearly the same ratio of aldehyde to ketone.

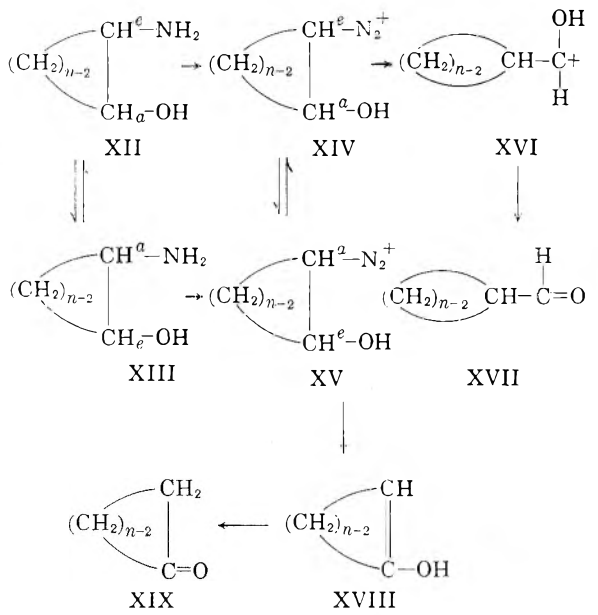
It is, therefore, difficult to reconcile the large proportion of cycloheptanone formed from *cis*-2-aminocycloheptanol purely in terms of conformational arguments. These apparently incompatible results may be interpreted in terms of the relatively great flexibility of the cycloheptane ring as compared with that of cyclohexane, however.

The mechanism of the deamination of aliphatic primary amines should proceed in a manner similar to that of aromatic amines,[9] namely the amine is first converted to a *N*-nitroso derivative, which can isomerize and dehydrate to an aliphatic diazonium salt. This diazonium salt loses nitrogen forming a carbonium ion, or undergoes nucleophilic attack to yield the product of the reaction. In the case of the *cis*-aminocyclanols this reaction can be pictured in terms of the formulas (XII) to (XIX).

If it is assumed that the principal conformation of both *cis*-2-aminocyclohexanol and *cis*-2-aminocycloheptanol is that where the amino group is

(9) (a) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, 1956, p. 364. (b) E. R. Alexander, "Ionic Organic Reactions," Wiley, New York, 1950, p. 266.

equatorial (XII), then the equatorial diazonium salt (XIV) will be that initially formed in the largest amount. This diazonium salt may then follow



one of two reaction paths; either it may undergo decomposition with group migration to give ultimately the aldehyde (XVII), or it may be considered to be in equilibrium with the axially substituted diazonium salt (XV). (XV) also has open to it two paths, namely, decomposition with loss of hydrogen to yield the cyclanone (XIX), or equilibration with (XIV). A similar course of reasoning may be applied to the conversion of the axial-amino conformation of the amino alcohol (XIII), which may be assumed to be in equilibrium with (XII).

In order to explain the course of the deaminations of the *cis*-amino-alcohols, it is necessary to assume that the rate of the reaction to lose hydrogen[10] (XV → XVIII) is fast with respect to the movement of a ring bond, (XIV → XVI). It may also be postulated, because of the flexibility of the cycloheptane ring, that the rate of equilibration of the two conformations of the diazonium salt from *cis*-2-aminocycloheptanol (XIV → XV, n = 7) is much faster than the rate of equilibration between the two forms of the diazonium salt from *cis*-2-aminocyclohexanol (XIV → XV, n = 6), and that as a result the ratio of rate constants k (XIV → XV)/k (XIV → XVI) for n = 7 is larger than for n = 6. Assuming that k (XV → XIV)/k (XV → XVIII) is relatively small because of the rotational barrier in cyclohexane, one would expect a greater proportion of cyclanone to be formed from *cis*-2-aminocycloheptanol than from *cis*-2-aminocyclohexanol.[11]

Thus the ratio of aldehyde to ketone from *cis*-2-aminocycloheptanol is determined by the ratio of the rate of group migration to proton loss k(XIV → XVI)/k (XV → XVIII), while in the deamination of *cis*-2-aminocyclohexanol the product ratio is determined by the position of the equilibrium for the conformational change (XII → XIII).

Effects of this type may be considered to be of no consequence in the deamination of the *trans*-2-aminocyclanols, because the rate of conversion of the diequatorial conformer to the diaxial will be negligible and the equilibrium will be greatly in favor of the diequatorial conformation, consequently the product of the reaction will be virtually exclusively aldehyde.

EXPERIMENTAL[12]

Trans-2-(p-nitrobenzoylamino)cycloheptanol. To a solution of 3.9 g. of *trans*-2-aminocycloheptanol, m.p. 74–75°,[6] in 75 ml. of water was added 5.58 g. of freshly recrystallized *p*-nitrobenzoyl chloride in 70 ml. of benzene. To the resulting heterogeneous mixture was added 24 ml. of 5% sodium hydroxide, the reaction mixture was shaken 10 min. at room temperature, cooled, and the product collected by filtration. Recrystallization from ethanol afforded 6.60 g. (77%) of cream colored crystals m.p. 190–191°; the melting point was not increased by additional recrystallizations.

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.53; N, 10.06. Found: C, 60.19; H, 6.73; N, 10.08.

2-p-Nitrophenyl-4,5-cis-cycloheptanoöxazoline. To 6.60 g. of *trans*-2-(*p*-nitrobenzoylamino)-cycloheptanol was added 11.3 g. of thionyl chloride. The flask was protected from atmospheric moisture with a calcium chloride tube and allowed to stand at room temperature for twelve hours. A large excess of dry ether was added, the precipitated solid collected, and recrystallized from aqueous alcohol to give 3.0 g. (58%) of white crystals, m.p. 118–119°. Several recrystallizations from aqueous ethanol gave material, m.p. 120–121°.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.57; H, 6.19; N, 10.76. Found: C, 65.09; H, 6.08; N, 11.11.

Cis-2-aminocycloheptanol.[13] A solution of 6.0 g. of the cycloheptanoöxazoline was dissolved in 50 ml. of 4*N* hydrochloric acid, heated under reflux for 24 hr., refrigerated for twelve hours, and the precipitated *p*-nitrobenzoic acid collected. The clear filtrate was made alkaline with 20% sodium hydroxide and continuously extracted with ether for twenty-four hours. Evaporation of the ether gave 2.4 g. (80%) of white powder, which was purified by sublimation at 10 mm. and 70° to give white crystals, m.p. 81–82°.

Anal. Calcd. for $C_7H_{15}N_2$: C, 65.07; H, 11.70; N, 10.83. Found: C, 64.64; H, 12.03; N, 10.91.

The *p*-nitroamide was prepared in the manner described for the *trans* amino alcohol, and formed cream-colored needles from aqueous ethanol, m.p. 129–130°.

(10) We have some evidence that the enol of cycloheptanone is an intermediate in the formation of the ketone, specifically, in one deamination the infrared spectrum of the crude reaction mixture showed a distinct band at 5.68 μ which can be attributed to cycloheptanone enol acetate. In the absence of this data there is little to choose between the conversion of (XV) to (XVIII), and the direct conversion of (XV) to (XIX) by hydride transfer.

(11) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **77**, 354 (1955), have postulated a similar effect to explain an abnormally large amount of *p*-anisyl migration in the deamination of *erythro*-1-*p*-anisyl-1-phenyl-2-aminopropanol.

(12) Analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Infrared spectra were carried out in chloroform solution or as liquid films on a Perkin Elmer Model 137 Spectrophotometer. Melting points were determined on a Fisher-Johns block, and are uncorrected.

(13) J. Sicher and M. Svoboda, *Coll. Czech. Chem. Comm.* **23**, 1252 (1958), have recently reported the synthesis of this compound and find it to have m.p. 79–81°. Their *p*-nitrobenzamide has m.p. 128–129.5°.

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.11; H, 6.36; N, 10.25.

Deaminations. a. A solution of 0.129 g. of *trans*-2-aminocycloheptanol in 1.0 ml. of glacial acetic acid and 2.0 ml. of water was cooled in salt-ice bath. To this cooled solution was added a chilled solution of 1.4 g. of sodium nitrite in 3.0 ml. of water, and the solution allowed to stand in the cold for 30 min. The reaction was made basic with 20% sodium hydroxide solution, and extracted with ether. The ethereal extracts were dried and the solvent removed on the steam bath through a short column, affording 0.106 g. (96%) of yellow oil. This oil was treated with 2,4-dinitrophenylhydrazine reagent to give a yellow powder, m.p. 165–169°. Recrystallization from ethanol–ethyl acetate gave yellow-orange crystals, m.p. 170–172°. A mixed melting point with the dinitrophenylhydrazone of hexahydrobenzaldehyde[14] showed no depression.

b. A solution of 0.135 g. of *cis*-2-aminocycloheptanol in 3.0 ml. of water was cooled in an ice bath. To this solution was added a cold solution of 1.0 g. of sodium nitrite in 3.0 ml. of water and 1.0 ml. of glacial acetic acid. The reaction mixture was allowed to stand in the cold 30 min., made basic with dilute sodium hydroxide, and extracted with two portions of ether. The solvent was removed on the steam bath to give 0.073 g. (62%) of oil which was converted to the 2,4-dinitrophenylhydrazone, obtained as a yellow powder, m.p. 142–145°. Recrystallization from ethanol gave yellow crystals m.p. 147–148°, undepressed on mixing with an authentic sample of cycloheptanone-2,4-dinitrophenylhydrazone.[15] Treatment of 0.073 g. of the crude product with dimedone solution gave 0.039 g. of the dimedone derivative of cyclohexylmethanal. A blank run on pure cyclohexylmethanal indicated 50% recovery of the aldehyde. Consequently the deamination mixture contained 18% of cyclohexylmethanal.

Acknowledgment. This work was supported in part by the Georgia Institute of Technology Engineering Experiment Station, project number E-181. We would like to thank Professor Jack Hine for his helpful suggestions concerning some of the theoretical aspects of this work.

ATLANTA, GA.

(14) M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Bull. soc. chim.*, 1042 (1952).

(15) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, 3rd Ed., New York, 1948, p. 262.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BRIGHAM YOUNG UNIVERSITY]

Rhenium and Its Compounds as Hydrogenation Catalysts. III. Rhenium Heptoxide[1,2,3]

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Received June 3, 1959

The hydrogenation catalytic activity of some rhenium "blacks" obtained by the reduction of commercially available rhenium heptoxide has been examined. The catalysts were prepared by hydrogenation of the heptoxide in a solvent prior to the addition of the reducible substrate (*ex situ*), or in the presence of the substrate subsequently and/or simultaneously being reduced (*in situ*). These rhenium "blacks" have been shown to be easily the most effective catalysts yet reported for the hydrogenation of the carboxylic acids to alcohols. They promote this conversion with a wide variety of acids at 150–250° (usually 160°)/*ca.* 200 atm. in a few hours, giving excellent yields of alcohols accompanied occasionally by ester by-product. Unreduced acid rarely survives. They are also unusually effective in the hydrogenation of amides. On the other hand, these catalysts show only moderate but definite activity toward many of the common organic functions reducible through the agency of platinum or nickel catalysts.

Relatively little work on the catalytic properties of rhenium metal in hydrogenation has been reported[5] and none on its oxides. Schmidt[6] reports that rhenium displays average activity as a hydrogenation catalyst being less active than platinum, palladium, or nickel. A colloidal rhenium sol was reported to be effective in reducing the ethylenic bonds of maleic and cinnamic acids with very high ratios of rhenium to substrates[7] Rhenium supported on unglazed porcelain by reducing the ammonium perrhenate-soaked carrier in a hydrogen stream at 500–600° was ineffective toward maleic acid and cyclohexene at 20° at 1 atm., but at 350° cyclohexene was reduced and benzene slowly decomposed stepwise to methane.[8] Nitric oxide was re-

(1) Part I of this series: H. S. Broadbent, L. H. Slaugh, and N. L. Jarvis. "Rhenium Sulfides as Liquid-Phase Hydrogenation Catalysts. A Comparison with Molybdenum Sulfide and Cobalt Polysulfide," *J. Am. Chem. Soc.*, **76**, 1519 (1954).

(2) This research was supported by Contract No. AF 18 (600)-1164 with the United States Air Force through the Office of Scientific Research of the Air Research and Development Command. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(3) Presented in part at the 131st meeting of the American Chemical Society in Miami, Florida, April 11, 1957.

(4) This paper is based largely upon theses submitted by Mr. Campbell (1955) and by Mr. Bartley (1958) in partial fulfillment of the requirements for the degree of Master of Science, Brigham Young University.

(5) For a complete review to 1940 see "Gmelin's Handbuch der anorganischen Chemie," 8th Ed., Verlag Chemie, Berlin, 1941, No. 70, pp. 37–40. Since that time very little has been reported.

(6) Schmidt, *Z. physik. Chem.*, **165**, 212, 224 (1933).

(7) C. Zenghelis and K. Stathi, *Compt. rend.*, **209**, 797 (1939); *Chem. Abstr.*, **34**, 669 (1940).

(8) S. B. Anisimov, V. M. Kraseninnakova, and M. S. Platanov, *Ber.*, **68**, 762 (1935).

duced to ammonia and nitrogen at 400° and nitrobenzene to aniline at 250°. The same type catalyst hydrogenated ethylene at 300°[9] and unsaturated hydrocarbons of at least three carbon atoms "at sufficiently high temperatures."[10] A quartz sand supported rhenium catalyst reduced carbon monoxide to methane about as well as osmium.[11] Hydrogenation as well as desulfurization of certain oxygen containing compounds as phenols, cresols etc. is reported either by rhenium alone or with other catalysts.[12] The nitrogen-hydrogen(deuterium)-ammonia system over rhenium[13] and rhenium-iron mixtures[14] has been studied.

A number of catalytic hydrogenations of carboxylic acids to alcohols using non-rhenium catalysts have been reported under a variety of conditions—all of them strenuous. Representative among them are the use of copper catalysts at 300–400° above 200 atms. pressure,[15] of copper-chromium catalysts (for the higher acids) at near 300° and 250–300 atm.,[15,16] of copper-cadmium catalysts at 280° and 130 atm.,[17] of copper–cobalt–nickel promoted catalysts at 120–300° and 30–400 atm.,[18] of ferrous metals modified with various non-ferrous chromites at 200–400° and 100–200 atm.,[19] and most recently, after this work was in progress, of ruthenium dioxide at 150° and 500–1000 atm.[20] Cadmium-nickel salts of the carboxylic acids have been shown to yield alcohols using copper chromite at 240° and 235 atm. if the system is scrupulously dry.[21] The self-catalyzed reduction of certain acid salts if reported at 240–400° at above 135 atm.[22] The reduction of acids to esters by a modified cobalt catalyst is likewise reported.[23] An interesting transhydrogenation of acids to aldehydes using formic acid and titanium dioxide catalyst has been recorded,[24] but a subsequent investigation was unable to confirm it.[25]

(9) H. Tropsch and R. Kassler, *Ber.*, **63**, 2149 (1930).

(10) French Patent **761,632**, Mar. 23, 1934. (Druce, "Rhenium," Cambridge U. Press, Cambridge, 1948, p. 73.)

(11) H. Tropsch and P. Dilthey, *Brennstoff-Chem.*, **6**, 271 (1925) ("Gmelin," *op. cit.*, p. 38).

(12) N. V.-de Bataafsche Petroleum Mattschappij, British Patent **358,180**, July 29, 1930; German Patent **693,707**, June 20, 1940 (*Chem. Abstr.*, **26**, 4924 (1932); **35**, 4941 (1941)).

(13) Taylor, *J. Chem. Phys.*, **47**, 1225 (1950) [*Chem. Abstr.*, **44**, 7132 (1950)].

(14) McGeer and Taylor, *J. Am. Chem. Soc.*, **73**, 2743 (1951).

(15) W. Schrauth, O. Schenck, and K. Stickdorn, *Ber.*, **64**, 1314 (1931).

(16) A. Guyer, A. Bieler, and K. Jaberg, *Helv. Chim. Acta*, **30**, 39 (1947); Sandoz Ltd., German Patent **711,180**, Aug. 21, 1941 [*Chem. Abstr.*, **37**, 3767 (1941)].

(17) G. Schuckmann, U. S. Patent **2,332,834**, Oct. 26, 1944; Bohme-Fellchemie-Ges.m.b.H., French Patent **819,255**, Oct. 13, 1937 [*Chem. Abstr.*, **32**, 2143 (1938)].

(18) O. Schmidt, U. S. Patents **2,322,095–9**, June 15, 1943; G. Schiller, U. S. Patents **2,121,367–8**, June 21, 1938.

(19) H. R. Arnold and W. A. Lazier, U. S. Patent **2,116,-552**, May 10, 1938.

(20) T. A. Ford, U. S. Patent **2,607,807**, Aug. 19, 1952; J. E. Carnaham, T. A. Ford, W. A. Gresham, W. E. Grigsby, and G. F. Hager, *J. Org. Chem.*, **77**, 3766 (1955).

(21) P. T. Adams, R. E. Selff, and B. M. Tolbert, *J. Org. Chem.*, **74**, 2416 (1952).

EXPERIMENTAL

Catalysts. Rhenium heptoxide. This compound was used as purchased from A. D. Melaven, Department of Chemistry, University of Tennessee, Knoxville, Tennessee. Great care was employed to retain dryness in transfer because of its extreme hygroscopicity, comparable to phosphorus pentoxide.

Ex Situ reduction of rhenium heptoxide to rhenium black without extrinsic catalysis. The finely powdered heptoxide (1 g.) was suspended or dissolved in ca. 50 ml. of the appropriate solvent (anhy. ethanol, anhy. *p*-dioxane, glac. acetic acid or water) and hydrogenated at an initial hydrogen pressure of 136 atm. (2000 p.s.i.) in a glass-lined shaker tube under conditions designed to give approximately minimal times and temperatures of reduction. (*Cf.* Part I of this series[1] for the general procedure of determining minimal conditions.) The conditions of preparation of the catalysts given in Table I are representative of a large number of individual runs. While the conditions for preparation in different solvents varied greatly, of course, duplicability for a given solvent was good. *With extrinsic catalysis.* The foregoing procedure was varied by the addition of traces of platinum dioxide, 5% rhodium on alumina, 5% ruthenium on carbon, palladous oxide or previously prepared rhenium black, in amounts equivalent to 0.01 times the formal concentration of rhenium heptoxide. These reductions were usually performed in a glass shaker bottle at low pressures and temperatures (4 atm., 60°) rather than at higher pressures and temperatures. Table II gives representative conditions for reduction of the heptoxide to the catalyst.

The finely divided rhenium blacks were isolated by filtration or centrifugation, then washed several times and stored until ready for use under the solvent to be used in subsequent reductions with the catalyst. Occasionally the catalyst was dried *in vacuo* and stored under nitrogen. So long as the catalyst remained out of contact with oxygen its activity was unimpaired. In many cases where *in situ* hydrogenation conditions were observed the presence of small amounts of oxygen was not deleterious.

Completeness of reduction was determined by analysis of the filtrate, using nitron, tetraphenylarsonium chloride, or electrolysis. In most cases reduction was complete.

Hydrogenation procedures. Both Aminco 550 ml. and Parr 1000 ml. standard rocking type reactors were used. Both operated at fixed speeds of 36 rocking cycles per minute. In later experiments a Pressure Products Industries 300 ml. shaking type "Pendaclave" reactor having a variable rate of shaking was also used. It was operated at 45 cycles/min. at full amplitude. Faster agitation did not seem to appreciably increase the rate of hydrogenation within the range of conditions used. Pyrex glass liners were used in every case. Temperature and pressure changes were recorded simultaneously throughout the course of the reactions *via* Bourdon tube, Baldwin fluid pressure cell, and

(22) S. Kamori and Y. Shigeno, *Technol. Repts. Osaka Univ.*, **3**, 171 (1953) [*Chem. Abstr.*, **49**, 152 (1955)]; **53**, 223 (1950) [*Chem. Abstr.*, **46**, 9871 (1952)]; **54**, 662-4 (1951) [*Chem. Abstr.*, **48**, 2477 (1954)]; A. S. Richardson and J. E. Taylor, U. S. Patents **2,340,687–91** (Feb. 1, 1944).

(23) W. Norman and G. V. Schuckmann, German Patent **659,495**, May 10, 1938 [*Chem. Abstr.*, **32**, 5852 (1938)].

(24) R. Davies and H. Hodgson, *J. Chem. Soc.*, **1943**, 84.

(25) Barduhn and Kobe, *J. Chem. Soc.*, **1954**, 1651.

TABLE I

CONDITIONS FOR THE *ex situ* REDUCTION OF RHENIUM HEPTOXIDE TO RHENIUM "BLACKS" BY HYDROGENATION IN VARIOUS SOLVENTS *Without* EXTRINSIC CATALYSIS

Run No.	Solvent[a]	Avg. Temp. (°C.)	Avg. Pressure (atm.)	Time (hr.)	Comment[b]
9	*p*-Dioxane	120	167	2	Black, coarse particles[c]
3	Ethanol	220	211	1	Black, coarse particles[d]
21	Acetic acid	165	153	1	Black, very finely divided, partly colloidal[e]
25	Water	140	177	2	Shiny flakes[f]

[a] Rhenium heptoxide was in the powdered state. The approximate solubilities by weight in these solvents are as follows: *p*-dioxane, 5%; ethanol, 10%; acetic acid and water, very large. [b] Reduction was complete in every case. [c] Analysis: Re, 97.4, 97.5, 97.0%. [d] Analysis: Re, 102.0, 102.5%. These values are representative of many. The catalyst is doubtless rhenium metal. Some methodical error such as coprecipitation probably caused the high values. [e] Analysis: Re, 84.1, 84.5%. [f] Analysis: Re, 82.9, 84.8%.

TABLE II

CONDITIONS FOR THE *ex situ* REDUCTION OF RHENIUM HEPTOXIDE TO RHENIUM "BLACKS" BY HYDROGENATION IN THE PRESENCE OF TRACE AMOUNTS (0.01 FORMAL EQUIVALENT) OF EXTRINSIC CATALYTIC SURFACE

Run No.	Trace Catalyst	Solvent	Avg. Temp. (°C.)	Avg. Pressure (atm.)	Time (hr.)	Comment
1	PtO_2	*p*-Dioxane	60	4	13	71% reduction[a]
12	PtO_2	Water	65	4	1	85% reduction[a]
7	Ru on C	*p*-Dioxane	60	4	12	100% reduction[b]
14	Ru on C	Water	65	4	5	100% reduction[b]
8	Re on C	*p*-Dioxane	76	4	8	46% reduction
9	Norit A[c]	*p*-Dioxane	76	4	10	37% reduction

[a] Precipitate had an olive drab cast. [b] Precipitate was an intense dull black. [c] Extrinsic surface provided by 58.5 mg. activated charcoal only/g. rhenium heptoxide.

thermocouple. The compound to be reduced (usually 0.1 or 0.2 mole), sometimes a solvent or diluent (usually absolute ethanol) to bring the total volume to 50 ml. and the catalyst (usually 1.0 g. rhenium/mole of substrate), all as indicated in the accompanying tables, were placed in the reactor. The catalyst was a rhenium "black," suspended in a diluent or the substrate in the *ex situ* reductions, or it was pure rhenium heptoxide in the *in situ* reductions. After adequate flushing to remove air, the reactor was then charged to a pressure of 2000 p.s.i.g. (136 atm.) or to 3000 p.s.i.g. (204 atm.). The hydrogenation was so managed as to obtain minimal conditions of reduction by operating at successively higher temperature increments until the reaction occurred readily, as outlined in more detail in Part I of this series.[1] In almost all cases more than one run of a kind was performed. Duplicability was good. After completion of the reaction as indicated by pressure drop, the reactor was cooled, vented and opened. The catalyst was filtered off for recovery or analysis and the solvent or diluent (if any) removed by distillation or extraction.

Analysis of reaction products was accomplished by fractional distillation, chemical extraction, spectrophotometry, titration, refractometry, and especially in the latter part of the problem by the exceptionally useful technique of gas chromatography.

Analysis of catalysts. (A) *Ultimate analysis.* After thorough washing and centrifugation from abs. ethanol, the catalyst was divided into portions in screw cap vials and dried in Abderhalden pistols *in vacuo* over phosphorous pentoxide or barium oxide with refluxing bromobenzene, nitrobenzene, or phenyl ether to constant weight. During the transferring and weighing operations they came in contact with a pure nitrogen atmosphere only. The weighed samples were dissolved in ammoniacal 30% hydrogen peroxide or with more refractory samples with concentrated nitric acid carefully added dropwise to the boiling mixture. The analyses were completed by precipitation and weighing the rhenium as tetraphenylarsonium perrhenate.[26]

B. *Oxidation state determination.* Large (*ca.* 1 g.) samples of the catalysts dried to constant weight were weighed into 125 ml. Erlenmeyer flasks and dissolved in a weighed (*ca.* 2-fold) excess of potassium dichromate, 1.0 ml. sulfuric acid and 10–25 ml. distilled water. After completion of the oxidation, the unused dichromate was reduced with excess potassium iodide. The liberated iodine was titrated with 0.1*N* sodium thiosulfate to the starch end-point. These data together with a knowledge of the rhenium content of the sample enabled a determination of the oxidation state of the rhenium in the catalyst.

Discussion of Results. The authors have chosen the term *ex situ* to describe the reactions carried out using a catalyst which had been previously prepared by hydrogenation of rhenium heptoxide *out of the site* of the substrate subsequently to be reduced by the catalyst; the term *in situ* has been chosen to describe those reactions in which

(26) H. H. Willard and G. M. Smith, *Ind. Eng. Chem. Anal. Ed.*, 11, 305 (1939).

TABLE III

A COMPARISON OF THE CATALYTIC ACTIVITY OF RHENIUM "BLACKS" DERIVED FROM RHENIUM HEPTOXIDE BY *ex situ* REDUCTION WITHOUT EXTRINSIC CATALYSIS

No.	Substrate	Solvent for Catalyst Preparation	Amt. Cat. g./ mole	Solvent for Reduction	Avg.[a] Temp. (°C.)	Avg.[a] Pressure (atm.)	Time[a] (hr.)	Yield(s),[b] %	Product(s)
1	Nitrobenzene	*p*-Dioxane	2.5	Ethanol	110	150	4	100	Aniline
2	Nitrobenzene	Acetic acid	2.1	Ethanol	100	160	12	90	Aniline
3	Nitrobenzene	Ethanol	2.5	Ethanol	100	143	3	100	Aniline
4	Nitrobenzene	Water	1.0	Ethanol	108	243	12	34	Aniline
5	Styrene	*p*-Dioxane	1.0	Ethanol	108	156	3.5	100	Ethylbenzene
6	Styrene	Acetic acid	3.0	Ethanol	170	207	2.5	24	Ethylbenzene
7	Styrene	Ethanol	2.0	Ethanol	130	170	22	0	100% polymer
8	Acetophenone	*p*-Dioxane	2.9	Ethanol	60	143	18	78	Methylphenylcarbinol
9	Acetophenone	Acetic acid	2.5	Ethanol	67	143	4.5	38	Methylphenylcarbinol
10	Acetophenone	Ethanol	2.6	Ethanol	155	184	14	47	Methylphenylcarbinol
11	Acetophenone	Water	1.0	Ethanol	135	242	9.5	50	Methylphenylcarbinol
12	Cyclohexanone	Acetic acid	2.5	None	64	143	12	84	Cyclohexanol
13	Acetic acid	*p*-Dioxane	1.0	None	147	355	9	40	Ethanol, 41% ethyl acetate
14	Acetic acid	Acetic acid	0.2	None	160	129	60	68	Ethanol, 41% ethyl acetate
15	Acetic acid	Ethanol	1.1	None	146	258	15	38	Ethanol, 41% ethyl acetate
16	Acetic acid	Water	1.1	None	175	275	2.5	27	Ethanol, 41% ethyl acetate
17	Maleic acid	*p*-Dioxane	2.6	*p*-Dioxane	148	177	2.5	100	Succinic acid
18	Maleic acid	Acetic acid	2.5	*p*-Dioxane	158	163	12	93	Succinic acid
19	Maleic acid	Ethanol	1.1	Water	151	254	4	100	Succinic acid
20	Maleic acid	Water	1.0	Water	200	194	8	0	Succinic acid
21	Succinic acid	Water	1.1	Water	205	272	12	39	Tetrahydropyran
								35	1,4-Butanediol
								6	*n*-Butyl alcohol
22	Crotonaldehyde	*p*-Dioxane	1.0	None	145	152	1.25	94	Crotyl alcohol
								3	Butyraldehyde
								3	Crotonaldehyde
23	Cinnamic acid	Acetic acid	2.5	*p*-Dioxane	160	176	3	55	Hydrocinnamic acid
								39	Hydrocinnamyl hydrocinnamate
								6	Hydrocinnamyl alcohol
24	Isobutyl isobutyrate	Acetic acid	1.0	None	165	176	5	59	Isobutyl alcohol
								41	Isobutyl isobutyrate

[a] Figures in these columns refer to the average temperature (usually quite constant) and average total system pressure during the time of hydrogenation. [b] The yield's column shows only reduced products. Unless otherwise specified the remainder of recovered material was unreduced substrate. The percentage figure given is based on 100% recovery of all products of reaction. Because of mechanical loss etc. the recovery was always slightly less than this. These same considerations apply to all other Tables given in this paper.

the rhenium heptoxide was added directly to the substrate and hydrogenated to the "black" *in the presence* of the substrate subsequently and/or simultaneously being reduced through the agency of the catalyst.

Preparation of catalysts. The ease of *ex situ* reductions of rhenium heptoxide to rhenium "blacks" was found to vary markedly with the solvent or suspending medium (see Table I). Thus conditions for reaction were rather mild in *p*-dioxane or water solution, less so in acetic acid, and relatively drastic in ethanol. Moreover, their physical appearance as well as catalytic activity was found to be greatly different. The material obtained in acetic acid was largely colloidal whereas that from *p*-dioxane was a dull black powder and that from ethanol or water lustrous, metallic flakes. In the absence of any extrinsic catalytic surface, the heptoxide is at first very slowly reduced on the walls of the containing vessel during the relatively long induction period, followed by a relatively rapid reduction of the remaining heptoxide, predominantly on the surface of the material already formed.

As evidence for this hypothesis, it was found that traces (0.01 formal equivalents) of extrinsic catalytic surfaces such as platinum oxide, activated carbon, or previously prepared rhenium black enormously increased the ease of reduction of rhenium heptoxide (Table II). These traces of added material were present in amounts too small to be catalytically significant in the hydrogenation reactions subsequently observed with the rhenium blacks formed in their presence. The ease of reduction of the heptoxide did not seem to depend greatly on the nature of the added surface among those examined, although there were some differences. The hydrogenation promotion activity did so depend, as will be evident below. Alcohol as a solvent was found to demand more drastic conditions for reduction just as when extrinsic surface was absent. On the other hand while the yields of

TABLE IV

COMPARISON OF THE CATALYTIC ACTIVITY OF RHENIUM "BLACKS" DERIVED FROM RHENIUM HEPTOXIDE BY *ex situ* REDUCTION WITH VARIOUS EXTRINSIC CATALYSTS

No.	Substrate	Amt. Cat. g./mole	Trace[a] Catalyst	Solvent for Reduction	Avg. Temp. (°C.)	Avg. Pressure (atm.)[b]	Time (hr.)	% Yields, Product
1	Nitrobenzene	1.0	PtO_2	Ethanol	215	285	4	64% Aniline
2	Styrene	1.1	PtO_2	Ethanol	110	238	2	100% Ethylbenzene
3	Acetophenone	0.8	PtO_2	Ethanol	80	224	3	70% Methylphenylcarbinol, 30% ethylbenzene
4	Acetophenone	1.3	Ru on C	Ethanol	93	251	9	91% Methylphenylcarbinol, 9% ethylbenzene
5	Acetophenone	0.5	Norit A	Ethanol	155	258	3	50% Methylphenylcarbinol, 8% ethylbenzene
6	Acetophenone	1.1	Re	Ethanol	150	256	3	100% Methylphenylcarbinol
7	Acetic acid	1.1	PtO_2	None	200	286	7	43% Ethanol, 30% ethyl acetate
8	Maleic acid	1.0	PtO_2	Water	180	290	3	52% Succinic acid

[a] The catalyst was obtained in each case by reduction of rhenium heptoxide at low temperature and pressure in *p*-dioxane solution in the presence of traces (0.01 mole equivalent) of extrinsic catalysts. [b] Total pressure under the conditions of hydrogenation at the temperature shown.

insoluble rhenium black were substantially quantitative in every case under the high temperature-high pressure conditions, the yields in the relatively mild extrinsically catalyzed procedures were not always quantitative, and the product then had the greenish yellow cast of unreduced heptoxide.

Catalytic activity of rhenium heptoxide reduced ex situ in the absence of extrinsic catalytic surface. In Table III some data are presented comparing the activity of the rhenium blacks obtained in the four solvents, *p*-dioxane, acetic acid, ethanol, and water, in the hydrogenation of several representative types of compounds. While the pattern of behavior is different for the catalysts prepared in each of the different solvents, that obtained from water is least effective. The differences are relatively small against nitrobenzene and acetic acid; however, against styrene that obtained from *p*-dioxane is markedly superior; against acetophenone the use of either *p*-dioxane or acetic acid is decidedly better than ethanol or water, and against maleic acid water is much inferior to the other solvents as a vehicle for the preparation of the catalyst.

As far as general hydrogenation catalytic activity is concerned these substances are relatively unexceptional in their behavior toward the compounds reduced by most known catalysts: nitrobenzene, styrene, acetophenone, olefinic bond of maleic acid. However, it will be noticed that the carbonyl function was more easily reduced than the olefinic—the reverse of the most commonly observed catalytic behavior. Advantage of this fact was realized in the noteworthy reduction of crotonaldehyde to crotyl alcohol in high yield. Corresponding attempts with cinnamaldehyde resulted only in resinification—perhaps because of traces of unreduced rhenium heptoxide which yields the strong perrhenic acid in the presence of moisture.

Furthermore, attention should be particularly called toward the uniquely high activity displayed in promoting the reduction of the carboxyl function (acetic acid, succinic acid, cinnamic acid). Rhenium heptoxide *in situ* (see below) displays this activity to a much higher degree. The analytical data suggest that the active catalyst is rhenium metal when prepared in *p*-dioxane or ethanol solution and rhenium dioxide when prepared in water or acetic acid; however, in the last two cases hydrated forms of still lower oxides may well be involved, as oxidation state determinations made on rhenium heptoxide reduced in acetic acid in the presence of excess water (see below) indicates hydrated rhenium monoxide to be the active form of the catalyst.

In the presence of extrinsic surfaces the rhenium blacks, which were obtained in high yields, had the same general but slightly lower degree of activity as those obtained under more drastic conditions in the absence of extrinsic catalytic surface, with the exception of nitrobenzene substrate. This exception is probably attributable to the presence of traces of unreduced rhenium heptoxide, which appears to have a very adverse effect on the reduction of this function as will later appear. The two rhenium black preparations obtained in low yield (Runs 8 and 9, Table II) were anomalous in that they were much less effective catalysts (*cf.* Nos. 5, 6, Table IV), probably because they were different in composition from the others. Taken as a whole the evidence of the catalysts prepared in the presence of extrinsic surfaces is of interest principally because of the light it may shed on the mechanism of reduction of rhenium heptoxide solutions to insoluble rhenium blacks. In a practical sense they offer no advantage over the catalysts formed in the absence of extrinsic surfaces.

Hydrogenations catalyzed by rhenium heptoxide reduced in situ. A small but representative fraction of the data obtained by adding pure, dry rhenium

TABLE V

HYDROGENATIONS WITH RHENIUM HEPTOXIDE REDUCED *in situ* AS CATALYST

No.	Substrate	Solvent	Avg. Temp. (°C.)	Avg. Pressure (atm.)[g]	Time (hr.)	Yields, %, Product(s)
1	Benzene[a]	None	330	232	13	49% Benzene, 11% cyclohexane, gaseous hydrocarbons
2	Cyclohexene[a]	None	100	156	6	98% Cyclohexane
3	1-Hexene[b]	None	100	150	2.5	100% Hexane
4	Styrene[b]	Ethanol	109	165	4	86% Ethylbenzene, 14% polymer
5	Nitrobenzene[a]	Ethanol	250	204	3	0% Aniline
6	Nitrobenzene[a]	None	165	143	3	100% Aniline
7	Cyclohexanone[b]	Ethanol	154	270	3	100% Cyclohexanol
8	Acetophenone[a]	Ethanol	115	160	18	100% Condensation products
9	Formic acid[a]	None	240	238	12	100 mg. "Polymethylene," ca. 98% water, much methane, 1% carbon dioxide
10	Acetic acid[a]	None	150	163	10	77% Ethanol, 23% ethyl acetate
11	Acetic acid[b]	Water	150	168	10	100% Ethanol
12	Trifluoroacetic acid[b]	Water (20 ml.)	207	300	18.5	100% Trifluoroethanol
13	Dichloroacetic acid[b]	Water (20 ml.)	220	315	11.5	0% Reduction
14	Trichloroacetic acid[b]	Water (20 ml.)	172	298	27	0% Reduction
15	Propionic acid[a]	None	165	252	1.5	92% *n*-Propyl alcohol, 8% *n*-propyl propionate
16	Formic acid + propionic acid[a]	None	250	224	2.3	67% *n*-Propyl alcohol, 29% *n*-propyl formate, 4% *n*-propyl propionate
17	Butyric acid[a]	None	163	153	4.5	70% *n*-Butyl alcohol, 30% *n*-butyl butyrate
18	Butyric acid[b]	Water (3 ml.)	150	178	11	89% *n*-Butyl alcohol, 11% *n*-butyl butyrate
19	Heptafluorobutyric acid[b]	Water (20 ml.)	190	302	17	70% Heptafluorobutanol, 29% heptafluorobutyl heptafluorobutyrate
20	Isobutyric acid[a]	None	165	156	4	75% Isobutyl alcohol, 28% isobutyl isobutyrate
21	Valeric acid[a]	None	160	173	10	55% *n*-Amyl alcohol, 43% *n*-amyl valerate
22	Pivalic acid[a]	None	264	248	5	0% Reduction
23	Caproic acid[a]	None	174	170	3.2	61% *n*-Hexyl alcohol, 39% *n*-hexyl caproate
24	Caproic acid[b]	Water (4.5 ml.)	200	188	2	93% *n*-Hexyl alcohol, 7% *n*-hexyl caproate
25	Caprylic acid[a]	None	163	163	2.5	52% *n*-Octyl alcohol, 48% *n*-octyl caprylate
26	Caprylic acid[b]	Water (50 ml.) and *p*-dioxane	163	193	14	100% *n*-Octyl alcohol
27	Capric acid[a]	None	164	169	2.5	70% *n*-Decyl alcohol, 30% *n*-decyl caproate
28	Capric acid[b]	Water (25 ml.) and *p*-dioxane	137	173	3.5	100% *n*-Decyl alcohol
29	Lauric acid[a]	None	145	177	8	42% *n*-Dodecyl alcohol, 58% *n*-dodecyl laurate
30	Lauric acid[b]	Water (10 ml.) and *p*-dioxane	160	186	10	100% *n*-Dodecyl alcohol
31	Stearic acid[a]	None	167	268	5	36% *n*-Octadecyl alcohol, 54% *n*-octadecyl stearate
32	Stearic acid[b]	Water (10 ml.) and *p*-dioxane	265	245	23.5	43% *n*-Octadecyl alcohol, 29% stearic acid, 28% unknown
33	Benzoic acid[a]	Benzene	254	190	15	91% Toluene
34	Phenylacetic acid[a]	None	149	160	14	78% β-Phenylethyl alcohol, 22% β-phenylethyl phenylacetate
35	Lactic acid[a]	None	150	258	8	84% Propylene glycol, 16% lactic acid and lactide
36	Crotonic acid[a]	None	163	150	12	30% *n*-Butyl alcohol, 70% *n*-butyl butyrate
37	Levulinic acid[a]	None	106	150	18	71% γ-Valerolactone, 29% polymeric esters
38	Glycine[a]	*p*-Dioxane	220	326	14	72% Glycine, 6% ethanol, 11% β-aminoethyl glycinate
39	β-Alanine[a]	*p*-Dioxane	250	300	8	24% β-Alanine, 35% *n*-propyl alcohol, 41% *n*-propyl 3-aminopropionate
40	β-Alanine[b]	Water (50 ml.)	250	210	32	92% *n*-Propyl alcohol, 4% β-alanine, 4% unknown
41	Maleic acid[a]	None	196	286	12	91% Succinic acid, 9% 1,4-butanediol
42	Succinic acid[a]	*p*-Dioxane	205	184	30	61% Butyrolactone, 33% 1,4-butanediol, 6% polyesters
43	Succinic acid[a]	None	210	245	4	94% 1,4-Butanediol, 6% *n*-butyl alcohol
44	Succinic acid[a]	Water	210	258	6.5	13% Tetrahydrofuran, 59% 1,4-butanediol, 3% polyesters
45	Glutaric acid[a]	*p*-Dioxane	210	184	5	82% 1,5-Pentanediol, 18% polyesters
46	Glutaric acid[b]	Water (50 ml.)	250	179	50	100% 1,5-Pentanediol

TABLE V (*Continued*)

No.	Substrate	Solvent	Avg. Temp. (°C.)	Avg. Pressure (atm.)[g]	Time (hr.)	Yields, %, Product(s)
47	Ethyl acetate[b]	None	148	191	11	100% Ethanol
48	Ethyl benzoate[b]	Cyclohexane	250	290	48	89% Benzyl alcohol, 11% ethyl benzoate[e]
49	Isobutyl formate[a]	None	165	167	2	35% Methanol, 35% isobutyl alcohol
50	Isobutyl isobutyrate[a]	None	151	340	3	57% Isobutyl alcohol
51	Azobenzene[b]	Cyclohexane	125	249	24	92% Aniline
52	Hydrazobenzene[b]	Cyclohexane	185	280	42	97% Aniline
53	Acetamide[b]	Cyclohexane	217	312	6	39% Ethylamine[f]
54	Acetanilide[b]	Cyclohexane	170	280	52	66% *N*-Ethylaniline, 34% aniline[e]
55	*N*-Ethylacetanilide[b]	Ethanol	245	352	22	95% *N,N*-Diethylaniline, 5% unidentified

[a] Amount of catalyst used: 1.0 g. Re/mole of substrate. [b] Amount of catalyst used: 1.0 g. Re/50 g. substrate. In later work it was deemed more desirable in comparing compounds of greatly differing molecular weights to use weight rather than molar ratios. [c] A small button of translucent white waxy resin was obtained, softening at 106° and melting at 121–122° with slow (1/2 hr.) heating. (*cf.* 111° melting of high pressure process polyethylene; 132°, Ziegler process polyethylene). *Anal.* Found: C, 85.4, 85.60%; H, 14.50, 14.53%. Calcd. for $C_{100}H_{202}$: C, 85.51%; H, 14.49%. Its properties and analysis suggest it to be a high molecular weight paraffinic resin. If this substance were a straightchain hydrocarbon its high melting point as well as its analysis would suggest a chain length of >70 carbon atoms (heptacontane melts at 105°); however, the molecular weight (Rast) indicates 30–33 carbon atoms. There seems reason to question the validity of the molecular weight determination in this case. [d] This run consisted of the hydrogenation of an equimolar mixture of the two acids. The yield data are adjusted to 100% excluding the methane and water formed by hydrogenation of most of the formic acid. No "polymethylene" was formed in this run. [e] Yields given are based on residue obtained after evaporating off the ethanol and cyclohexane. [f] A leak which developed during the hydrogenation resulted in the loss of considerable of the volatile amine while the reaction was in progress. [g] Total pressure in the system at the temperature shown.

heptoxide directly to a substrate followed by hydrogenation is presented in Table V. This is the most significant group of findings reported in this paper not only because of the simplicity of the procedures but also because of some of the remarkable transformations which can be accomplished.

In every case the rhenium can be recovered from the reactor as an insoluble black following hydrogenation. Analysis showed a rhenium content of 83.82, 83.75, 82.80% for the rhenium black obtained in the hydrogenation of acetic acid without solvent. No oxidation state determinations were made. The rhenium black resulting when carrying out the hydrogenation of acetic acid in water solution gave values of 88.17, 89.20, 90.54% rhenium in successive examples with corresponding values of 5.43, 5.19, and 5.31 equivalents of dichromate required for oxidation to +7 state. This suggests that the catalyst may be a hydrated rhenium monoxide.

Benzene and olefins are reduced by rhenium heptoxide *in situ* more difficultly than with many common catalysts. Nitrobenzene is much more difficultly reduced by rhenium heptoxide *in situ* than by the catalyst obtained *ex situ*. The peculiar, adverse effect of ethanol solvent in this reaction is common to other rhenium oxide catalysts which have been studied. Acetophenone is converted completely to complex condensation products, doubtless because of the highly acidic character of rhenium heptoxide.

Most outstanding among the reactions which rhenium heptoxide derived catalysts promote is the extraordinarily facile reduction of carboxylic acids to alcohols. These transformations occur at 150–170° for monocarboxylic acids, 200–250° for dicarboxylic acids, under 135–270 atm. total operating pressure in a few hr. Virtually no unreduced acid survives the reaction.

The effect of carrying out the hydrogenations of acids in the presence of solvent water as contrasted to reactions run without added water is particularly noteworthy. (*Cf.* Table V, Nos. 10, 11; 17, 18; 23, 24; 25, 26; 27, 28; 29, 30; 31, 32; 39, 40; 45, 46.) While the hydrogenations run on the anhydrous acids always resulted in some by-product ester formation, those run in water solvent gave markedly reduced ester formation, or in most cases no ester by-product at all. The mechanism of this effect is not definitely understood although a number of experiments were carried out testing various hypotheses.

The conditions for carrying out these hydrogenations are in general 100–250° lower than required for the same or closely similar transformations previously recorded, with the exception of the use of ruthenium dioxide.[19] In the latter case the conditions of time, temperature, and yields for a much more limited set of reported examples are comparable, but the pressures required appear to be much greater.

The rhenium heptoxide catalyzed hydrogenation of carboxylic acids is apparently general for the normal homologous series beginning with acetic acid and also for not too highly branched isomers. It is also successful with dicarboxylic acids.

The reduction occurs with various substituted acids: phenylacetic acid is reduced to β-phenylethyl alcohol without affecting the aromatic ring; lactic acid yields propylene glycol; crotonic acid yields *n*-butyl alcohol; levulinic yields predominantly γ-valerolactone. The amino acids, glycine, and

TABLE VI

COMPARISON OF THE CATALYTIC ACTIVITY OF PLATINUM DIOXIDE, RANEY NICKEL, COPPER–CHROMIUM OXIDE, AND RHENIUM HEPTOXIDE IN THE HYDROGENATION OF FIVE REPRESENTATIVE SUBSTRATES

Substrate	Catalyst	Amt. Cat. g./mole	Avg. Temp. (°C.)	Avg. Pressure (atm.)[a]	Time (hr.)	% Yields, Product
Nitrobenzene	PtO_2	1.0	25	4[b]	0.25	100% Aniline
	Ni	3.0	25	4[b]	0.25	100% Aniline
	$CuO{\cdot}CuCr_2O_4$	8.0	205	163	1.5	98% Aniline
	Re_2O_7[e]	2.1	100	159	12	90% Aniline
Styrene	PtO_2	1.0	25	4[b]	0.25	100% Ethylbenzene
	Ni	3.0	30	4[b]	1.5	100% Ethylbenzene
	$CuO{\cdot}CuCr_2O_4$	8.0	122	146	0.33	82% Ethylbenzene
	Re_2O_7[e]	1.0	108	156	3.5	100% Ethylbenzene
Cyclohexanone	PtO_2	1.0	25	4[b]	5	91% Cyclohexanol
	Ni	3.0	60	4[b]	3	92% Cyclohexanol
	$CuO{\cdot}CuCr_2O_4$	8.0	115	150	0.25	94% Cyclohexanol
	Re_2O_7[e]	2.5	64	143	12	84% Cyclohexanol
Isobutyl isobutyrate	PtO_2	1.0	320	252	5	5% Isobutyl alcohol
	Ni	2.5	315	368[c]	4.5	0% Isobutyl alcohol
	$CuO{\cdot}CuCr_2O_4$	21.0	180	272[c]	2.5	100% Isobutyl alcohol
	Re_2O_7[f]	1.0	151	340[d]	3	57% Isobutyl alcohol
Acetic acid	PtO_2	1.0	300	258	12	0% Ethanol, 7% ethyl acetate
	Ni	3.0	Catalyst dissolves—no hydrogenation			
	$CuO{\cdot}CuCr_2O_4$	8.0	250	306[c]	21	0% Ethanol, 20% ethyl acetate
	Re_2O_7[f]	2.0	150	168	10	100% Ethanol

[a] Total pressure during hydrogenation at the temperature given. Initial pressure of hydrogen at room temperature was 136 atm. unless otherwise specified. [b] Initial hydrogen pressure was 4 atm. at room temperature. [c] Initial hydrogen pressure was 204 atm. at room temperature. [d] Initial hydrogen pressure was 272 atm. at room temperature. [e] Reduced *ex situ*. [f] *In situ*.

β-alanine, are anomalous in that the alcohol obtained is deaminated. Di- and trichloroacetic acids were not successfully reduced, but both trifluoroacetic acid and heptafluorobutyric acids gave the corresponding alcohols in excellent yields.

Formic acid is exceptional in that the temperature required for reduction is nearly 100° above that for other monocarboxylic acids and the principal reduction product is methane accompanied by small amounts of "polymethylene," a high molecular weight, paraffinic resin. The addition of small amounts of (5 mole %) di-*tert*-butyl peroxide to the formic acid did not alter the amount of "polymethylene" formed, but that which was obtained had a much lower molecular weight.

The highly branched trimethylacetic (pivalic) acid could not be reduced to any recognizable product even at 264°. Some uncharacterized resinous material resulted. This is not unexpected, as there is no way for the trimethylacetic acid molecule to be absorbed flat on the catalytic surface.

The optimum temperature for alcohol formation from acetic acid was 150°; at 240° it was slowly converted to ethane.

A comparison of the catalytic activity of platinum dioxide, Raney nickel, copper–chromium oxide and rhenium heptoxide (Table VI). These data represent actual experimental comparisons made in our laboratories in order to minimize the effects of apparatus and procedure. Rhenium heptoxide reduced *ex situ* is less effective in catalyzing reduction of nitrobenzene, styrene, or cyclohexane than either platinum dioxide or Raney nickel, more effective than copper–chromium oxide. Copper–chromium oxide is the best in the reduction of isobutyl isobutyrate with rhenium heptoxide next; platinum dioxide and Raney nickel fail completely. Against acetic acid rhenium heptoxide *in situ* is the only one which is effective.

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[CONTRIBUTION FROM THE ENGELHARD INDUSTRIES RESEARCH LABORATORIES]

Low Pressure Hydrogenation of Ketones with Platinum Metal Catalysts

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Aliphatic, aromatic, and α,β-unsaturated ketones were hydrogenated at atmospheric pressure and room temperature in a number of solvents by palladium, platinum, rhodium, and ruthenium on high-surface carbon. Conditions for rapid and selective hydrogenation were determined.

Ketones have often been hydrogenated with platinum metal catalysts, but no previous systematic study has been made of the interdependence of solvent and catalyst on the rate and selectivity of hydrogenation. This paper examines the rate and course of low pressure hydrogenations in various solvents of three types of ketones by palladium, platinum, rhodium, and ruthenium on high-surface carbon.

From the results, a combination of catalyst and solvent that will give rapid and selective hydrogenation of aliphatic, aromatic, or α,β-unsaturated ketones can be chosen. The work was directed mainly toward laboratory preparations, and factors such as resistance to poisoning, catalyst life; effect of temperature and pressure, which would be of interest in commercial applications, was not examined. For convenience a large ratio of catalyst to substrate was used in determining the rates, but experience has shown the relative effectiveness of the various catalysts will be maintained, when a ratio more suitable for synthesis is used.

EXPERIMENTAL

The catalysts studied were all commercial preparations, manufactured by Engelhard Industries, of 5% reduced metal on high-surface carbon (Norit), and carried the designating numbers, 5% Pd-#3433, 5% Pt-#3635, 5% Rh-#3525, 5% Ru-#2403. Ruthenium catalysts were activated immediately before use by shaking the catalyst and solvent together under one atmosphere pressure of hydrogen for 1 hr., after which the flask was flushed with nitrogen and the substrate was added. The other catalysts were used directly as received. Electrolytic hydrogen and reagent grade solvents were used without further purification. The substrates were redistilled before use.

Rate measurements were made by a differential manometer using sensitive strain gauges with an electronic recording potentiometer. One arm of the manometer was connected to a flask containing the catalyst, solvent, and substrate, and the other arm to a flask containing only catalyst and solvent. Any contribution to the rate by adsorption of hydrogen on the catalyst was thus eliminated. All rate measurements were at 25° and an initial pressure of 1 atm., with 300 mg. of catalyst, 0.004 mol. of substrate, and 100 ml. of solvent. During the course of the experiment the pressure fell 5 to 10%. In all cases agitation by shaking was sufficiently vigorous to eliminate any contribution of hydrogen transport on the observed reaction rates. Identification of the product was made by comparison of the infrared spectrum with that of known samples. In the rate experiments a large amount of catalyst, relative to the substrate, was used to provide a convenient rate and to minimize the chance of a small amount of poison materially affecting the rate. One hydrogenation was made with each catalyst and with each compound using double the amount of substrate (and hence double any poison), but no appreciable change in rate was observed.

RESULTS AND DISCUSSION

In Table I the rates[1] of hydrogenation of cyclopentanone, cyclohexanone, and methyl isobutyl ketone are given.

All reductions were continued, except when the rate was very slow, until hydrogenation ceased. A few reactions, noted in Table I by p′, showed evidence of poisoning and the rate gradually declined. These experiments showing gradual poisoning are reproducible. The shape of the rate curve was unaltered by doubling the amount of solvent. All other rates were zero order over almost the entire range. Under the conditions employed no hydrogenolysis occurred and the alcohol was the only product. The rates of hydrogenation of these ketones depend markedly on catalyst, substrate, and solvent.

Palladium was ineffective in all solvents tested,[2] with the technique used. The failure of palladium to hydrogenate these aliphatic ketones might be attributed to exceptionally strong adsorption of the ketone, if the ketone were added dropwise instead of all at once to the palladium in solvent, hydrogenation would proceed at a slow but tolerable rate. Palladium has been used to hydrogenate ketones, but usually at elevated temperature and pressures and for long periods of time. This is not the catalyst of choice.

Platinum in aqueous acid hydrogenated all three compounds satisfactorily, but, in base, poisoning was observed with cyclopentanone and methyl isobutyl ketone. This poison is formed during the hydrogenation and is not initially in the substrate; when the ratio of substrate and solvent to catalyst was doubled, the rate curve was unchanged. A similar poisoning of platinum in neutral or basic solution was observed in the hydrogenation of

(1) The rate is expressed in ml. of hydrogen absorbed per min. p′ indicates poisoning. A slow decline in rate was observed as reduction progressed.

(2) Colloidal platinum and palladium have also been found ineffective for carbonyl reduction in alcohol and acetic acid. Z. Csüros and I. Sello, *Hung. Acta Chim.*, I, 27 (1949).

TABLE I

RATE[1] OF HYDROGENATION OF ALIPHATIC KETONES

	Catalyst											
	5% Pd/C			5% Pt/C			5% Rh/C			5% Rn/C		
Solvent	I	II	III	I	II	III	I	II	III	I	II	III
CH_3COOH	0.2	0.0	0.0	0.2	7	0.3	0.2	11	p′	0.0	0.0	0.0
H_2O	0.0	0.1	0.0	6	22	18	16	25	15	26	24	11
0.5*N* NaOH	0.2	p′	0.2	p′	20	p′	20	26	22	14	24	45
0.5*N* HCl	0.0	0.1	0.1	11	22	10	5	16	4	0.2	p′	0.2
CH_3OH	0.0	0.2	0.0	0.2	0.2	0.3	0.1	0.3	0.3	p′	0.1	p′
$CH_3CO_2C_2H_5$	0.0	0.1	0.0	0.2	0.3	0.2	0.0	0.2	0.0	0.0	0.1	0.0

I = Methyl isobutyl ketone. II = Cyclohexanone. III = Cyclopentanone.

TABLE II

RATE[1] OF HYDROGENATION OF AN UNSATURATED KETONE AND ALCOHOL

		Catalyst							
		5% Pd/C		5% Pt/C		5% Rh/C		5% Ru/C	
Solvent		I	II	I	II	I	II	I	II
CH_3COOH	C=C	55	45	44	23	44	42	0.0	0.0
	C=O	0.2	—	0.1	—	0.2	—	0.0	—
H_2O	C=C	55	21	44	23	44	23	28	16
	C=O	0.0	—	6	—	10	—	7	—
0.5*N* NaOH	C=C	45	9	8	6	20	16	16	7
	C=O	0.2	—	p′	—	20	—	16	—
0.5*N* HCl	C=C	60	32	40	25	36	16	p′	p′
	C=O	0.0	—	12	—	5	—	0.1	—
CH_3OH	C=C	65	—	56	—	48	—	10	—
	C=O	0.0	—	0.1	—	0.1	—	p′	—
$CH_3COOC_2H_5$	C=C	80	20	60	20	80	21	0.0	0.3
	C=O	0.0	—	0.0	—	0.0	—	0.0	—

I = Mesityl oxide. II = 4-Methyl-3-pentene-2-ol.

oximes,[3] and unsaturated amines.[4] In these instances poisoning was reasonably attributed to formation of the strongly basic amine, but other compounds formed in the reduction may have also contributed to the poisoning.

Rhodium and ruthenium, unlike platinum, hydrogenate most rapidly in neutral or basic solution and are relatively slow in acid. In favorable environment both rhodium and ruthenium were exceptionally active for carbonyl reduction, and are certainly the most desirable metals to use in a nonacidic solution. The statement[5] has been made that rhodium will not hydrogenate ketones unless they are activated. This conclusion was reached because alcohol was used exclusively as the solvent.

Cyclohexanone hydrogenates more rapidly than methyl isobutyl ketone, perhaps because of less steric hindrance. Except in alkaline solution, cyclohexanone also hydrogenates more rapidly than cyclopentanone. The more rapid reduction of cyclohexanone is in accord with the generalization,[6] based partly upon kinetics, that exo double bonds in 5-membered rings are relatively stable; exo double bonds in 6-membered rings, relatively unstable.

α,β-Unsaturated Ketones. The effect of conjugation on the rate of reduction of an α,β-unsaturated ketone and the best way of achieving a selective hydrogenation was examined using mesityl oxide. This material could be reduced to the saturated alcohol by several routes, but, in fact, reduction proceeded entirely through the saturated ketone. In Table II, the rates of hydrogenation of 4-methyl-3-pentene-2-ol, and of mesityl oxide are given. The rate of absorption of the second mole of hydrogen by mesityl oxide is, in general, that to be expected if the intermediate product is methyl isobutyl ketone. The reduction is in all cases highly selective. When the reaction was interrupted after absorption of one mole of hydrogen, only methyl isobutyl ketone was found; there was no saturated or unsaturated alcohol.

The rate of absorption of the first mole of hydrogen is, therefore, the rate of olefin saturation. These data do not preclude the possibility that the carbonyl was involved in the olefin reduction through 1,4 addition. In every case the rate of hydrogenation of the olefin is faster for the unsaturated ketone than it is for the unsaturated alcohol, although both probably have similar steric requirements.

(3) E. Breitner, E. Roginski, and P. N. Rylander, *J. Chem. Soc.*, in press.

(4) J. M. Devereux, K. R. Payne, and E. R. A. Peeling, *J. Chem. Soc.*, 2845 (1957).

(5) W. P. Dunworth and F. F. Nord, *J. Am. Chem. Soc.*, **74**, 1459 (1952).

(6) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

TABLE III

RATE[1] OF HYDROGENATION OF ACETOPHENONE

Solvent		Catalyst			
		5% Pd/C	5% Pt/C	5% Rh/C	5% Ru/C
CH_3COOH	C=O	30	p′	[26	0.0
	CH—OH	3	p′	[26	0.0
	ring	0	p′	[7	0.0
H_2O	C=O	11	10	[26	9
	CHOH	0	1	[26	[2
	ring	0	—	[11	[2
0.5*N* NaOH	C=O	3	4	[13	9
	CHOH	0	0	[4	[2
	ring	0	—	[4	[1
0.5*N* HCl	C=O	24	12	[11	0.1
	CHOH	0	12	[7	0
	ring	0	2	[3	0
CH_3OH	C=O	24	12	[11	0.1
	CHOH	0	12	[7	0
	ring	0	2	[3	0
$CH_3COOC_2H_5$	C=O	0.8	2	[22	0.1
	CHOH	0	1	[8	0
	ring	0	0	[6	0

The rate curves for hydrogenation by rhodium and ruthenium in base are interesting. These catalysts hydrogenate at constant rate over the entire reaction, which would imply that 2 mol. of hydrogen are absorbed by the substrate in a single residence on the catalyst and give the saturated alcohol directly. This was not the case, however. When the reaction was stopped after 1 mol. of hydrogen was absorbed, methyl isobutyl ketone was the only product. The constant rate arose fortuitously because mesityl oxide and methyl isobutyl ketone hydrogenate separately at the same rate. But in competition with mesityl oxide, methyl isobutyl ketone is not hydrogenated at all, because of the much stronger adsorption of the unsaturated ketone by the catalyst. Even when the initial reaction mixture consisted of three parts methyl isobutyl ketone and one part mesityl oxide, the olefin was first completely reduced and subsequently the carbonyl.

AROMATIC KETONES

Selective hydrogenation of aromatic ketones presents a more difficult problem than selective hydrogenation of aliphatic or α,β-unsaturated ketones. In aromatic ketones hydrogenolysis and reduction of the ring occur readily, as can be seen from the data for the hydrogenation of acetophenone[7] given in Table III.

Because two or more reactions do occur simultaneously, the inflections in the rate curves do not always occur at integral numbers and, furthermore, the change in rate is not always abrupt. To this extent the rates given in Table III are idealized and thus some of the rates in the table were put in brackets indicating concurrent reductions. Pure products cannot be expected in these cases, although one may be preponderant. However, they adequately describe the extent of hydrogenation and give approximately the relative rates of formation of phenylethyl alcohol (1 mol. of hydrogen absorbed), ethylbenzene (2 mol.), α-cyclohexylethanol (4 mol.), and ethylcyclohexane (5 mol.). Platinum in acetic acid hydrogenated acetophenone at a rapid but constantly declining rate; it is noted, therefore, only by p′.

Palladium is the best catalyst for side-chain hydrogenation without ring saturation. Under these conditions acetophenone does not absorb more than 2 mol. of hydrogen, and by using the proper solvent it stops abruptly after 1 mol. to give phenylethyl alcohol. The much faster reduction by palladium of aromatic ketones compared to aliphatic is striking, especially when contrasted with the much smaller, and sometimes opposite, changes with the other catalysts.

Rhodium is seen to be very active for ring hydrogenation,[8] and would be the catalyst of choice for total reduction. Reductions with rhodium, stopped after 1, 2, or 3 mol. of hydrogen absorption gave mixtures in which some ring hydrogenation occurred. When the reduction was done without solvent or in methanol and stopped after four moles about an 80% yield of cyclohexyl methylcarbinol was obtained.

NEWARK, N. J.

(7) The hydrogenation of acetophenone in dioxane and acetic acid with palladium and platinum black has been studied, W. Theilacker and H. G. Drossler, *Chem. Ber.* **87**, 1676 (1954). The course of hydrogenation was shown to be profoundly influenced by acids and bases.

(8) a. H. A. Smith and R. G. Thompson, "Advances in Catalysis," Academic Press Inc., New York, 1957, Vol. IX, P. 727. b. G. Gilman and G. Cohn, "Advances in Catalysis," p. 733.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, ETHYL CORPORATION]

Studies of Metallosiloxane Polymers

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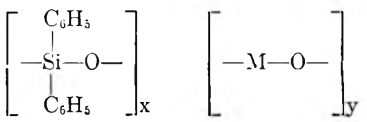
The preparation of some new metallosiloxane polymers has been achieved by the reaction of disodium diphenylsilanediolate with metal chlorides and by the reaction of diphenylsilanediol with metal alkyls. Most of these polymers decomposed rather easily to form siloxane derivatives and metal oxides; in a few cases they were obtained only as short-lived intermediates. The ease of decomposition of these polymers is compared with that of the structurally analogous silicones.

The study of metallosiloxane polymers is of considerable interest due to their possible high thermal stability, particularly in view of the stability of the structurally related silicones.[1] It has been supposed that modifications of the silicone structure by the introduction of other elements into the siloxane chain might result in polymers which are even more stable than the silicones.

Aluminosiloxane,[2] antimonosiloxane,[3] arsonosiloxane,[4] borosiloxane,[5] stannosiloxane[6] and titanosiloxane[2a,6b,7] polymers have been reported. In most of these polymers the hetero elements bear organic substituents, but there have been few reports[2,6a] of metallosiloxanes in which the metal atoms are unsubstituted. In the present work the search for thermally stable polymers has been extended to several new metallosiloxane systems of the type indicated by formula I, where M is Sn, Pb, Mg, Cu, Zn, or Hg.



I

Two synthetic approaches were investigated: (1) the reaction of disodium diphenylsilanediolate with metal chlorides, and (2) the reaction of diphenylsilanediol with metal alkyls. The results obtained provide some information concerning the mode of decomposition of these polymers and permit a comparison of their ease of decomposition with that of the silicones.

The reaction of disodium diphenylsilanediolate with stannous chloride gave a stannosiloxane polymer (I. M = Sn); a somewhat similar material had been prepared previously by a different method.[6a] With lead chloride, however, the products were a mixture of a plumbosiloxane polymer (I. M = Pb), a phenyl-substituted cyclic siloxane (II) and lead oxide. Magnesium chloride gave some evidence of metallosiloxane polymer formation, but the products ultimately isolated were the same cyclic siloxane (II) and magnesium oxide. The reaction with cupric chloride proceeded through a short-lived, colored intermediate and gave octaphenylcyclotetrasiloxane and cupric oxide. The product from the reaction with zinc chloride were hexaphenyltrisiloxane-1,5-diol and zinc oxide. With mercuric chloride a colored intermediate was again formed which decomposed to give octaphenylcyclotetrasiloxane; definite evidence for the concurrent formation of mercuric oxide was not obtained.

These results suggest that the reaction of disodium diphenylsilanediolate with metal chlorides proceeds through a polymeric intermediate in which the expected Si—O—M bonds are formed. In most of the cases investigated, however, the polymer easily decomposes to form a siloxane derivative and, except in the case of mercury, the corresponding metal oxide. The isolation of polymers in some cases where the presence of both silicon and the other metal could be confirmed, and the formation of colored intermediates in others, are considered as evidence for this interpretation. In addition, the observation that different metal chlorides lead to different siloxane derivatives indicates that considerably more than simple silanediolate condensation is involved.

Further evidence for these interpretations was obtained from the reaction of diphenylsilanediol with metal alkyls, a reaction which was investigated as another approach to these metallosiloxane polymers. Diethylmagnesium reacted with diphenylsilanediol to form a metallosiloxane polymer (I. M = Mg) which decomposed rather easily upon heating to give the cyclic siloxane (II) and magnesium oxide. Diethylzinc also formed a metallosiloxane polymer (I. M = Zn) which decomposed somewhat less

(1) D. W. Scott, *J. Am. Chem. Soc.*, 68, 356 (1946).

(2) (a) K. A. Andrianov, A. A. Zhdanov, N. A. Kurasheva, and V. G. Deluva, *Doklady Akad. Nauk S.S.S.R.*, 112, 1050 (1957); (b) K. A. Andrianov and A. A. Zhdanov, *Doklady Akad. Nauk S.S.S.R.*, 114, 1005 (1957); (c) K. A. Andrianov and T. N. Ganina, *Izvest. Akad. Nauk S.S.S.R.*, 74 (1956).

(3) F. A. Henglein, R. Lang, and K. Scheinost, *Makromol. Chem.*, 18–19, 102 (1956).

(4) R. M. Kary and K. C. Frisch, *J. Am. Chem. Soc.*, 79, 2140 (1957).

(5) R. W. Upson, U. S. Patent 2,517,945 (1947); F. A. Henglein, R. Lang, and K. Scheinost, *Makromol. Chem.*, 15, 177 (1953); K. A. Andrianov and L. M. Volkova, *Izvest. Akad. Nauk S.S.S.R.*, 303 (1957); M. G. Voronkov and V. N. Zgonnik, *Zhur. Obschei Khim.*, 27, 1476 (1957).

(6) (a) F. A. Henglein, R. Lang, and L. Schmack, *Makromol. Chem.*, 22, 103 (1956); (b) K. A. Andrianov, T. N. Ganina, and E. N. Khrustaleva, *Izvest. Akad. Nauk S.S.S.R.*, 798 (1956).

(7) H. C. Gulledge, U. S. Patent 2,152,058 (1958).

rapidly when heated to give hexaphenyltrisiloxane-1,5-diol and zinc oxide. Since the decomposition products obtained from these polymers are identical to those isolated in the corresponding silanediolate–metal chloride reactions, it appears likely that the silanediolate–metal chloride reactions also proceed through similar polymeric intermediates.

The polymeric nature of the metallosiloxanes isolated was inferred from their resinous nature and from their tendency to form viscous solutions in organic solvents. Cryoscopic molecular weight determinations or solution viscosity measurements could not be made due to a very facile, slight decomposition in solution to form minute quantities of interfering, insoluble solids.[8]

The organic solubility of the polymers isolated which contained both silicon and a hetero metal, and the formation of metal oxides upon their decomposition, strongly indicate that these materials have the metallosiloxane structure.[9] The consistency of the analytical data with this structure in cases where pure polymers were obtained may also be mentioned as evidence for this interpretation. The reaction of alkali metal salts of the mono-functional silanols with metal halides has in fact been shown previously to yield monomeric metallosiloxanes.[10] Determination of structure by infrared study was precluded by the tendency of most of the polymeric products to decompose to a slight extent upon standing to form the interfering, insoluble solids mentioned above.

It is of interest to compare the decomposition of the metallosiloxane polymers with that of the structurally analogous silicones. It appears from the results obtained that the decomposition of the metallosiloxanes investigated in this work occurs by scission of the Si—O—M bonds. This result is quite similar to that observed in the thermal decomposition of linear dimethylpolysiloxanes, which produces cyclic siloxanes,[1,11] apparently by rupture of Si—O—Si bonds. The ease of decomposition of these metallosiloxanes, however, is considerably greater than that of the silicones, implying a lower thermal stability for Si—O—M bonds in these polymers than the Si—O—Si bonds in the silicones. It appears unlikely that the decomposition of the metallosiloxanes could have been caused by hydrolysis or the presence of trace impurities, so the inference that we are dealing here with thermal decomposition seems valid. The slight decomposition of these polymers upon standing, however, could be due to trace impurities or adventitious moisture, but we are inclined to believe that it is a reflection of the possibly different thermal stabilities of the various polymeric fractions.

EXPERIMENTAL[12]

Reaction of disodium diphenylsilanediolate with metal chlorides. A. *With stannous chloride.* To a stirred solution of 9.4 g. (0.05 mole) of anhydrous stannous chloride in 100 ml. of anhydrous acetone was added in portions 13.0 g. (0.05 mol.) of disodium diphenylsilanediolate,[10] and the mixture was refluxed in a dry atmosphere with stirring for 2 hr. The insoluble solids were filtered and washed thoroughly with boiling acetone, then with boiling benzene, and finally with water; evaporation of the aqueous washings gave 5.0 g. of sodium chloride (86%). The 0.1 g. of pale yellow powder remaining after this treatment was shown by qualitative analysis[13] to contain both tin and silicon, a result which was not altered by repeated extraction with boiling benzene.

Evaporation of the combined acetone filtrate and acetone and benzene extracts gave 16.9 g. of a brittle, yellow resin. The resin was dissolved in benzene, filtered to remove traces of insoluble solids, and precipitated by adding the benzene solution to an excess of petroleum ether. There was obtained 14.3 g. (86%) of a stannosiloxane polymer as a light colored powder upon filtration and drying.

Anal. Calcd. for $[(C_6H_5)_2SiO]_6[SnO]_4$: Si, 9.14; Sn, 31.1. Found: Si, 9.20; Sn, 31.0.

The formula $[(C_6H_5)_2SiO]_6[SnO]_4$ indicated by the analysis of course represents an average composition, probably of many molecular species. That tin was incorporated with silicon in a large proportion of these species was indicated by the benzene solubility of the material and by its separation into several fractions, all of which contained both silicon and tin, by numerous reprecipitations from benzene–petroleum ether mixtures.

Reliable values for the molecular weight of this polymer could not be obtained since in solution there was very rapidly formed traces of an insoluble, pale yellow precipitate which was found by analysis[13] to contain both tin and silicon. The resinous nature of the stannosiloxane and its tendency to form viscous solutions, however, indicated that it was undoubtedly polymeric.

The stannosiloxane polymer was stable for 1 hr. up to around 175° when it darkened somewhat. This darkening also occurred at lower temperatures upon longer heating.

B. *With other metal chlorides.* The procedure used in reactions with other metal chlorides was quite similar to that in the above reaction with stannous chloride. Pertinent details are shown in Table I.

Cyclic siloxane (II). Some comment should be made concerning the nature of the cyclic siloxane (II). Its identity as a phenylsubstituted cyclic siloxane was established from its empirical formula and from infrared data. The presence of a strong absorption in the 9.15–9.25 micron region in the infrared, which is characteristic of cyclic siloxanes of larger rings size than the trimer,[14] and the absence of hydroxyl

(8) The referee has suggested that these solids are probably metal oxides. We are in substantial agreement with this view. In most cases the quantity of solids formed was too small for identification; in a few cases where larger amounts were obtained they were found to be metal oxides.

(9) The referee has pointed out that the metallosiloxane polymers may be considered as metal "salts" of the silanediol. This implies a regularly alternating arrangement of silicon and metal atoms in the polymeric chain. In view of the methods of preparation employed, it seems likely that the polymers first formed must have this structure, but since they decompose to eliminate the elements of a metal oxide it appears that the polymers ultimately isolated are better represented by the more general formula I.

(10) W. S. Tatlock and E. G. Rochow, *J. Org. Chem.*, **17**, 1555 (1952).

(11) W. Patnode and D. F. Wilcock, *J. Am. Chem. Soc.*, **68**, 358 (1946).

(12) All melting points are corrected.

(13) The qualitative analyses for the metals were obtained by examination of the emission spectra of the compounds in question.

(14) C. W. Young, *et al.*, *J. Am. Chem. Soc.*, **70**, 3758 (1948).

TABLE I

REACTION OF DISODIUM DIPHENYLSILANEDIOLATE WITH METAL CHLORIDES

Metal Chloride	Mol.[a]	Solvent	Time, Hr.	Temp., °C.	Products[b]	Yield, G.[c]
$PbCl_2$	0.075	Dimethyl sulfoxide	8	80	Plumbosiloxane polymer-cyclic siloxane (II) mixture[d]	20.5
					Lead oxide	2.7
$MgCl_2$	0.05	Acetone	3	Reflux	Cyclic siloxane (II)[e]	2.5
					Magnesium oxide	0.9
$CuCl_2$	0.025	Acetone	2	Reflux	Octaphenylcyclotetrasiloxane[f]	4.2
					Cupric oxide	1.9
$ZnCl_2$	0.025	Acetone	3	Reflux	Hexaphenyltrisiloxane-1,5-diol[g]	1.7
					Zinc oxide	1.9
$HgCl_2$	0.025	Acetone	2	Reflux	Octaphenylcyclotetrasiloxane[f]	3.8
					Inorganic Hg compound[h]	3.9

[a] Equimolar ratios of metal chloride and diol salt were used. [b] NaCl was also a product. [c] The yields given refer to purified products. [d] *Anal.* Found: Si, 8.11; Pb, 30.8. Calcd. values are 6.65% Si and 49.2% Pb for $[(C_6H_5)_2Si—O—Pb—O—]_x$ and 14.16% Si for $[(C_6H_5)_2SiO]_x$. Fractional reprecipitation of mixture from benzene–petroleum ether gave a few mg. of the cyclic siloxane (II), m.p. 187.5–189.5°. [e] Isolated from 10.7 g. of colorless, nearly transparent resin (containing both Mg and Si) by treating the resin with boiling benzene, filtering the MgO formed and recrystallizing the benzene-soluble material from benzene–petroleum ether. M.p. 188–189.5°. *Anal.* Calcd. for $C_{12}H_{10}SiO$: C, 72.67; H, 5.08; Si, 14.16. Found: C, 73.20; H, 5.74; Si, 14.35. [f] Recrystallized from acetone, m.p. 202–202.5°; did not depress mixture m.p. with authentic octaphenylcyclotetrasiloxane. *Anal.* Calcd. for $C_{12}H_{10}SiO$: C, 72.67; H, 5.08; Si, 14.16. Found: C, 72.35; H, 5.44; Si, 13.78. [g] Purified by recrystallization from benzene–petroleum ether, m.p. 111–112°. *Anal.* Calcd. for $C_{36}H_{32}Si_3O_4$: C, 70.55; H, 5.26; Si, 13.75. Found: C, 70.42; H, 5.52; Si, 14.14. Lit. m.p. 111° [C. A. Burkhard, *J. Am. Chem. Soc.*, 67, 2173 (1945)]. Showed hydroxyl absorption at 2.75–3.00 microns in infrared and the doublet absorption at 9–10 microns characteristic of a linear siloxane [R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 124 (1949)]. [h] Contained 93.2% Hg; insoluble in warm dilute hydrochloric acid, in common organic solvents, and did not contain halogen. Did not appear to be HgO due to its white color and because it left a black residue on ignition.

absorption in the 2.75–3.00 micron region established the cyclic nature of the compound. That it was not identical with hexaphenylcyclotrisiloxane, which melts at 188–189°, was further shown by the fact that a mixture with authentic hexaphenylcyclotrisiloxane[15] melted at 163–169°. Cryoscopic molecular weight determinations in benzene gave the values 532 and 543, but these can be viewed only as indicating an order of magnitude in view of the known difficulties with this determination in the case of phenylsubstituted cyclic siloxanes.[16] Since the compound showed no change of melting point on standing for weeks, it does not appear to be the unstable polymorph of octaphenylcyclotetrasiloxane which melts at the same temperature.[16] The fact that the melting point of the cyclic siloxane (II) is lower than the known stable polymorph[16] of the cyclic tetramer and its markedly greater solubility in acetone further differentiates the two compounds. We conclude that the cyclic siloxane (II) must be at least a pentamer or a cyclic siloxane of even greater ring size.

Reaction of diphenylsilanediol with metal alkyls. A. *With diethylmagnesium.* To a solution of 0.07 mol. of diethylmagnesium[17] in 100 ml. of anhydrous ether was added dropwise with stirring under a nitrogen atmosphere during 1.5 hr. a solution of 15.1 g. (0.07 mole) of diphenylsilanediol in 50 ml. of anhydrous dioxane. Gas evolution was vigorous, and a white precipitate formed during the addition. The reaction mixture was refluxed for 0.5 hr., filtered, and the precipitate was washed with ether. After drying there was obtained 11.1 g. of a white powder which was soluble in dioxane; analysis showed that it contained 10.2% silicon and 15.8% magnesium, a result which corresponds to the average composition $[(C_6H_5)_2SiO][MgO]_{1.8}$. Filtered dioxane solutions on brief standing in an anhydrous atmosphere deposited traces of magnesium oxide which interfered with molecular weight determinations. That the reaction product was probably polymeric, however, was indicated by the formation of viscous solutions by concentration of dioxane solutions of the product under reduced pressure and by the formation of brittle resins upon complete removal of the solvent from these solutions. That the product was not contaminated with siloxanes at this point was shown by the failure to extract any material from the product upon washing it with either acetone, ether, or benzene at room temperature.

The reaction product dissolved in boiling benzene, but shortly thereafter large quantities of white powder separated from the hot solution. Filtration and repeated extraction of the powder with boiling benzene left 2.8 g. of magnesium oxide contaminated with traces of a silicon-containing material.[13] Evaporation of the combined benzene extracts and filtrate and recrystallization of the residue from benzene-methanol gave 3.8 g. of the cyclic siloxane (II) which melted at 189–190° and did not depress a mixture melting point with the cyclic siloxane obtained from the reaction of magnesium chloride and disodium diphenylsilanediolate.

Concentration of the original filtrate from the reaction mixture and extracting the residue from acetone gave an additional 1.2 g. of the cyclic siloxane. The residue remaining after the extraction was largely magnesium oxide.

B. *With diethylzinc.* The reaction of diethylzinc with diphenylsilanediol proceeded quite similarly to that described above. From 18.9 g. (0.154 mol.) of diethylzinc in 300 ml. of dry ether added under nitrogen to 33.2 g. (0.154 mol.) of diphenylsilanediol in 150 ml. of dry dioxane there was obtained after 1 hr. 26.9 g. of a white powder. From this product there was isolated 1.1 g. of hexaphenyltrisiloxane-1,5-diol, m.p. 111–112° (which did not depress a mixture melting point with the diol obtained from the reaction of zinc chloride and disodium diphenylsilanediolate), by extraction with ether and recrystallization from benzene–petroleum ether. The extracted powder contained 8.66% silicon and 27.36% zinc, which corresponds rather closely to the average composition $[(C_6H_5)_2SiO][ZnO]_{1.35}$. It was insoluble in most of the common solvents but dissolved in dimethyl sulfoxide. Dimethyl sulfoxide solutions of this

(15) Purchased from Anderson Chemical Co., Weston, Mich.

(16) J. F. Hyde, *et al.*, *J. Am. Chem. Soc.*, 69, 488 (1947) and references cited therein.

(17) J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Am. Chem. Soc.*, 78, 1221 (1956).

material, however, deposited traces of zinc oxide on brief standing in an anhydrous atmosphere which interfered with molecular weight determinations. That the product was probably polymeric, however, was indicated by the formation of viscous solutions upon concentration of dimethyl sulfoxide solutions of the reaction product under reduced pressure.

Repeated extraction of the reaction product with boiling benzene eventually gave 9.2 g. of hexaphenyltrisiloxane-1,5-diol and left 10.2 g. of zinc oxide contaminated with traces of a silicon-containing compound.

Evaporation of the original filtrate from the reaction mixture and reprecipitating the residue from benzene–petroleum ether gave 9.0 g. of a white powder which was soluble in ethanol and from which no pure compounds could be separated by repeated fractional reprecipitation. The analysis of this material (13.04% Si; 1.09% Zn) indicated that it might be a mixture of metallosiloxane polymer and hexaphenyltrisiloxane-1,5-diol (or other siloxanes).

Decomposition of polymers for analysis. The polymers were decomposed for analysis by the conventional wet-ashing technique using concentrated sulfuric and nitric acids.

Acknowledgment. The authors are indebted to Dr. W. E. Foster, who suggested this problem, to Dr. P. E. Koenig for many helpful discussions, to Dr. R. P. Curry for the infrared spectra and their interpretation and to Mr. G. Z. Smith for the emission spectra. Thanks are due also to the members of the Analytical Group who performed the analyses reported.

BATON ROUGE, LA.

[CONTRIBUTION FROM THE BIOMEDICAL RESEARCH GROUP OF THE LOS ALAMOS SCIENTIFIC LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Liquid Scintillators. VII. 2,5-Diaryl Substituted Thiazoles as Liquid Scintillator Solutes[1]

V. N. KERR, F. N. HAYES, D. G. OTT, AND E. HANSBURY

Received March 30, 1959

A number of 2,5-diaryl substituted thiazoles have been evaluated as liquid scintillator solutes. A comparison of the effect of substituent groups upon the pulse height of the thiazoles has shown a marked improvement only with the 4-pyridyl and the *p*-dimethylaminophenyl groups. The thiazole pulse heights, fluorescence spectra, and ultraviolet absorption spectra have been compared with the analogous oxazoles.

In an effort to improve upon the existing liquid scintillator counting solutions and to provide data which would help to correlate chemical structure with the ability of various solutes to scintillate, a large number of organic compounds have been investigated.[2-4]

By and large, those solutes which contain sulfur are generally thought to scintillate with a low efficiency, if at all. Thus when Arnold[5] tested a substituted phenylbenzothiazole, it gave a wholly unexpected result. This compound, 2-(*p*-dimethylaminophenyl)benzothiazole, gave a pulse height which was 75% of that of the best solute which had been tested, whereas 2-phenylbenzothiazole was "dead."[6]

There were available in this laboratory a number of oxazole intermediates which could be readily converted to thiazoles. The products of these syntheses would give thiazoles which would have directly comparable oxazoles and thus could provide a comparison of the effects of substituent groups.

Table I contains the data for evaluation of the thiazoles; the maximum relative pulse height (I_{max}); the concentration of solute at I_{max} (c_{max}); the wave length of maximum emission and the mean wave length of the fluorescence spectra (λ^{fl}_{max} and $\bar{\lambda}$, respectively); and the ultraviolet absorption data (λ^{abs}_{max} and ϵ_{max}).

A comparison of the thiazole pulse heights with those of the corresponding oxazoles (in parentheses) shows that in no case does the thiazole equal or excel the oxazole. The highest pulse height obtained is only 80% of that of the analogous oxazole.

The importance of the effects produced by substitution has been noted by several authors.[6,7]

The effect of substitution can be measured relative to 2,5-diphenylthiazole, which can be regarded as the parent member of this series. Several groups produce very little change in the ability of the solute to scintillate. These are the *p*-chlorophenyl, *p*-fluorophenyl, 1-naphthyl, 3-pyridyl, and styryl groups. The 2-naphthyl and 4-biphenylyl groups

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(1) (a) Work performed under the auspices of the U. S. Atomic Energy Commission. (b) Paper VI: M. D. Barnett, G. H. Daub, F. N. Hayes, and D. G. Ott, *J. Am. Chem. Soc.*, **81**, 4583 (1959).

(2) F. N. Hayes, V. N. Kerr, D. G. Ott, E. Hansbury, and B. S. Rogers, Los Alamos Scientific Laboratory Report **LA-2176**, Office of Technical Services, U. S. Dept. Commerce, Washington 25, D. C. (1958).

(3) H. Kallman and M. Furst, *Phys. Rev.*, **79**, 857 (1950).

(4) H. Kallman and M. Furst, *Nucleonics*, **13**, No. 3, 32 (1951).

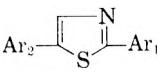
(5) J. R. Arnold, *Science*, **122**, 1139 (1955).

(6) F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, *Nucleonics*, **13**, No. 12, 38 (1955).

(7) H. Gilman, E. A. Weipert, T. Soddy, and F. N. Hayes, *J. Org. Chem.*, **22**, 1169 (1957).

TABLE I

PULSE-HEIGHT AND SPECTRAL DATA



Ar_1	Ar_2	I_{max}[a]	c_{max}	λ^{fl}_{max}	$\bar{\lambda}$	λ^{abs}_{max1}	$\epsilon_1 \times 10^{-4}$	λ^{abs}_{max2}	$\epsilon_2 \times 10^{-4}$
p-FC_6H_4	C_6H_5	0.23 (*0.96*)	7.5	392	424	323	2.35	221s[b]	1.08
p-ClC_6H_4	C_6H_5	0.26 (*0.94*)	6.0	400	428	330	2.69	228	1.02
o-IC_6H_4	C_6H_5	0.10 (>*0.10*)	...	403	436	315	1.76	247s	1.08
m-IC_6H_4	C_6H_5	0.10 (>*0.10*)	...	394	424	330	2.54	224	1.94
p-$(CH_3)_2NC_6H_4$	C_6H_5	0.72 (*0.95*)	2.3	434	444	365	3.40	232	1.52
4-C_6H_5-C_6H_4	C_6H_5	0.39 (*1.18*)	6.0	414	440	339	3.48	220s	1.76
1-$C_{10}H_7$	C_6H_5	0.22 (*0.93*)	4.4	425	456	337	1.80	288	1.12
C_6H_5	2-$C_{10}H_7$	0.42 (*1.02*)	5.0	410	440	339	2.84	221[c]	5.60
Styryl	C_6H_5	0.21 (*0.71*)	10.0	430	470	352	3.20	222	1.40
2-Thienyl	C_6H_5	0.10 (>*0.41*)	...	424	456	343	2.63	...	...
3-Pyridyl	C_6H_5	0.26 (*0.93*)	5.2	396	424	324	2.26	226s	0.92
4-Pyridyl	C_6H_5	0.70 (*0.79*)	2.9	400	422	333	2.16	225s	0.80
2-(5-Phenyl-thiazolyl)	C_6H_5	0.13 (*0.76*)	3.2	454	484	370	3.58	223s	1.64
C_6H_5	C_6H_5	*0.23*[d]	*5*	*396*	*428*	*337*	*2.75*	*223s*	*1.00*

[a] Pulse heights are relative to 2,5-diphenyloxazole at 3 g./l. = 1.00. Italicized figures in parentheses for corresponding oxazoles.[6,8] [b] s following a wave length signifies a shoulder. [c] Other maxima occur at 295, 284, 254, and 246 mμ. [d] Refs. (6) and (8).

produced a doubling of the pulse height. These results are quite in line with those found in the oxazole series.

The most striking change is wrought by the *p*-dimethylaminophenyl and the 4-pyridyl groups. In both instances, the pulse height has been raised by a factor of three. While this effect has been noted before in connection with the *p*-dimethylamino group,[5,7] this is the first instance where the same effect can be attributed to the 4-pyridyl substituent. It is interesting to compare the effect of the pyridyl substituents upon the oxazole and the thiazole. With the former, the 4-pyridyl substituted compound has a smaller pulse height than the 3-pyridyl substituted one. Here, with the thiazoles, the effect is reversed and the differences in pulse height are much greater.

This increase in pulse height with dimethylamino substitution has been attributed to the increase in extinction coefficient of the ultraviolet absorption spectrum with a consequent diminution of the lifetime of the excited state, thereby eliminating some internal quenching.[8] Such an explanation would not apply in the case of 4-(5-phenyl-2-thiazolyl)-pyridine, since its extinction coefficient is lower even than that of 2,5-diphenylthiazole.

A further introduction of sulfur into the scintillator molecule proved to be quite detrimental. Thienyl substitution rendered the molecule inactive, and phenylthiazolyl substitution lowered the pulse height by one half.

Though the lighter halogens produced no large objectionable effect, the heavier halogens did. A solution of 2-(*m*-iodophenyl)-5-phenylthiazole in toluene was exposed to light for a period of several days and soon produced a color characteristic of free iodine. Thus, in addition to other modes of quenching, these halo compounds are inherently unstable and could decompose to give nonscintillating materials.

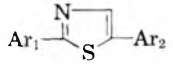
The replacement of an oxygen atom by a sulfur atom produced a bathochromic shift both in fluorescence and absorption spectra, with one exception. Although the absorption spectrum of 2-(*m*-iodophenyl)-5-phenylthiazole had shifted to longer wave lengths, the fluorescence spectrum showed a hypsochromic shift. The ultraviolet absorption spectra were quite similar to those of the oxazoles. In general, there were three bands present, though only the first was well resolved. The other bands were represented by shoulders. The shoulder which represented the second absorption band occurred in the same place (225 ± 5 mμ) as $\lambda^{abs}_{max_2}$ of the oxazole,[7] and thus this band seemed to be a characteristic shared in common.

Structure in the thiazole fluorescence spectra was much less well defined. The long wave-length shoulder was missing in some of the spectra and the relative intensities were lower, which was in agreement with the decreased pulse heights. The mean wavelength is important, since the detector system is discriminatory with regard to wave length of the light. Though thiazoles produce light which is more favorably treated in the detector system, their inherent low efficiency for scintillation makes them less preferred in general for application as liquid scintillator solutes.

(8) D. G. Ott, F. N. Hayes, E. Hansbury, and V. N. Kerr, *J. Am. Chem. Soc.*, 79, 5448 (1957).

TABLE II

THIAZOLES



Ar_1	Ar_2	Formula	M.P., °C.[a]	Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %		Yield, %	Amide Ref.
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found		
p-FC_6H_4	C_6H_5	$C_{15}H_{10}FNS$	137–138.5	70.57	70.65	3.95	4.22	5.49	5.56	...	...	62	[b]
p-ClC_6H_4	C_6H_5	$C_{15}H_{10}ClNS$	144.5–145	66.29	66.50	3.71	3.75	5.15	5.17	11.80	11.85	56	[b]
o-IC_6H_4	C_6H_5	$C_{15}H_{10}INS$	77–78	49.60	49.89	2.78	2.98	3.86	3.79	8.83	8.73	12	[b]
m-IC_6H_4	C_6H_5	$C_{15}H_{10}INS$	117–117.5	49.60	49.80	2.78	2.78	3.86	3.78	8.83	8.83	38	[b]
p-$(CH_3)_2NC_6H_4$	C_6H_5	$C_{17}H_{16}N_2S$	160–162	72.82	72.88	5.75	5.94	9.99	10.17	11.44	11.31	13	8
4-C_6H_5-C_6H_4	C_6H_5	$C_{21}H_{15}NS$	190–191	80.47	80.78	4.82	4.88	4.47	4.57	10.23	10.15	59	[b]
1-$C_{10}H_7$	C_6H_5	$C_{19}H_{13}NS$	93.5–96.5	79.41	79.33	4.56	4.55	4.87	4.90	11.16	11.15	54	[c]
C_6H_5	2-$C_{10}H_7$	$C_{19}H_{13}NS$	145–146.5	79.41	79.44	4.56	4.62	4.87	4.95	11.16	11.32	28	[d]
Styryl	C_6H_5	$C_{17}H_{13}NS$	137–138	77.53	77.55	4.98	4.93	5.32	5.37	12.18	12.24	11	[c]
2-Thienyl	C_6H_5	$C_{13}H_9NS_2$	93.5–95.5	64.16	64.26	3.73	3.97	5.76	5.77	26.35	26.35	23	[b]
3-Pyridyl	C_6H_5	$C_{14}H_{10}N_2S$	104–104.5	70.56	70.66	4.23	4.53	11.76	11.99	13.46	13.50	62	[e]
4-Pyridyl	C_6H_5	$C_{14}H_{10}N_2S$	147–148.5	70.56	70.44	4.23	4.34	11.76	11.64	13.46	13.64	21	[e]
2-(5-Phenyl-thiazolyl)	C_6H_5	$C_{18}H_{12}N_2S_2$	240–241	67.47	67.28	3.78	3.64	8.74	8.67	20.01	19.88	9	[b]

[a] All melting points are uncorrected and were taken on a Fischer-Johns melting point block. Microanalyses performed by Micro-Tech Laboratories, Skokie, Ill. Solvents for recrystallization were either hexane or a mixture of hexane and toluene. [b] F. N. Hayes, B. S. Rogers, and D. G. Ott, *J. Am. Chem. Soc.*, **77**, 1850 (1955). [c] J. Lister and R. Robinson, *J. Chem. Soc.*, 1297 (1912). [d] F. N. Hayes, L. C. King, and D. E. Peterson, *J. Am. Chem. Soc.*, **74**, 1106 (1952). [e] D. G. Ott, F. N. Hayes, and V. N. Kerr, *J. Am. Chem. Soc.*, 78, 1941 (1956).

EXPERIMENTAL

The compounds in Table II were synthesized by the method of Gabriel[9] from previously reported amides. The specific references for the amides are listed in the table.

Details concerning the experimental methods for obtaining the fluorescence spectra,[8] the ultraviolet absorption spectra,[8] and the pulse heights[6] may be found in previous papers. The infrared absorption spectra may be found in the Sadtler Standard Spectra.[10]

Los Alamos, N. M.

(9) S. Gabriel, *Ber.*, **43**, 137 (1910).

(10) Samuel P. Sadtler and Son, Inc., Philadelphia, Pa.

[Contribution from the Biomedical Research Group of the Los Alamos Scientific Laboratory of the University of California]

Liquid Scintillators. VIII. The Effect of the Dialkylamino Group[1]

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Received March 30, 1959

A number of dialkylamino substituted 2,5-diaryloxazoles have been synthesized. The effect of the dialkylamino group upon the capability of these and other compounds to perform as liquid scintillator solutes is discussed.

Since 1955, this laboratory has maintained a screening program for potential liquid scintillator solutes.[2] A number of the solutes which contained the dialkylamino group were found to be rather good solutes when compared to the parent compound which would not scintillate at all. Since the time that the screening program was started, there have appeared in the literature a number of instances of the effect of this group upon liquid scintillator solutes.[3-10]

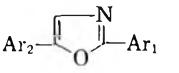
In addition to the beneficial effects of this group, it has also been noted that it can be harmful or ineffective.[5,8,9] The harmful effect of this group appeared with substitution in compounds which already had an appreciable pulse height. Evidently the beneficial effects are here outweighed by the quenching effect.[11]

Until now, observations on the effect of this group have been only incidental to other studies. The dialkylamino substituted oxazoles present an opportunity to study this group with a series of compounds which are notably good scintillator solutes.

It can be seen from Table I that the presence of

TABLE I

Pulse-Height and Spectral Data



Ar_1	Ar_2	I_{max}[a]	c_{max}	λ^{fl}_{max} (mμ)	$\bar{\lambda}$ (mμ)	λ^{abs}_{max1} (mμ)	$\epsilon_1 \times 10^{-4}$
p-$(CH_3)_2NC_6H_4$	C_6H_5	0.95[b]	3.2	403	428	345	4.08
C_6H_5	*p*-$(CH_3)_2NC_6H_4$	0.87	3.8	426	446	340	3.28
p-$CH_3C_6H_4$	*p*-$(CH_3)_2NC_6H_4$	0.85	4.2	420	440	339	3.38
p-$CH_3OC_6H_4$	*p*-$(CH_3)_2NC_6H_4$	0.97	6.4	414	426	337	3.80
p-$(CH_3)_2NC_6H_4$	*p*-$(CH_3)_2NC_6H_4$	0.69	2.5	422	450	355	4.52
1-$C_{10}H_7$	*p*-$(CH_3)_2NC_6H_4$	0.66	3.3	470	492	360	2.62
3-Pyridyl	*p*-$(CH_3)_2NC_6H_4$	0.90	2.7	439	460	352	2.87
N,N-Diethyl-4-biphenylamine[c]		0.62	6.1	368	373	301	3.00
Biphenyl[c]		...	...	312	319	...	...

[a] Relative to 2,5-diphenyloxazole at 3 g./l. = 1.00. [b] Ref. (9). [c] Eastman Kodak, recrystallized.

(1) (a) Work performed under the auspices of the U. S. Atomic Energy Commission. (b) Paper VII: Ref. 10.

(2) F. N. Hayes, V. N. Kerr, D. G. Ott, E. Hansbury, and B. S. Rogers, Los Alamos Scientific Laboratory Report *LA-2176*, Office of Technical Services, U. S. Dept. Commerce, Washington 25, D. C. (1958).

(3) J. R. Arnold, *Science*, 122, 1139 (1955).

(4) H. Gilman, E. A. Weipert, T. Soddy, and F. N. Hayes, *J. Org. Chem.*, **22**, 1169 (1957).

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(6) H. Gilman, E. A. Weipert, and F. N. Hayes, *J. Org. Chem.*, **23**, 910 (1958).

(7) R. H. Wiley, C. H. Jarboe, Jr., and F. N. Hayes, *J. Org. Chem.*, **23**, 268 (1958).

(8) R. H. Wiley, *et al.*, *J. Org. Chem.*, **23**, 732 (1958).

(9) D. G. Ott, F. N. Hayes, E. Hansbury, and V. N. Kerr, *J. Am. Chem. Soc.*, **79**, 5448 (1957).

(10) V. N. Kerr, F. N. Hayes, D. G. Ott, and E. Hansbury, *J. Org. Chem.* **24**, 1861 (1960).

(11) V. N. Kerr, F. N. Hayes, and D. G. Ott, *Intern. J. Appl. Radiation and Isotopes*, 1, 284 (1957).

TABLE II

OXAZOLES

Ar_1	Ar_2	M.P., °C.[a]	Formula	Carbon, %[b]		Hydrogen, %		Nitrogen, %		Yield, %	Corresponding Ketoamide				
				Calcd.	Found	Calcd.	Found	Calcd.	Found		Formula	M.P., °C.	Nitrogen, % Calcd.	Found	Yield, %
C_6H_5	p-$(CH_3)_2NC_6H_4$	148–149.5	$C_{17}H_{16}N_2O$	77.25	77.52	6.10	5.84	10.60	11.07	95	$C_{17}H_{18}N_2O_2$	158.5–160	9.92	9.89	60
p-$CH_3C_6H_4$	p-$(CH_3)_2NC_6H_4$	174–176.5	$C_{18}H_{18}N_2O$	77.67	77.60	6.52	6.27	10.07	9.92	91	$C_{18}H_{20}N_2O_2$	188–191	9.45	9.58	51
p-$CH_3OC_6H_4$	p-$(CH_3)_2NC_6H_4$	134–135	$C_{18}H_{18}N_2O_2$	73.45	73.55	6.16	6.28	9.52	9.54	94	$C_{18}H_{20}N_2O_2$	187–188.5	8.97	8.94	58
p-$(CH_3)_2NC_6H_4$	p-$(CH_3)_2NC_6H_4$	206–208	$C_{19}H_{21}N_2O$	74.24	74.32	6.89	6.95	13.67	13.83	87	$C_{19}H_{23}N_3O_2$	244.5–251.5	12.91	12.83	31
1-$C_{10}H_7$	p-$(CH_3)_2NC_6H_4$	117–118.5	$C_{21}H_{18}N_2O$	80.23	80.16	5.77	5.92	8.91	9.03	64	$C_{21}H_{20}N_2O_2$	150–152	8.43	8.30	47
3-Pyridyl	p-$(CH_3)_2NC_6H_4$	137–138	$C_{16}H_{15}N_3O$	72.43	72.56	5.70	5.79	15.84	15.86	90	$C_{16}H_{17}N_3O_2$	178.5–182	14.83	14.73	43

[a] All melting points were taken on a Fisher-Johns melting point block and are uncorrected. [b] Microanalyses by Micro-Tech Laboratories, Skokie, Ill. Solvents for recrystallization were either hexane or a mixture of hexane and toluene.

other substituents can considerably modify the effect of the dialkylamino group. When it is introduced into 2,5-diphenyloxazole, with no other substituents present, there is a resultant pulse height (I_{max}) drop, the extent of which is dependent upon the position of the substituent. When the *p*-dialkylamino group is on the 2-phenyl substituent of the oxazole, the drop is less than when this group is on the 5-phenyl substituent. The presence of the *p*-methoxyphenyl or the 3-pyridyl group prevents any large drop in pulse height. These alkylamino substituted compounds have a pulse height which is only slightly lower than that of the parent oxazole. A *p*-tolyl substituent is effectively the same as a phenyl group. The largest pulse height drop occurs when substitution is made in a compound which contains another alkylamino group or when one aryl substituent is the 1-naphthyl group.

Self-quenching is higher with the alkylamino substituted oxazoles as evidenced by the lower values for c_{max}. This could be anticipated since these compounds are more polar than the non-dialkylamino substituted oxazoles, and hence the chance for collisional deactivation is increased (since these molecules could be expected to have a more prolonged contact time).[12]

An instance of the striking beneficial effect of this group, as opposed to the effect on the oxazoles, can be seen with the diethylamino substituted biphenyl.[13]

Both the fluorescence and the ultraviolet absorption spectra show a bathochromic shift relative to the nonaminated compounds. The largest shift is shown in the fluorescence spectra with a maximum shift of up to 70 mμ. This bathochromic shift contributes largely to the increased pulse height of the substituted biphenyl, since the region of fluorescence of biphenyl is considerably below the sensitive region of the pulse height detector system.[14] The fluorescence spectra of the aminated oxazoles are structureless showing none of the shoulders or minor peaks which are associated with the other oxazoles. The bathochromic shift does not affect I_{max} of the oxazoles, since the fluoresence spectra of both the aminated and the nonaminated oxazoles lie within the plateau region of the detector's spectral sensitivity curve.

In addition to the bands normally found in the ultraviolet absorption spectra of the oxazoles, there is a band at 270 ± 5 mμ, which is associated with the dialkylamino substituent. The extinction coefficient of the first absorption band is greater with the aminated oxazoles than with the nonaminated oxazoles.

(12) E. J. Bowen and F. Wokes, *Fluorescence of Solutions*, Longmans, Green and Co., London, 1953, p. 31–33.

(13) This effect could be expected to have been greater had the alkyl groups been methyl rather than ethyl.[4,9]

(14) R. K. Swank, W. L. Buck, F. N. Hayes, and D. G. Ott, *Rev. Sci. Instr.*, 29, 279 (1958).

The difference in the extinction coefficients of 2-(*p*-dimethylaminophenyl)-5-phenyloxazole and 5-(*p*-dimethylaminophenyl)-2-phenyloxazole could account for the difference in relative pulse heights of the two. It is thought that an increase in the extinction coefficient with the consequent diminution of the life-time of the excited state would allow fluorescence to occur before internal quenching could interfere.[9] In the case of the two isomeric dialkylamino substituted oxazoles, it can be seen that the compound with the higher pulse height is indeed the one with the larger extinction coefficient. In all cases, the extinction coefficient of the aminated oxazole is higher than that of the analogous nonaminated oxazole. Any expected improvement from this cause is offset by other, detrimental effects, as is evident in the lowered pulse heights.

It seems, in conclusion, that a molecule with an extended resonance system but with strong internal quenching or too short an emission wave length can be helped by dialkylamino substitution; however, such substitution does not improve a good scintillator.

EXPERIMENTAL

All compounds listed in Table II were synthesized according to the following general scheme:

$$Ar_1COCl + Ar_2COCH_2NH_2.HCl \xrightarrow{C_5H_5N} Ar_1CONHCH_2COAr_2$$

$$Ar_1CONHCH_2COAr_2 \xrightarrow{-H_2O} Ar_1\text{-}C_3NO\text{-}Ar_2$$

The general procedure of Hayes, Rogers, and Ott[15] was used to obtain the intermediate ketoamides from the acid chlorides and the *p*-dimethylaminophenacylammonium chloride.[16]

The cyclization of the ketoamides, with 98% phosphoric acid in acetic anhydride, to form the oxazoles was performed in the same manner as that given for the pyridylphenyl oxazoles in a previous paper.[17]

Details concerning the methods for obtaining the pulse heights[18] and the fluorescence[5] and the ultraviolet absorption spectra[8] may be found in previous publications. The infrared absorption spectra are in the Sadtler Standard Spectra.[19]

LOS ALAMOS, N. M.

(15) F. N. Hayes, B. S. Rogers, and D. G. Ott, *J. Am. Chem. Soc.*, **77**, 1850 (1955).

(16) Product of Pilot Chemicals, Inc., Watertown, Mass.

(17) D. G. Ott, F. N. Hayes, and V. N. Kerr, *J. Am. Chem. Soc.*, **78**, 1941 (1956).

(18) F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, *Nucleonics*, **13**, No. 12, 38 (1955).

(19) Samuel P. Sadtler and Son, Inc., Philadelphia, Pa.

[CONTRIBUTION FROM THE INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Synthesis of Condensed Cyclic Systems. I.[1] New Synthesis of 7-Methylbicyclo-[3.3.0]octan-3-one and 8-Methylbicyclo[4.3.0]nonan-4-one

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7-Methylbicyclo[3.3.0]octan-3-one (II) was obtained in good yield by application of an analogous method which had been reported for 8-methylbicyclo[4.3.0]nonan-4-one. (I). This modification, however, failed with the latter compound. A new simple method for its synthesis is described.

In the course of the synthesis of degradation products of antirachitic vitamins, Bagchi and Banerjee reported the synthesis 8-methylbicyclo-[4.3.0]nonane-4-one (I).[2] The present experiments were undertaken to improve the previously developed method.

Synthesis of 7-methylbicyclo[3.3.0]octan-3-one (II) was attempted first, using simplifications of the analogous reported procedure for I. Excellent result were obtained. Fewer steps were required and a higher yield was achieved than had been reported for 8-methylbicyclo[4.3.0]nonan-4-one.

The condensation of 2-methyl-2-carbethoxylcyclopentanone with ethyl cyanoacetate according to the method of Cope *et al.*,[3] was studied by Bagchi and Banerjee.[2] In the present investigation when the condensation was carried out according to the modification of Cragoe *et al.*,[4] the condensation product (III) was obtained in a reproducible yield exceeding 90%. The unsaturated cyano ester (III) was condensed with ethyl chloroacetate according

(1) A preliminary note embodying a part of the experimental results appeared in *Science and Culture (India)*, **21**, 545 (1956) and *Proc. 45th Session Indian Science Congress*, (1958), p. 129. Taken from the thesis of K. Sen submitted for the degree of Doctor of Philosophy (Science) of the University of Calcutta, April, 1957.

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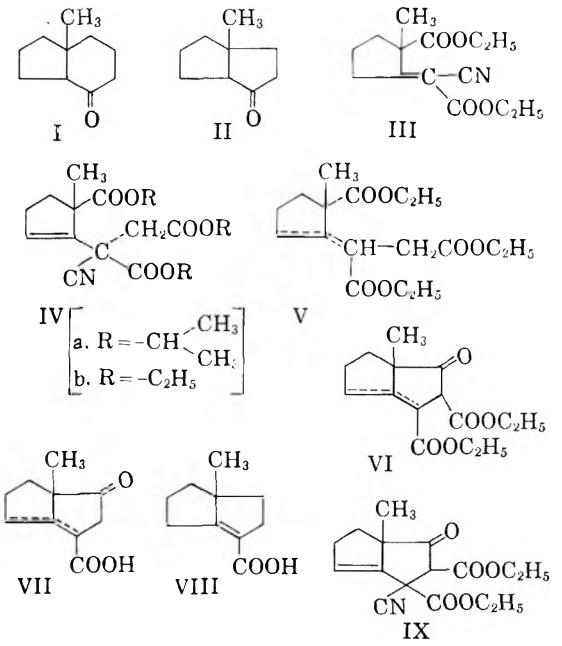
(2) P. Bagchi and D. K. Banerjee, *J. Indian Chem. Soc.*, **23**, 397 (1946).

(3) A. C. Cope, C. M. Hofmann, C. Wyckoff, and F. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

(4) E. J. Cragoe, C. M. Robb, and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950).



to Cope *et al.*,[5] in ethanol as well as in isopropyl alcohol. In the latter case ester exchange simultaneously took place, the triisopropyl ester (IVa) being obtained. The cyanoester (IVb) was hydrolyzed by boiling with concentrated hydrochloric acid and the crude hydrolysate was directly esterified with ethanol and concentrated sulfuric acid. The product of esterification was separated into two fractions through distillation. The lower boiling fraction gave analytical figures required for the triester (V). The higher boiling product proved to be a γ-lactonic ester from elementary analysis and infrared examination. Chatterjee and Bhattacharyya[6] also mention the formation of a γ-lactonic acid in connection with the hydrolysis of diethyl α-cyano-α-(6-methyl-6-carbethoxy cyclohexenyl) succinate.

The triester (V) on Dieckman cyclization followed by direct hydrolysis of the β-keto ester (VI) gave a keto acid (VII) m.p. 122°, in which the exact position of the double bond has not been assigned with certainty as the product may be a mixture of bond isomers. When (VII) was subjected to Huang-Minlon reduction, not only was the keto group reduced, but also the double bond was brought into conjugation with the carboxyl as was proved by the easy conversion of (VIII) to the ketone (II) through the Schmidt reaction.[7]

A further simplification of the above scheme was achieved by cyclization of (IV) followed by direct hydrolysis of the intermediate β-keto ester (IX), when the keto acid (VII) m.p. 122° was obtained in 36% overall yield.

(5) A. C. Cope and C. M. Hofmann, *J. Am. Chem. Soc.*, 63, 3456 (1941).

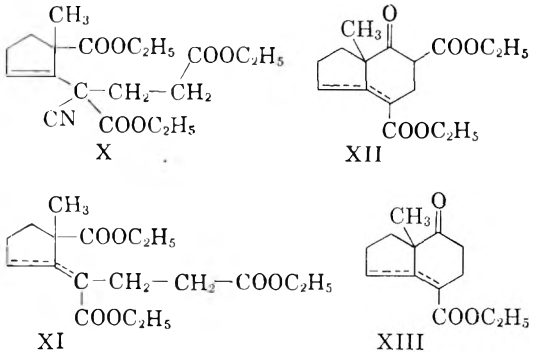
(6) R. C. Chatterjee and B. K. Bhattacharyya, *Science and Culture (India)*, 21, 543 (1956); *J. Indian Chem. Soc.*, 34, 515 (1957).

(7) H. Wolff, *Org. Reactions*, III, 307 (1947).

The steps involved in the present scheme are smooth and the yields in different steps on the whole workable. The present procedure thus appeared to be an improvement over that of Bagchi and Banerjee.[2]

In view of the encouraging results obtained in the synthesis of the ketone (II), we decided to extend the above procedure to the synthesis of 8-methylbicyclo[4.3.0]nonan-4-one (I).

The unsaturated cyano ester (III) was condensed with ethyl β-chloro- or β-bromo-propionate to yield X. Attempts to introduce a propionic acid chain by cyanoethylation[8] in presence of Triton B or through Michael addition of methyl acrylate in the presence of sodium ethoxide in ethanol failed to yield the desired product. Hydrolysis of (X) followed by esterification with ethanol and sulfuric



acid yielded two products. The lower boiling product showed analytical data required for the ester (XI). The position of the double bond is uncertain, for reasons stated previously. The other fraction, which was the major product in this case, is apparently a γ-lactonic ester, as its infrared spectrum is almost identical with the lactonic ester obtained earlier.

The triester (XI) was cyclized with sodium dust in benzene and the crude β-keto ester (XII) was directly hydrolyzed. Unlike the previous case the keto acid could not be obtained in the crystalline state and even after repeated sublimations an analytically pure sample could not be obtained. In the subsequent experiments, therefore, the crude keto acid was converted into the ethyl ester (XIII), which was obtained in the pure state.

The modification of the original procedure of Bagchi and Banerjee[2] did not prove very fruitful in the case of the synthesis of the ketone (I). A major set back was our inability to utilize the lactonic ester (obtained as the major product) for the succeeding steps.

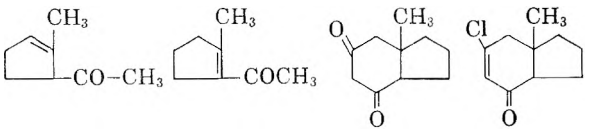
Recently a method has been developed in this laboratory[9] for the synthesis of 10-methylbicyclo-[4.4.0]decan-1-one from 10-methylbicyclo[4.4.0]-decan-1,3-dione. This method was utilized with

(8) H. A. Bruson and T. W. Riene, *J. Am. Chem. Soc.*, 70, 214 (1948).

(9) U. Ghatak, N. N. Saha, and P. C. Dutta, *J. Am. Chem. Soc.*, 79, 4487 (1957).

success for the synthesis of the ketone (I) in a satisfactory yield, and has turned out to be the simplest method for its synthesis.

A simple method has been developed for the synthesis of 1-acetyl-2-methyl-Δ^1 (and Δ^2)-cyclopentene (XIV and XV) through the condensation of acetic anhydride with 1-methylcyclopentene in the presence of zinc chloride. It was found that the reaction temperature, purity of the zinc chloride



XIV XV XVI XVII

and the time of reaction represented the most important factors in controlling the uniformity of yield and purity of the products. Under proper experimental conditions pure ketonic product (XIV and XV) was obtained in about 50–60% yield. The ketonic fraction exhibited a maximum ultraviolet absorption at 250 mμ (log ϵ 3.6). That this extinction coefficient is low compared with that of pure α,β-unsaturated ketone (XV)[10] and that the melting point of semicarbazone prepared from our ketone was raised from 208 to 221–222° on crystallization (lit. 223–224° m.p. of the semicarbazone from XV)[10] revealed that the ketonic product obtained by us consisted of a mixture of two isomeric products (XIV and XV). It is interesting to record here the difference between the acetylation of 1-methylcyclopentene and 1-methylcyclohexene. In the latter case β,γ-unsaturated ketone was found to be the only product.[11] The isomeric 1-acetyl-2-methyl-Δ^1 (and Δ^2)-cyclopentene (XIV and XV) was condensed with diethyl malonate according to Clemo and Dickenson.[12] The condensation product on subsequent alkaline hydrolysis yielded the diketone (XVI) m.p. 90–91° (lit. 91–92°)[12] as a white powder; 45% after sublimation. The diketone (XVI) was converted to the chloroketone (XVII) by treatment with phosphorus trichloride and the latter was reduced to the bicyclic ketone (I) in an excellent yield.

The homogeneity as well as the structure of the above ketone obtained was proved from its formation of a single semicarbazone in about 93% yield, which was found to be identical with an authentic sample of semicarbazone of the ketone (I), prepared according to Bagchi and Banerjee.[2] The structure of the final product incidentally established the structure of the chloroketone as XVII.

EXPERIMENTAL[13]

Ethyl 2-methyl-2-carbethoxycyclopentylidenecyanoacetate (III). A mixture of 2-methyl-2-carbethoxycyclopentanone (22 g.), ethyl cyanoacetate (17.5 g.), glacial acetic acid (5.2 ml.) and benzene (25.8 ml.) was refluxed on an oil bath in a flask fitted with a water separator for 15 hrs., during which ammonium acetate (3.9 g.) was added in three equal portions. The dark red reaction mixture was washed with water (10 times). The benzene was removed and the residual oil was distilled. Product boiled at 170–172°/5 mm. (30.8 g.; 90%), $n_D^{34.5}$ 1.4800.

Diisopropyl α-cyano-α-(5-methyl-5-carbisopropoxycyclopentenyl)succinate (IVa). Ethyl 2-methyl-2-carbethoxycyclopentylidenecyanoacetate (28.5 g.) was added to ice cold sodium isopropylate (prepared from isopropyl alcohol, 115 ml., and sodium, 2.6 g.). To the complex was added ethyl chloroacetate (15.2 g.), whereby the contents turned wine red. The mixture was refluxed for 32 hr. (neutral). After removal of the isopropyl alcohol under suction, water was added and the precipitated oil was extracted with benzene. The solution was washed and evaporated and the residual oil distilled. The product boiled at 188–190°/2 mm. (27.4 g.; 65%).

Anal. Calcd. for $C_{21}H_{31}O_6N$: C, 64.1; H, 7.8. Found: C, 63.9; H, 7.7.

Diethyl α-cyano-α-(5-methyl-5-carbethoxycyclopentenyl)-succinate (IVb). Ethyl 2-methyl-2-carbethoxycyclopentylidenecyanoacetate (28 g.) was added under nitrogen atmosphere to a suspension of sodium ethoxide (from 2.6 g. sodium and 115 ml. ethanol) cooled in ice. After some time ethyl chloroacetate (15.2 g.) was added and the mixture refluxed till neutral to litmus (17–19 hr.). Water was then added and the oil extracted with benzene. The benzene extract was washed with water, and benzene removed. The residual oil distilled at 175–176°/0.6 mm. (24.9 g.; 67%).

Anal. Calcd. for $C_{18}H_{26}O_6N$: C, 61.5; H, 7.1. Found: C, 61.1; H, 7.4.

Hydrolysis of the ester (IVb). The ester (IVb) (45 g.) was refluxed with concentrated hydrochloric acid (150 ml.) for 30 hr. The hydrolysate was then evaporated to dryness and the residue extracted with ether. The ether extract was dried, the ether evaporated and the residue esterified by refluxing with ethanol (225 ml.) and concentrated sulfuric acid (25 ml.). The reaction product was then worked up in the usual way. The residual oil gave two fractions on distillation. Fraction I, b.p. 167–70°/5 mm. (17.6 g.; 42%) was found to analyze correctly for diethyl 2-methyl-2-carbethoxycyclopentylidenesuccinate.

Anal. Calcd. for $C_{17}H_{26}O_6$: C, 62.6; H, 8.0. Found: C, 62.4; H, 7.7.

Fraction II, b.p. 185–194°/4 mm. This was found to be the lactonic ester. Infrared spectrum (film on KBr pellet) ν_{max} 1775 cm.$^{-1}$ (lactone), ν_{max} 1726 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.4; H, 7.3. Found: C, 60.1; H, 7.5.

7-Methylbicyclo[3.3.0]oct-$\Delta^{3:8}$ or $^{4:8}$-ene-1-one-3-carboxylic acid (VII). (a) *From ester* (V). Ester (V, 13.5 g.) was refluxed with sodium dust (1.2 g.) in thiophene free benzene (50 ml.) under nitrogen atmosphere for 3 hr. The reaction mixture was then decomposed with dilute hydrochloric acid and the benzene layer was washed with water. The oil obtained by evaporation of benzene was hydrolyzed by refluxing with hydrochloric acid (150 ml., 1:10) for 36 hr. The product was then extracted with ether and the ether layer extracted with sodium carbonate solution (5%). The alkaline layer was acidified and the precipitated oil extracted with ether. Sublimation of the residue gave an oil which solidified. It was recrystallized from benzene, m.p. 122° (3.5 g.; 47%).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.6; H, 6.6. Found: C, 66.4; H, 6.3.

(b) *From ester* (IVb). Ester (IV, 17.5 g.) was refluxed under nitrogen with sodium dust (2.4 g.) in benzene (50

(10) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 1403 (1951).

(11) N. C. Deno and H. Chafetz, *J. Am. Chem. Soc.*, **74**, 3940 (1952).

(12) G. R. Clemo and H. G. Dickenson, *J. Chem. Soc.*, 735 (1935).

(13) All melting points and boiling points are uncorrected.

ml.) for 3 hr. The product was decomposed with dilute hydrochloric acid. The benzene layer was separated and the oil obtained on evaporation of the benzene was hydrolyzed by refluxing with hydrochloric acid (20 ml.), water (50 ml.) and glacial acetic acid (130 ml.) for 30 hr. The acids were then removed under reduced pressure and the product worked up as in the previous case. It had an m.p. of 122° and showed no depression when mixed with the product described before.

7-Methylbicyclo[3.3.0]oct-$\Delta^{3:8}$-ene-3-carboxylic acid (VIII). Acid (VII, 4 g.) was heated with hydrazine hydrate (6.5 ml.; 100%) and caustic potash (4.4 g.) in diethylene glycol (33 ml.) for 4 hr. After cooling the reaction mixture was diluted and then acidified. The precipitated oil was then repeatedly extracted with ether. On removal of ether an oil was obtained which distilled at 135–136°/1.5 mm. (1.1 g.; 30%).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.2; H, 8.4. Found: C, 71.8; H, 8.4.

7-Methylbicyclo[3.3.0]octan-3-one (II). Acid (VIII, 1.5 g.) in benzene was treated with hydrazoic acid (13 ml.; 5.5%). The mixture was then cooled and treated with concentrated sulfuric acid (5 ml.) with stirring. Then the temperature was maintained at 40–45° for 2 to 2.5 hr. Water was next added and the mixture refluxed on a water-bath for 1.5 hr. The benzene layer was separated, washed with water and benzene removed. The residual oil was distilled; b.p. 85–90°/5 mm. (0.38 g.; 31%).

Anal. Calcd. for $C_9H_{14}O$: C, 78.2; H, 10.1. Found: C, 77.8; H, 10.1.

The 2,4-dinitrophenylhydrazone was prepared and crystallized from ethanol-ethyl acetate; m.p. 177–178°.

Anal. Calcd. for $C_{15}H_{18}O_4N_4$: N, 17.6. Found: N, 17.6.

Diethyl α-cyano-α-(5-methyl-5-carbethoxycyclopentenyl) glutarate (X). To an ice-cold solution of sodium ethanol (prepared from 3.6 g. sodium and 75 ml. ethanol) was added ethyl 2-methyl-2-carbethoxycyclopentylidenecyanoacetate (39 g.) in an atmosphere of nitrogen. After 5 min. ethyl β-chloropropionate (21 g.) was added to the dark solution whereby intense heat developed. Within a very short time sodium chloride precipitated out. The mixture was refluxed in a nitrogen atmosphere for 16 hr. until neutral to litmus. After addition of water the separated oil was extracted with benzene and the solution was thoroughly washed with water. After removal of the solvent the ester distilled at 195–200°/0.6 mm. (42.9 g.; 80%).

Anal. Calcd. for $C_{19}H_{27}O_6N$: C, 62.4; H, 7.4. Found: C, 61.9; H, 7.7.

Diethyl 2-meihyl-2-carbethoxycyclopentylideneglutarate (XI). Cyanoester (X, 20 g.) and concentrated hydrochloric acid (100 ml.) were refluxed for 30 hr. The reaction mixture was evaporated to dryness and the residue was mixed with 20% ethanolic sulfuric acid (150 ml.) and refluxed for 20 hr. The product was treated with excess water and the separated oil collected in ether. The ethereal solution was washed with water and sodium bicarbonate solution, dried over sodium sulfate, and distilled. Two distinct fractions were obtained.

Fraction I, 167°/0.4 mm. (21.5%) was found to be diethyl 2-methyl-2-carbethoxycyclopentylideneglutarate (XI).

Anal. Calcd. for $C_{18}H_{28}O_6$: C, 63.5; H, 8.2. Found: C, 62.8; H, 7.9.

Fraction II, 185–190°/0.4 mm. (38%) was found to be lactonic ester. Infrared spectra (film on KBr pellet), ν_{max} 1775 cm.$^{-1}$ (ν lactone), ν_{max} 1726 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{16}H_{24}O_6$: C, 61.5; H, 7.6. Found: C, 61.4; H, 7.6.

Ethyl 8-methylbicyclo[4.3.0]non-$\Delta^{3:9}$ or $^{4:9}$-ene-7-one-4-carboxylate (XIII). The ester (XI, 32 g.) was refluxed for 3 hr. with (4.8 g.) sodium dust in a nitrogen atmosphere using benzene (200 ml.) as solvent. The resulting deep red solution was decomposed with 1:1 hydrochloric acid. The benzene solution was washed with water and evaporated. The crude keto ester which gave a distinct ferric chloride test was hydrolyzed by refluxing with 6% hydrochloric acid (150 ml.) for 20 hr. The hydrolyzed product was collected as usual and esterified with 5% ethanolic sulfuric acid (100 ml.). The product was taken up in ether. The extract was washed with sodium bicarbonate, dried and distilled. The product, ketoester (XIII), boiled at 115°/5 mm. (33%).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.2; H, 8.1. Found: C, 70.4; H, 8.2.

The 2,4-dinitrophenylhydrazone, m.p. 140°, could not be crystallized.

1-Acetoxy-2-methylcyclopentenes (XIV *and* XV). To an ice-cold (0°) stirred mixture of 1-methylcyclopentene (10 g.)[14] and acetic anhydride (60 ml.), powdered and freshly fused zinc chloride (25 g.) was added in small portions (during about 1 hr.) so that the temperature remained below 10°. Stirring was continued for another 15 min. The dark reaction mass was decomposed with iced water and extracted with ether (50 × 3 ml.). The extract was washed with cold sodium hydroxide solution (5%) until alkaline, with water and finally dried over calcium chloride. Distillation yielded a colorless sweet smelling liquid, b.p. 58–65°/8 mm. (18.5 g.; 61%) λ_{max}^{alc} 250 mμ, log ε 3.6.

Semicarbazone, m.p. 208° (crude) on three crystallizations from ethanol melted at 221–222°.

6-Chloro-8-methylbicyclo[4.3.0]non-5-ene-4-one (XVII). The diketone (XVI) was prepared in about 45%, yield by the condensation of the ketone (XIV and XV mixture) with diethyl malonate and subsequent alkaline hydrolysis according to the method of Clemo *et al.*[12]

The diketone (XVI, 10.2 g.) in dry chloroform (25 ml.) was refluxed on a water-bath for 3 hr. with phosphorous trichloride (2.5 ml.). The solvent was distilled off under reduced pressure. The residue was cooled and treated with an excess of ice-cold water. The ethereal extract was washed with cold sodium hydroxide solution (2%). Product distilled at 115–116°/6 mm. as a colorless liquid (6 g.; 53%).

Anal. Calcd. for $C_{10}H_{13}OCl$: C, 65.0; H, 7.0. Found: C, 64.8; H, 7.3.

8-Methylbicyclo[4.3.0]nonan-4-one (I). The enol-chloride (5.8 g.) in ethanol (20 ml.) was hydrogenated with palladium-carbon (200 mg.; 10%) at room temperature. The hydrogenated product was worked up. The ketone, b.p. 90–91°/6 mm. was a colorless, sweet-smelling liquid (3.9 g.; 81.5%).

Semicarbazone was obtained in 93% yield, m.p. 185–186°; crystallized from ethanol m.p. 186–187°. The melting point was undepressed when mixed with an authentic sample.

Anal. Calcd. for $C_{11}H_{19}ON_3$: C, 63.1; H, 9.09; N, 20.09. Found: C, 62.9; H, 9.0; N, 20.1.

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CALCUTTA, INDIA

(14) Prepared in 60% yield from crude 1-methylcyclopentanol, obtained through the condensation of methylmagnesium iodide and cyclopentanone and subsequent dehydration by distillation in presence of a trace of iodine.

[CONTRIBUTION FROM THE NAVAL STORES RESEARCH STATION[1]]

The Preparation of Some Mono- and Dialkyl Pinates from Pinic Acid[2]

J. B. LEWIS AND G. W. HEDRICK

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Half saponification of diethyl pinate has been reported by Guha and Rao to involve the acetate moiety. This reaction has been used for the preparation of a number of half esters, *viz.* 2,2-dimethyl-3-(alkoxycarbonyl) cyclobutaneacetic acids when the alkyl was ethyl, *n*-butyl, 2-ethylhexyl, and hydronopyl. Direct esterification of pinic acid with an equimolar amount of ethyl, *n*-butyl, 2-ethylhexyl, and hydronopyl alcohols gave in addition to 10 mol. % each of diester and pinic acid, the corresponding alkyl 2,2-dimethyl-3-carboxycyclobutaneacetates. Conversion of each of the half esters, to mixed esters and half saponification gave essentially the pure free acetic acid form of monoester. Similarly, direct esterification was proved to yield only the 3-carboxycyclobutane form.

A program in this laboratory involving the preparation of a number of vinyl esters for use as comonomers for internal plasticization studies of polyvinyl chloride[3] included the preparation of a number of vinyl alkyl pinates[4] derived from monoalkyl pinates. There are no literature references alluding to higher monoalkyl pinates and mixed esters. It has been found that either half ester of pinic acid can be prepared readily, one by half saponification of diesters and the other by direct monoesterification of the free acid. The pinic acid used in this work was obtained by the usual hypohalite oxidation of pinonic acid prepared by permanganate oxidation of commercial α-pinene. Although Guha and Rao,[5] to whom reference is made later, considered pinic acid thus prepared to be the *trans-* form, the recent assignment by Trave and Cignarella[6] of the *cis* structure to *dl*-pinic acid, m.p. 100–102°, appears to be correct. The corresponding optically active isomers, m.p. 78°, obtained in the same manner[7] must also have the *cis* configuration. The Trave *et al.* assignment is used in this paper.

Guha and Rao[5] prepared a liquid 2,2-dimethyl-3-(ethoxycarbonyl)cyclobutaneacetic acid (amide m. p. 97°) by half saponification of diethyl pinate (presumably *cis*) but failed to record its optical rotation. They established the existence of the free acetic acid group in this particular ester and reported additional confirming evidence in another reference.[8]

In the work reported herein half saponification of diethyl pinate by the Guha and Rao procedure[5] resulted in two monoesters. One was a solid, m.p. 80–81°, which gave an amide, m.p. 74.8–75.6°. Acid hydrolysis of the ester and its amide gave *cis-dl*-pinic acid, m.p. 100–102°. The other was a liquid consisting of a mixture of monoesters. The amide from the liquid melted at 97° which on hydrolysis gave *cis-d*-pinic acid m.p. 78° described by Grandperrin. The solid half ester was obviously *cis-dl*-2,2-dimethyl-3-(ethoxycarbonyl)cyclobutaneacetic acid. Furthermore, the principal component of the liquid half ester and the product of Guha and Rao must have been the *cis-d*-isomer of the ethoxycarbonyl derivative of pinic acid. It was concluded that the pinic acid used for the work reported herein was a mixture of *cis-d* and *cis-dl* isomers.

Both the *cis-d-* and the *cis-dl*-2,2-dimethyl-3-(ethoxycarbonyl)cyclobutaneacetic acids had sharp, moderate to strong absorbances at 7.5 microns in the infrared. This same band is present in *cis-dl*-2,2-dimethyl-1,3-bis(alkoxycarbonyl)cyclobutanes and in *cis-d* and *cis-dl*-dialkyl pinates but absent in *cis-dl*-dialkyl 2,2-dimethyl-1,3-cyclobutanediacetates, and hence appears to be characteristic of the alkoxycarbonylcyclobutane group.

Direct esterification of pinic acid with one mole of ethanol using *p*-toluenesulfonic acid as a catalyst gave a half ester which did not absorb in the infrared at 7.5 microns and could not be induced to crystallize. The amides from a number of amines were all liquids. It was concluded this reaction resulted in the formation of ethyl *cis-d-* and *cis-dl*-2,2-dimethyl-3-(carboxy)cyclobutaneacetate with little or none of the alkoxycarbonyl form present in the mixture.

The presence of the characteristic absorbance at 7.5 microns in the infrared in a number of half esters prepared by half saponification of higher di- and mixed esters and absence of the absorbance in a number of monoesters prepared by direct monoesterification with higher alcohols demonstrates that the selectivity in these reactions observed for the ethyl esters also holds for higher esters. Furthermore, when mixed esters were subjected to

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

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(3) In cooperation with Dr. C. S. Marvel, University of Illinois, under contract with the U. S. Department of Agriculture.

(4) J. B. Lewis and G. W. Hedrick, *J. Org. Chem.*, in press.

(5) P. C. Guha and P. L. N. Rao, *Ber.*, 71, 1591 (1938).

(6) R. Trave and G. Cignarella, *Rend. ist. lombardi sci.*, 91, 329 (1957); *Chem. Abstr.*, 52, 11782 (1958).

(7) M. Grandperrin, *Ann. chim.*, 6, 5 (1936).

(8) P. C. Guha and P. L. N. Rao, *J. Ind. Chem. Soc.*, 20, 97 (1943).

half saponification the monoester obtained was always the alkoxycarbonyl derivative. Thus, ethyl *cis*-2,2-dimethyl-3-(*n*-butoxycarbonyl)cyclobutaneacetate on half saponification gave *cis*-2,2-dimethyl-3-(*n*-butoxycarbonyl)cyclobutaneacetic acid. This was true when the mixed ester was prepared from ethyl *cis*-2,2-dimethyl-3-(chlorocarbonyl)cyclobutaneacetate by reacting with *n*-butanol or obtained by reduction of vinyl *cis*-2,2-dimethyl-3-(*n*-butoxycarbonyl)cyclobutaneacetate.[4]

The lability of the alkyl group in the acetate form of the half ester led to ester interchange and formation of symmetrical as well as mixed diesters during direct esterification using an acid catalyst. Little or no ester interchange occurred with the alkoxycarbonyl half ester under the same conditions. Pure mixed esters were readily prepared from the alkyl acetate forms by way of the acid chloride.

EXPERIMENTAL

2,2-Dimethyl-3-(carboxy)cyclobutaneacetic acid (pinic acid). Crude pinic acid was prepared by hypochlorite oxidation of pinonic acid, $[\alpha]_D^{26}$ +29.1° (10% acetone) obtained from α-pinene $[\alpha]_D^{20}$ +23.1° (1 dm.) in the usual manner.[9] Esterification of the crude product according to Wielicki, *et al.*[10] and distillation yielded good quality *cis*-diethyl pinate, $[\alpha]_D^{25}$ 0.0 (8%, acetone), +2.2 (1 dm.).

For the preparation of pinic acid, acid hydrolysis was superior to alkaline saponification which was slow and often incomplete. Diethyl pinate, 484.6 g. (2 mol.) was dissolved in 420 g. glacial acetic acid (7 mol.). Aqueous 6*N* sulfuric acid, 500 ml., was added and ethyl acetate azeotrope (8.5% water) was distilled, b.p. 71°, through a 24-in. Vigreux column. Residual acetic acid was removed by steam distillation or by washing with water. Ninety per cent yields of crude pinic acid, neut. equiv. 94 to 96, were obtained by ether or benzene extraction, drying the extract with sodium sulfate and stripping the solvent *in vacuo*. Pure acid, neut. equiv. 93 to 93.5 was obtained by distillation of the crude acid, b.p. 163–165° (0.2 mm.).

Monoalkyl pinates by half saponification. 2,2-Dimethyl-3-(ethoxycarbonyl)cyclobutaneacetic acid. Diethyl pinate, 800 g. (3.3 mol.), was dissolved in 1 l. of 95% ethanol. To this a solution consisting of 132 g. (3.3 mol.) sodium hydroxide dissolved in 132 ml. water was slowly added while stirring. The reaction mass warmed to about 70° and the *p*H changed from about 14 initially to between 7 and 8 at the end of the reaction. The ethanol was removed under reduced pressure and the residue was diluted with 1 to 2 l. water. Extraction with ether gave 80 g. (10 mol. %) of diester.

The monoester and pinic acid were recovered by acidification and ether extraction of the aqueous layer in the usual manner. Vacuum distillation of the dried extract after removal of solvent gave 656 g. (80 mol. %) of colorless monoester and 62 g. (10 mol. %) pinic acid, b.p. 163–165° (0.2 mm.).

On standing, the monoester partially solidified and the solid and liquid portions were separated by crystallization first from hexane and then from methyl ethyl ketone–hexane mixture (1:1). Treatment of the solid product, neut. equiv. 214.3, saponification equivalent 107.1 $[\alpha]_D^{26}$ 0.0 (10% acetone), m.p. 80–81°, with thionyl chloride and liquid ammonia in ether yielded an amide, m.p. 75–76°.

Anal. Calcd. for $C_{11}H_{19}O_5N$: N, 6.57. Found: N, 6.62.

Acid hydrolysis of the monoester and its amide using acetic acid–sulfuric acid gave *cis-dl*-pinic acid, m.p. 100–102°. The solid *cis-dl*-2,2-dimethyl-3-(ethoxycarbonyl)-cyclobutaneacetic acid was further characterized by reaction of its acid chloride with ethylene diamine to give an amide, m.p. 166–168°.

Anal. Calcd. for $C_{24}H_{40}O_6N_2$: N, 6.23. Found: N, 6.29.

Treatment of the liquid portion with thionyl chloride yielded an acid chloride, b.p. 87° (1 mm.) in 98% yield, from which an amide, m.p. 97°, $[\alpha]_D^{26}$ −8.1 (10% acetone) was obtained.

Anal. Calcd. for $C_{11}H_{19}O_3N$: N, 6.57. Found: N, 6.71.

This same amide was obtained when the crude monoester was converted to the amide and hence, appears to be identical with that reported by Guha and Rao.[5] Acid hydrolysis of this amide gave *cis-d*-pinic acid, m.p. 78°. The infrared (spectra of the two recovered pinic acids were identical with each other and with that of authentic *cis-dl*-pinic acid.

Higher monoalkyl pinates by half saponification. A number of higher monoalkyl pinates, 2,2-dimethyl-3-(alkoxycarbonyl)cyclobutaneacetic acids, Table I, were prepared similarly by half saponification of an appropriate symmetrical or mixed diester, *e.g.*, *n*-butyl or ethyl 2,2-dimethyl-3-(*n*-butoxycarbonyl)cyclobutaneacetate. The extent of saponification and yield was independent of the ester used. All these alkoxycarbonylcyclobutaneacetic acids had a sharp, moderate to strong absorbance in the infrared at 7.5 microns[11] which was attributed to the alkoxycarbonyl group.

Direct esterification of pinic acid. Monoethyl, *n*-butyl, 2-ethylhexyl, and hydronopyl[12] 2,2-dimethyl-3-(carboxy)-cyclobutaneacetates were prepared by refluxing 186 g. (1 mol.) of pinic acid and 1 mol. of the alcohol in 480 ml. benzene containing 6 g. *p*-toluene sulfonic acid. When all the water from the reaction had been removed azeotropically and the acid number indicated the reaction was complete, the mass was washed with water to remove the catalyst. The batch was diluted with water and made alkaline by adding approximately 1*N* sodium hydroxide buffered with sodium carbonate, the pinic acid, monoester, and diester separated. The yields were diester 10, monoester 80, and pinic acid 10 mol. %.

The properties and data obtained from characterization of the pinates are tabulated in Table I. None of these esters absorbed in the infrared at 7.5 microns as did the alkoxycarbonyl derivatives.

For comparison of this type ester with the alkoxycarbonyl-cyclobutaneacetic acids, ethyl 2,2-dimethyl-3-(carboxy)-cyclobutaneacetate was studied further. It was a liquid. The amide prepared by way of the acid chloride was a liquid, b.p. 154° (0.3 mm.), n_D^{20} 1.4817, d^{20} 1.0738.

Anal. Calcd. for $C_{11}H_{19}O_3N$: N, 6.57. Found: N, 6.57.

Similarly, amides prepared from *p*-nitroaniline, *p*-aminobenzoic acid, and ethylenediamine were all liquids. The corresponding amides of 2,2-dimethyl-3-(ethoxycarbonyl)-cyclobutaneacetic acid were all solids. These were not characterized.

Symmetrical and mixed dialkyl pinates. A number of dialkyl pinates were made for use in saponification studies. These were prepared by direct esterification, reduction of vinyl alkyl esters,[3] transesterification, and through use of the acid chlorides of some monoalkyl esters, Table II.

Mixed esters by reaction of monoalkyl pinates. Ethyl 2,2-dimethyl-3-(alkoxycarbonyl)cyclobutaneacetates. Ethyl 2,2-dimethyl-3-(carboxy)cyclobutaneacetate, 125 g. (0.58 mol.), was dissolved in 120 ml. benzene with one equivalent of 2-

(9) V. M. Loeblich, F. C. Magne, and R. R. Mod, *Ind. Eng. Chem.*, 47, 855 (1955).

(10) E. A. Wielicki, C. J. Boone, R. D. Evans, M. R. Lytton, H. B. Summers, Jr., and G. W. Hedrick, *J. Polymer Sci.*, in press.

(11) Two per cent carbon tetrachloride solution, Perkin Elmer Infrared Spectrometer, Model 21, sodium chloride optics.

(12) J. P. Bain, *J. Am. Chem. Soc.*, 68, 638 (1946).

TABLE I

MONOALKYL PINATES

	B.P.	Mm./ Hg	Composition, % a[a]	b[a]	c[a]	Neutral Equivalent Calcd.	Found	Saponification Equivalent Calcd.[b]	Found	Refractive Index, n_D^{20}	Density, d^{20}
Acetic Acid Form											
Ethyl	128	0.2		100		214.3	214.3	107.1	107.1	1.4569	1.0736
n-Butyl	142	0.25	2.4	97.6	0	242.3	233.2	120.2	120.1	1.4588	1.0407
2-Ethylhexyl	171	0.15	0	90.0	10.0	298.4	331.0	155.3	154.8	1.4554	.9901
Hydronopyl	202–208	0.45	0.8	99.2	0	336.5	330.3	166.8	166.1	1.4907	1.0572
3-Carboxycyclobutane Form											
Ethyl	125	0.1	0	100	0	214.3	214.3	107.1	107.1	1.4583	1.0706
n-Butyl	139.5–144	0.3	0	99.5	0.5	242.3	243.6	121.3	120.2	1.4590	1.0462
2-Ethylhexyl	174	0.17	11.6	88.4	0	298.4	237.4	139.4	139.1	1.4569	1.0090
Hydronopyl	199	0.1	7.2	92.8	0	336.5	283	159.0	158.2	1.4899	1.0652

[a] a. Pinic acid. b. Monoester. c. Diester. [b] Theoretical saponification equivalent calcd. from neutral equivalent found.

TABLE II

DIALKYL PINATES

	B.P.	Mm./ Hg	Refractive Index, n_D^{20}	Density, d^{20}	Saponification Equivalent Calcd.	Found	Formula	Analyses Calcd. C	Calcd. H	Found C	Found H
Diethyl	108	1.0	1.4457	1.0123							
Di-*n*-butyl	136	0.4	1.4505	0.9817	149.2	148.4	$C_{17}H_{30}O_4$	68.42	10.13	67.52	9.91
Di-2-ethylhexyl	188	0.12	1.4574	0.9394	205.3	201.0	$C_{25}H_{46}O_4$	73.12	11.29	72.80	11.03
Dihydronopyl	242	0.15	1.4966	1.0241	243.4	244.7	$C_{31}H_{50}O_4$	76.50	10.36	76.27	10.44
Ethyl Acetates											
n-Butyl	116	0.3	1.4470	0.9864	135.2	133.2	$C_{15}H_{26}O_4$	66.63	9.69	66.73	9.64
2-Ethylhexyl	151	0.3	1.4519	0.9610	163.2	162.4	$C_{19}H_{34}O_4$	69.90	10.50	69.93	10.48
Hydronopyl	181	0.1	1.4794	1.0201	182.3	184.0	$C_{22}H_{36}O_4$	72.49	9.96	72.71	10.17
Ethoxycarbonyl Esters											
n-Butyl	120	0.3	1.4468	0.9868	135.2	134.8	$C_{15}H_{26}O_4$	66.63	9.69	66.43	9.74
2-Ethylhexyl	148	0.3	1.4516	0.9612	163.2	162.2	$C_{19}H_{34}O_4$	69.90	10.50	70.01	10.30
Hydronopyl	182	0.1	1.4796	1.0192	182.8	185.8	$C_{22}H_{36}O_4$	72.49	9.96	72.67	9.75

ethylhexanol or hydronopyl alcohol and 8 g. *p*-toluene sulfonic acid. The water from the reaction was removed azeotropically and the product isolated by the usual procedure. Distillation of the 2-ethylhexanol ester gave three fractions; 52.3 g., b.p. 79–142° (0.3 mm.); 55.0 g., b.p. 132–142° (0.1 mm.); and 61.9 g., b.p. 142–188° (0.1 mm.). These fractions were redistilled and identified from boiling point and refractive index as diethyl pinate, ethyl 2-ethylhexyl pinate, and di-2-ethylhexyl pinate. With hydronopyl alcohol three fractions were taken: 27.5 g., b.p. 99–172° (0.4 mm.); 88.5 g., b.p. 172–186° (0.1 mm.); and 68.2 g., b.p. 186–250° (0.2 mm.). The distillates were characterized as above and found to be chiefly diethyl pinate, ethyl hydronopyl pinate, and dihydronopyl pinate.

Alkyl 2,2-dimethyl-3-(ethoxycarbonyl)cyclobutaneacetates. 2,2-Dimethyl-3-(ethoxycarbonyl)cyclobutaneacetic acid, 78.7 g. (0.367 mol.) was esterified with hydronopyl alcohol, 61.8 g. (0.367 mol.) in benzene, 200 ml., with 1 g. *p*-toluene sulfonic acid as a catalyst. By distillation of the ester two fractions were taken: 3.4 g., b.p. 76–164° (0.2 mm.) and a main fraction, 112 g., b.p. 181° (0.1 mm.), with 5 g. still residue. There was no more than a few drops of diethyl pinate, if any, in the forecut.

In another run using a five-fold increase in catalyst there was evidence of only slightly more diethyl pinate as a result of change in catalyst concentration. It was apparent that the alkoxycarbonyl form of monoester was much less susceptible to transesterification than the other form under the conditions of the reaction.

Ethyl 2,2-dimethyl-3-(alkoxycarbonyl)cyclobutaneacetates by use of acid chlorides. *n*-Butyl and hydronopyl alcohols were reacted with ethyl 2,2-dimethyl-3-(chlorocarbonyl)cyclobutaneacetate prepared with thionyl chloride by the Guha *et. al.* procedure.[5] Typically hydronopyl alcohol, 168 g.

(1 mol.) was dissolved in 500 ml. benzene in which 56 g. soda ash was kept suspended by agitation. The acid chloride, 232 g. (1 mol.) was added dropwise while holding the reaction mass at reflux temperature. After washing with water and stripping the solvent, the product was distilled. There was a forecut, 12 g., b.p. 103–178° (0.25 mm.) and the product, 266 g., 71% yield, b.p. 180–182° (0.1 mm.), with 32 g. still residue. An 86% yield was obtained with *n*-butyl alcohol, b.p. 116° (0.3 mm.).

Characterization of half esters by half saponification of mixed esters. Deviations from theoretical values for neutral and saponification equivalents of the various half esters and diesters were used in calculating purity and characterization of the esters. These results, however, gave no indication of the composition with respect to structural differences. This type of difference was established by half saponification of some of the mixed esters.

Half saponification of the butyl and hydronopyl ethyl pinates (ethyl acetate forms) from the above acid chloride reactions gave good yields of the corresponding alkoxycarbonyl half esters. Although some monoethyl pinate may have been present, the foreruns in the distillation (less than 10%) failed to crystallize when seeded with solid *cis-dl*-2,2-dimethyl-3-(ethoxycarbonyl)cyclobutaneacetic acid.

Similarly, saponification of alkyl ethoxycarbonylcyclobutaneacetates resulted in no detectable amounts of the alkylcarbonyl type monoester. The half ester obtained was good quality *cis*-2,2-dimethyl-3-(ethoxycarbonyl)cyclobutaneacetic acid.

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OLUSTEE, FLA

[CONTRIBUTION FROM DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, HEBREW UNIVERSITY]

Organic Carbonates. IV.[1a,b,c] Factors Affecting Formation of Homologous Cyclic Carbonates

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The preparation and properties of a number of branched 1,2-, 1,3-, and 1,4-cyclic carbonates are described. The formation of homologous cyclic carbonates by reaction of diols with diethyl carbonate is described as a two-step mechanism, involving first the formation of a mono-ester and then cyclization with an accompanying elimination of ethanol. The effect of both substitution and chain length in homologous alkylene glycols upon their tendencies to yield monomeric cyclic carbonates is discussed.

In a previous communication[1c] we have described the effect of substitution in 1,3-propanediol carbonates upon their tendencies to undergo reversible polymerization. This paper is concerned with a similar study regarding the effect of both substitution and chain-length in 1,2-, 1,3-, and 1,4-diol upon their tendencies to form cyclic and/or polymeric carbonates.

In this study we employed two methods: (1) ester interchange between an appropriate diol and diethyl carbonate in the presence of catalytic amounts (2.5–5% mole) of dry sodium methoxide[1c]; (2) the reaction of phosgene with diols in the presence of antipyrine, according to the method of Ludwig and Piech.[3] In each method it was found that the nature and yields of the reaction products obtained are largely dependent upon reaction conditions and molecular structure of reactants. For example, in the transesterification of neopentylene glycol by means of diethyl carbonate, three distinct organic carbonates (II, III, and V) could be obtained, upon varying the molar ratio catalyst/reactants. Thus, in the presence of large amounts of dry sodium methoxide catalyst (5–10 mol. %), high yields of the cyclic carbonates (IIId) are obtained. Upon 10-fold decrease of the amount of catalyst (0.5–1.0 mol. %), the polymeric form (Vd) is obtained almost exclusively. Upon further decrease in the amount of catalyst (0.45 mol. %) a monoester (IId) is obtained along with Vd, but none of IIId. A more detailed study of this phenomenon will be given in a subsequent paper.

In the series of 1,3-propanediols, we observed that branching at carbon atoms 1, 2, and 3, favors the formation of the requisite cyclic esters, and at the same time it exerts a hindrance upon their tendencies to undergo a polymerization reaction. Thus, upon ester interchange between 1,3-butanediol (Ib) and 2,4-pentanediol (Ic) and diethyl carbonate, the corresponding 1,3-cyclic carbonates (IIb and IIc) were produced in 70–72% yields, whereas IIIa was obtained in 50% yield. Similarly, disubstitution at carbon atom 2, while it suppresses or even abolishes the tendency to polymerization, has, however, an enhancing effect toward the formation

(1) (a) Part I, *Compt. rend.*, **245**, 2321 (1957); (b) Part II, *Bull. Research Council Israel*, **7A**, 42; (c) Part III, S. Sarel and L. A. Pohoryles, *J. Am. Chem. Soc.*, **80**, 4596 (1958).

(2) Formerly Shalom Israelashvili; to whom inquiries should be sent.

(3) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5779 (1951).

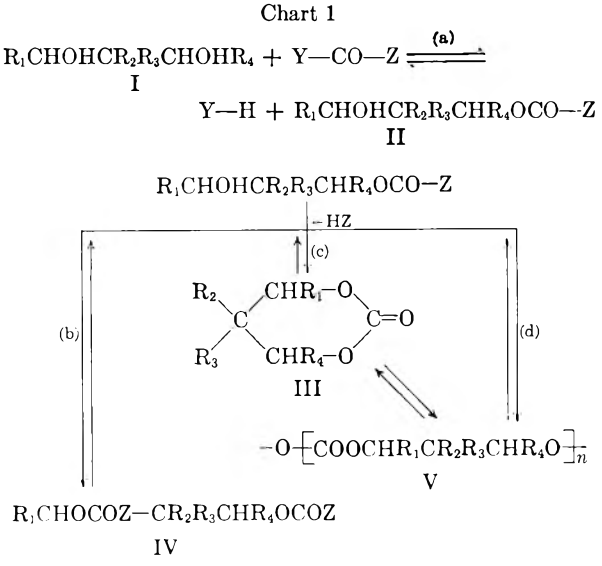
of cyclic esters (IIId–IIIh). On the other hand, the yields of the inner carbonates seemingly tend to drop markedly upon increasing the bulkiness of the alkyl substituents. For example, only a 25% yield of IIIi was obtained on condensation of Ii with diethyl carbonate, whereas similar reaction with Ie afforded IIIe in 75% yield.

Depending upon molar ratio, the condensation of 1,3-diols with ethyl urethane in the presence of ester-interchange catalysts may lead to the formation of either the mono- or dicarbamate derivatives along with small amounts of the corresponding cyclic carbonate. The latter is seemingly produced as a result of an intramolecular amide alcoholysis. Thus, in the case of monocarbamate of IIg (Z = NH_2) we found that its conversion into IIIg could be achieved only at high temperatures, and even then it was produced at an exceedingly slow rate as indicated by measuring the flow of ammonia liberated. This result is consistent with the theory concerning the reversible formation of amides from esters.[4] Chart I describes in outline all the reactions involved in the interactions between 1,3-glycols and appropriate derivatives of carbonic acid.

1,4-Cyclic carbonate. In contrast to the 1,2- and 1,3-cyclic carbonates, which can be prepared rather conveniently by either method described here, the synthesis of the seven-membered homolog has so far been unsuccessful. Thus, when VI was brought into reaction with diethyl carbonate in the presence of an ester-interchange catalyst both under nondilute[5] and dilute[6] conditions, no monomeric 1.4-cyclic carbonate could be isolated. Instead, the linear polymer, polytetramethylene carbonate XI, and a dimeric cyclic carbonate (XII) containing a fourteen-membered ring was obtained. Carothers and Van Natta[5] showed that, unlike polytrimethylene carbonate Va, XI was not reversibly converted to the monomeric form (IX), and that upon heating it produced only the fourteen-membered dimer.

In our hands, however, the requisite monomeric 1,4-cyclic carbonate IX was obtained under dilute conditions, by both the phosgene-antipyrine method and by ester-interchange reaction between VI and diethyl carbonate, in 26% and 12% yields, respectively. The structure of IX was indicated by its analysis, molecular weight determination and infrared spectra. Again, the main reaction product found consisted of fractions of an average molecular weight of 200–600, corresponding to an average chain length of 2–5 units. Under nondilute conditions, 11–12 structural units of —O—CO—$(CH_2)_3$—O— have been reported for the polymeric form.[5] In addition, the cyclic dimer (XII) has also been isolated, only in the ester-interchange reaction. Charts I and II, describe all the reactions between diols and carbonic acid derivatives as involving a multistage mechanism. This involves first the formation of a monoester (II or VII) and then its cyclization and/or polymerization with accompanying elimination of either ethanol or hydrogen chloride. In the series of 1,3-propanediols, factors such as would accelerate rates of reaction and/or the presence of alkyl substituents in the carbon chain of the diol, positively favor the formation of cyclic carbonates at the expense of the concurrent polymerization reaction.[7] However, the increase of the unit length in the series of polymethylene glycols does not favor the formation of the monomeric cyclic carbonates, but at the same time it does favor the formation of the polymeric forms. The same mechanism should hold similarly for the reactions of 1,2-diols, despite the fact that the presumed monoester has never been isolated in these reactions.[8] It appears, therefore, that in these systems the ring-closure stage of the reaction must be much more rapid than the first, and the monoester does not build up during the reaction.[9]

Chart 1



Z = Y = Cl, OEt; Z = OEt, Y = Cl; Y = OEt, Z = NH_2

Ia and IIIa. $R_1 = R_2 = R_3 = R_4 = H$.
Ib, IIb, and IIIb. $R_1 = R_2R_3 = H$; R_4 = Me
Ic and IIIc. $R_1 = R_4$ = Me; $R_2 = R_3 = H$.
Id, IId, and IIId. $R_1 = R_4 = H$; $R_2 = R_3$ = Me
Ie and IIIe. $R_1 = R_4 = H$; $R_2 = R_3$ = Et.
If and IIIf. $R_1 = R_4 = H$; R_2 = Me; R_3 = Ph
Ig and IIIg. $R_1 = R_4 = H$; R_2 = Et; R_3 = Ph.
Ih and IIIh. $R_1 = R_4 = H$; R_2 = Me; R_3 = *n*-Pr
Ii and IIIi. $R_1 = R_4 = H$; R_2 = Et; R_3 = *i*-Am

(4) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 782.

(5) W. M. Carothers and F. J. Van Natta, *J. Am. Chem. Soc.*, 52, 314 (1930).

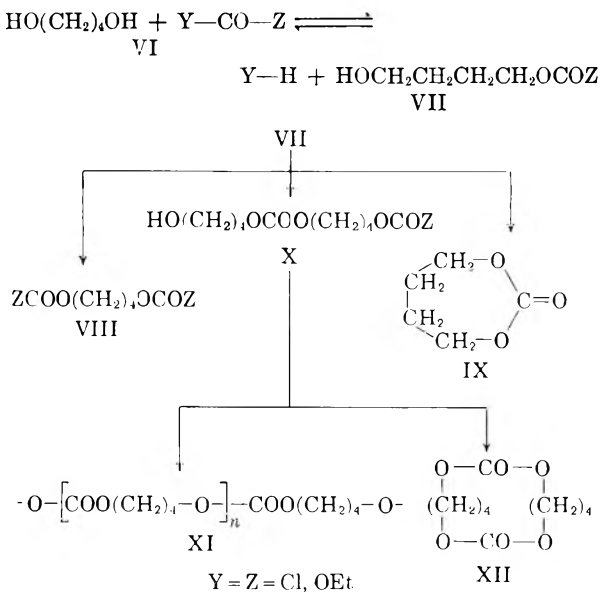
(6) W. J. Bailey and W. R. Sorenson, *J. Am. Chem. Soc.*, **78**, 2287 (1956).

(7) H. K. Hall, *J. Am. Chem. Soc.*, **80**, 6404 (1958).

(8) W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, 151 (1930); 2796 (1929); 2254 (1932). A. Contardi and A. Ercoli, *Gazz. chim. ital.*, 64, 522 (1934).

(9) S. Sarel, I. Levin, and L. A. Pohoryles, paper sent for publication.

Chart 2



It is interesting to note that upon ester-interchange conditions, pinacol tends to undergo, to some extent, a C—C bond fission, thus yielding a mixture of acetone and isopropanol. The former has actually been isolated and identified as its 2.4-dinitrophenyl-hydrazone.[10]

EXPERIMENTAL[11]

Materials. The sources and purification procedures for the diols were as follows: Commercial 2,3-butanediol (B.D.H.) was fractionated and the cut boiling at 83–85 (14 mm.), n_D^{25} 1.4368 was used.[12] Commercial trimethylene glycol was fractionated and the fraction of b.p. 106–110° at 15 mm., n_D^{15} 1.4418, d_4^{15} 1.0590 (reported[12] b.p. 217.4° at 760 mm., n_D^{21} 1.4394) was used. 2,2-Dimethyl-1,3-propanediol, 2,2-diethyl-1,3-propanediol ("Eastman"), and 2-methyl-2-*n*-propyl-1,3-propanediol (Abic) were used without further purification.

α-Phenylpropionaldehyde, b.p. 91–94° at 12 mm., was prepared in 65% yield by hydrolysis of phenylmethylglycidic ester as described.[13]

2-Methyl-2-phenyl-1,3-propanediol, b.p. 150–155° (2 mm.), was obtained by the reductive aldol condensation of formaldehyde with α-phenylpropionaldehyde, according to Franke and Frank[14] in 45–50% yield. Recrystallization from carbon tetrachloride gave a crystalline product melting at 75° (reported[14] m.p. 75°).

Pinacol was prepared according to the literature.[15] A cut of b.p. 86–90° (26 mm.) was used.

The following paper[16] describes the preparation of other diols employed herein.

Preparation of 1,2- and 1,3-cyclic carbonates. Method A. The general method adopted for the preparation of cyclic carbonate esters is essentially that previously described by Ludwig and Piech,[3] and the following procedure is typical for the preparation of compounds listed in Table I. To a solution containing 0.1 mol. of phosgene in dry toluene, was added dropwise, with stirring, at a rate to maintain the temperature between 30–40°. After addition being completed the mixture was stirred for an additional 30 min. and allowed to stand at room temperature overnight. It was then worked up in a manner as described.

Method B. The procedure previously described for the preparation of monomeric neopentylene carbonate[1(c)] illustrates the method that was adopted for the production of cyclic carbonates listed in Table I. As has previously been shown, the ratio catalyst/substrate may affect markedly both the course and the yields in the formation of cyclic carbonate esters. Bests yields are obtained upon employing 2.5–5.0% mol. of sodium methoxide catalyst and small excess (10%) of diethyl carbonate.

1,4-Cyclic carbonate. Method C. This illustrates an adaptation of Method A for dilute conditions which was used in the preparation of the seven-membered ring carbonate. A solution of 1,4-butanediol (30 g., 0.33 mol.) in 1400 ml. anhydrous chloroform was mixed with a solution of antipyrine (120 g., 0.67 mol.) in 100 ml. dry toluene, and to the resulting system was added dropwise, under stirring, a 43% solution (w/w) (70 g.) of phosgene in toluene at such a rate as to maintain a temperature of 45–50°. After being left overnight at room temperature, it was worked up in the usual way. Fractionation of reaction mixture afforded two cuts: (1) the desired monomeric cyclic carbonate (compound No. 14 listed in Table I), and (2) a dimeric cyclic carbonate (XII), 3.9 g. (10%), b.p. 110° (3 mm.), m.p. 174–175° (from chloroform) reported,[5,6] m.p. 175–176°. In the distillation flask a residue of a viscous low polymeric product remained (XI), n_D^{17} 1.4575, which amounted to 32% yield.

Anal. Calcd. for $(C_5H_8O_3)_x$: C, 51.7; H, 6.9. Found: C, 51.4; H, 7.4; av. mol. wt., 200–300 (Rast).

In nondilute conditions (Method A) the viscous polymeric product obtained constituted the main reaction product, having an av. mol. wt. 400–600 (Rast).

Method D. It represents Method B modified by diluting the reaction mixture with toluene. A mixture of tetramethylene glycol (45 g., 0.5 mol.) diethyl carbonate (65 g., 0.55 mol.) and about 2 mol. % of sodium methoxide was dissolved in 500 ml. dry toluene and refluxed for 10 hr. The ethanol-toluene azeotrope which formed (boiling at 72–76°) was removed continuously by distillation through a short Vigreux column. At the end, solvent and unreacted materials were removed by fractionation at reduced pressure using a Widmer column. The residue was then subjected to distillation in high vacuum, thereby yielding two cuts: (1) 1,4-butanediol cyclic carbonate (IX) (see Table I), and (2) colorless liquid (5 g.) b.p. 95–103° (0.6 mm.), n_D^{25} 1.4260, which, according to analysis and molecular weight determination, can be formulated as 1,4-bisethoxycarbonyloxybutane (VIII, Z = OEt).

Anal. Calcd. for $C_{10}H_{18}O_6$: C, 51.3; H, 7.7; mol. wt., 234. Found: C, 51.2; H, 8.4; mol. wt., 200.

(10) This observation is at variance with that described by C. B. Wooster and D. S. Latham, *J. Am. Chem. Soc.*, **58**, 76 (1936), who found that the reaction between ordinary pinacol and metallic sodium in liquid ammonia is confined to the replacement of one of the hydroxyl hydrogen atom.

(11) All melting points were determined by the use of Dr. Tottoli melting point apparatus, and are uncorrected. Infrared spectra were taken with a Baird double beam recording spectrophotometer, model B. Analyses were performed by Mrs. Marika Goldstein at the microanalytical laboratory of the department of organic chemistry, The Hebrew University.

(12) This fraction is mainly the meso- form. O. J. Schierholtz and M. L. Staples, *J. Am. Chem. Soc.*, **57**, 2710 (1935), give n_D^{25} 1.4364 for *meso*-2,3-butanediol. See also S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, 61, 1579 (1939).

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(16) L. A. Pohoryles, S. Sarel, and R. Ben-Shoshan, *J. Org. Chem.*, 24, 1878 (1959).

TABLE I

CYCLIC CARBONATES OF 1,2-, 1,3-, AND 1,4-DIOLS

No.	Compound Cyclic Carbonate of	M.P. or B.P.	Press., Mm. Hg	n_D^{15}	d_4^{15}	$(M_R)_D$ Calcd.	$(M_R)_D$ Found	Yield, %	Method	Formula	Analysis Calcd. C	Analysis Calcd. H	Analysis Found C	Analysis Found H
1	2,3-Butanediol[a]	93	3.5	1.4241	1.1408	26.39	25.98	55	B	$C_5H_8O_3$	51.72	6.94	51.37	7.03
2	2-Methyl-2,3-butanediol[b]	59–60						39	A	$C_6H_{10}O_3$	55.37	7.75	55.60	7.30
3	2,3-Dimethyl-2,3-butanediol[c]	180–181						42	A	$C_7H_{12}O_3$	58.31	8.39	58.80	8.19
								18	B					
4	Hydrobenzoin[d]	127						67	B	$C_{15}H_{12}O_3$	75.00	5.03	74.70	4.94
5	1,3-Propanediol[e]	45						50	B	$C_4H_6O_3$	47.06	5.92	46.86	6.10
6	1,3-Butanediol	113–115	0.2	1.4465	1.965	26.39	25.91	70	B	$C_5H_8O_3$	51.70	6.90	51.6	6.6
7	2,4-Pentanediol	116–117	2.5	1.4443	1.1179	31.01	30.85	66	B	$C_6H_{10}O_3$	55.4	7.8	55.0	8.0
8	2,2-Dimethyl-1,3-propanediol[f]	109–110						85	B					
9	2-Methyl-2-*n*-propyl-1,3-propanediol[g]	117–119	0.5	1.4545[h]	1.0733[h]	40.25	40.96	65	B					
10	2,2-Diethyl-1,3-propanediol[i]	44–45						75	B					
11	2-Ethyl-2-isoamyl-1,3-propanediol[j]	130–135	1.0	1.4705				25	B	$C_{10}H_{20}O_3$	63.79	10.71	64.50	10.56
12	2-Ethyl-2-phenyl-1,3-propanediol[k]	99–100						67	B	$C_{12}H_{14}O_3$	69.87	6.80	70.0	6.66
13	2-Methyl-2-phenyl-1,3-propanediol[l]	100						50	B	$C_{11}H_{12}O_3$	68.75	6.25	68.73	6.34
14	1,4-Butanediol[m]	88–93	0.8	1.4260[h]	1.0867[h]	26.39	27.38	16	C	$C_5H_8O_3$	51.7	6.9	51.3	7.5
								12	D					

[a] J. J. Kolfenbach, E. I. Fulmer, and L. A. Underkofler, *J. Am. Chem. Soc.*, **67**, 502 (1945) give b.p. 96° (8 mm.), n_D^{26} 1.4225, d_4^{26} 1.129. [b] Recrystallized once from ligroin and then from methanol. [c] Recrystallization solvent methanol. [d] Recrystallized from aqueous ethanol. [e] Purified by first distillation at reduced pressure, b.p. 123° (1 mm.), 119° (0.9 mm.), and then recrystallized from ether; Ref. 5 records b.p. 135° (4 mm.), 105° (0.2 mm.), m.p. 47–48° (ether). [f] It was purified by resublimation *in vacuo*; see also ref. 1(c). [g] Ref. 3 reports b.p. 95–104° (0.25 mm.), n_D^{25} 1.4550. [h] Determinations being carried out at 16°. [i] Recrystallized from aqueous ethanol; Ref. 3 records a m.p. 45–46° and 66% yield by means of Method A. Attempts to polymerize this product by using sodium methoxide as catalyst, according to W. H. Carothers and Van Natta, Ref. 5, failed. [j] Inspection of the infrared spectrogram revealed the presence of some starting diol but it could not be purified any further. [k] Recrystallized from carbon tetrachloride; Ref. 3 reports m.p. 99.5–100.5°. [l] Recrystallized from carbon tetrachloride. [m] Mol. wt., calcd.: 116; found: 122 (benzene).

The solid polymeric residue left in the distilling pot amounted to 55–60% yield, and gave, upon recrystallization from carbon tetrachloride, a white amorphous solid product, m.p. 63–65°.

Anal. Calcd. for $(C_5H_8O_3)_x$: C, 51.7; H, 6.9. Found: C, 51.5; H, 7.4; av. mol. wt., 600 (Rast).

The infrared spectrum of compound No. 14 (IX) listed in Table I shows bands (cm.$^{-1}$) at 2976, 2950 (C—H stretching), 1730, 1718 (carbonyl), 1476, 1404, 1390, 1374 (C—H deformation), 1282, 1266, 1251, 1093, 1043, 1036, 1020, 1012 (C—O ethers), 952, 876, 796.

2,2-Dimethyl-3-hydroxypropyl carbamate (IId, Z = NH_2). A mixture of neopentylene glycol (13 g., 0.125 mol.) and ordinary urethane (11 g., 0.123 mol.) was placed in a flask equipped with a 12-inch Vigreux column, and to it was added a solution of 0.3 g. of aluminum isopropoxide in 50 ml. dry xylene. The resulting solution was heated and the ethanol was removed, as soon as formed, by distillation. At the end, 1 ml. of water was added and then the solvent was removed by distillation at reduced pressure. Fractionation of the residue *in vacuo* gave: (1) 3 g. (23%) of starting glycol, b.p. 76–80° at 1 mm., m.p. 122–124° (from benzene); (2) 10 g. (55%) of 2,2-dimethyl-3-hydroxypropyl carbamate of b.p. 110–120° at 1 mm. (reported[3] m.p. 60–61°).

Anal. Calcd. for $C_6H_{13}NO_3$: C, 49.0; H, 8.8. Found: C, 49.4; H, 9.2.

The infrared spectrum of this monocarbamate shows bands (cm.$^{-1}$) at 3330, 2970, 1700, 1695, 1620.

In the distillation flask 1–2 g. of a solid residue remained, which gave after two recrystallizations from hot water a crystalline dicarbamate of neopentylene glycol melting at 147–149° (reported[3] m.p. 151.5–152.5°).

When the heating of the reaction mixture was continued, after collecting the estimated amount of ethanol formed, measurable amounts of ammonia could be detected at the receiving flask. Upon fractionation of the reaction residue, small amounts of neopentylene carbonate could be isolated.

Isolation of 3-ethoxycarbonyloxy-2,2-dimethyl-1-propanol[17] (IId, Z = OEt). When 2.0 mol. of Id brought to reaction with 0.3 mol. of diethyl carbonate in the presence of 0.45% mol. of sodium methoxide in a fashion described above, a reaction mixture was obtained, consisting of 13.5 g. (52%) of a polymeric product (Vd) and 15.8 g. (45%) of a crude monoester IId. Refractionation of the latter at reduced pressure afforded 10 g. (28.5%) of a colorless liquid of b.p. 85–90° (0.5 mm.), n_D^{28} 1.4320.

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.5; H, 9.1. Found: C, 54.6; H, 9.1.

The infrared spectrum shows band (cm.$^{-1}$) at 3430 (hydroxyl), 2963 (C—H stretching), 1739, 1731 (carbonyl), 1476, 1404, 1379 (C—H deformation), 1266–1262, 1190, 1122, 1053 (C—O ethers).

Conversion of IId into IIId.[17] To 8.8 g. (0.05 mol.) of IId (Z = OEt) was added 5 mol. % of catalyst and the resulting solution was heated at 130° in conditions described above. The ethanol was distilled as soon as formed, yielding the calculated amount (2.2 g.) after 3 hr. of heating. The residue was distilled *in vacuo* to give 6.0 g. (90%) of colorless product, boiling at 90° (0.5 mm.), m.p. 108–109°. It was identical, as to melting point, mixed melting point, and infrared spectrum, with an authentic sample of neopentylene carbonate. The infrared spectrum of pure neopentylene carbonate shows bands (cm.$^{-1}$) at 2920, 2878, 1739, 1730, 1476, 1408, 1377, 1323, 1294, 1242, 1227, 1198, 1187, 1124, 1117, 805, 774.

Isolation of 1-ethoxycarbonyloxy-3-butanol (IIb, Z = OEt). Transesterification of 1,3-butanediol by means of diethyl carbonate in the presence of a catalyst, gave, in one run, a considerable amount of a forerun, from which it was obtained upon refractionation, a colorless liquid, b.p. 81–84° (0.6 mm.), n_D^{29} 1.4235, in 10% yield.

Anal. Calcd. for $C_7H_{14}O_4$: C, 51.85; H, 8.64. Found: C, 51.60; H, 8.0.

Infrared: 3509 cm.$^{-1}$ (OH), 2985 cm.$^{-1}$ (C—H), 1780 cm.$^{-1}$, 1754 cm.$^{-1}$, 1739 cm.$^{-1}$ (C=O), 1471 cm.$^{-1}$, 1460 cm.$^{-1}$, 1370 cm.$^{-1}$ (C—H deformation), 1205 cm.$^{-1}$, 1149 cm.$^{-1}$, 1075–1058 cm.$^{-1}$, 1034 cm.$^{-1}$ (C—O ethers).

Cyclic carbonate of 1,3-butanediol (IIIb). The cyclization of 1-ethoxycarbonyloxy-3-butanol into the corresponding cyclic carbonate ester (IIIb) with accompanying elimination of the theoretical amount of ethanol was effected in a like manner as described above for IIId, with the same yield. The infrared spectrum of pure compound No. 6 (in Table I) shows bands (cm.$^{-1}$) at 3008, 2985 (methyl), 1733–1724 (carbonyl), 1498, 1488, 1408, 1365 (C—H stretching), 1250 (ester), 1200–1205, 1117 (C—O ethers), and at 772.

3-Carbamoxy-2-ethyl-2-phenyl-1-propanol (IIg, Z = NH_2). Ammonolysis of compound No. 12 in Table I (IIIg) to yield the monocarbamate IIg (Z = NH_2), was effected by means of concentrated aqueous ammonia solution (36–40%) at 0°. Five g. of IIIg were suspended in 50 ml. concentrated ammonia solution at 0–4°, and stirred for 2 hr., at which time the solution became completely clear, and then left to stand in an icebox overnight. From the acidified solution a crystalline monocarbamate m.p. 89–90° (lit.,[3] m.p. 89–90°) was recovered by removing the solvent *in vacuo*, followed by ether extraction and crystallization from carbon tetrachloride. The yield: 90%.

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.57; H, 7.62; N, 6.28. Found: C, 64.62; H, 7.67; N, 6.16.

Conversion of monocarbamate (IIg, Z = NH_2) *into cyclic carbonate ester* (IIIg). A solution of 3-carbamoxy-2-ethyl-2-phenyl-1-propanol (1 g.) in dry xylene (10 ml.) containing 15 mg. of sodium methoxide was refluxed for 100 hr. The ammonia was removed, as soon as formed, by a nitrogen stream bubbled through the solution, and was intermittently estimated. At the end no ammonia could be detected in the nitrogen stream, and heating was stopped. After removal of solvent and catalyst the residue was subjected to several recrystallizations from carbon tetrachloride, until it reached a m.p. of 95–98°. The infrared spectrum revealed that it was contaminated with some starting monocarbamate.

The infrared spectrum of 2-ethyl-2-phenyl-1,3-propanediol carbonate shows bands (cm.$^{-1}$) at 2985, 2933, 1739, 1731, 1605, 1586, 1488, 1413, 1399, 1389, 1359, 1258, 1205, 1190, 1183, 1147, 1110, 1099, 1064, 1058, 1034, 972, 946, 915, 794, 772, 757, 702.

Transesterification of pinacol. In the conditions described above, the reaction between ordinary pinacol and 20% excess of diethyl carbonate, in the presence of 3 mol. % of sodium methoxide (or more), was markedly slow, as shown by measuring the amount of ethanol formed at 1-hr. intervals. At the end of 12 hr., about 30% of the calculated amount of ethanol was collected. That this distillate contained other components than ethanol, is indicated by its positive response to carbonyl reagents, such as 2,4-dinitrophenylhydrazine. The carbonyl-containing component was proved to be acetone, yielding a 2,4-dinitrophenylhydrazone of m.p. 126–127° (lit.,[18] 128°), giving no depression of mixed melting point with an authentic specimen of dinitrophenylhydrazone of acetone. In addition to the desired cyclic carbonate (No. 3 in Table I), we were able to recover, from the reaction mixture, about 50% of starting materials.

The infrared spectrum of pinacole carbonate shows bands (cm.$^{-1}$) at 2975, 2912, 1782, 1754, 1563, 1460, 1379, 1294–1286, 1227, 1221, 1151, 1090, 1031, 1010, 883, 787, 716.

(17) Work done by Mrs. S. Joseph.

(18) C. F. H. Allen, *J. Am. Chem. Soc.*, 52, 2955 (1930)

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[CONTRIBUTION FROM DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, HEBREW UNIVERSITY]

Anomalous Reactions of Lithium Aluminum Hydride

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The preparation and properties of a number of branched 1,2- and 1,3-diols are described. The lithium aluminum hydride reduction of β-hydroxybutyraldehyde gives ethanol, among other products. The reduction of acetylacetone leads to a mixture consisting of 19% diketone (starting material), 70.5% pent-3-en-2-ol, and 2.5% of corresponding diol.

In connection with the study of the formation of homologous cyclic carbonates in the accompanying paper[2] it was necessary to prepare the required diols. The present paper describes the methods of preparation and properties of some of the needed compounds.

The methods used for the synthesis of the necessary diols were: (1) lithium aluminum hydride reduction of ketols and esters of dicarboxylic acids; (2) addition of Grignard reagents to β-hydroxyketones; (3) solvolysis of olefin dibromides.

The lithium aluminum hydride reduction of esters of ethylphenyl- and ethylisoamylmalonic acids proceeds smoothly, giving the corresponding 1,3-diols in 75% and 72% yield, respectively. However, the reduction of diethyl succinate resulted in a low yield of the desired 1,4-diol. This result is probably due to incomplete extraction of the diol from the reaction mixture.[3]

In the reduction of benzoin, we observed temperature-dependence in the stereochemical specificity of the hydride attack. Thus, whereas the reduction at 0° produced mesohydrobenzoin in 90% yield, the reduction similarly in boiling tetrahydrofuran gave a mixture of the isomers, meso- and isohydrobenzoins, in a ratio 3:1. This ratio is changed into 1.5:1, upon performing the reduction in boiling dioxane. The data here produced amplify the observations already recorded regarding the effect of temperature on the stereospecificity of the hydride attack.[4]

Unlike compounds described above, the lithium aluminum reduction of aldol took an anomalous course. This reaction yielded a complex mixture consisting of the required diol, ethanol, crotyl alcohol, and some other unidentified polymeric materials. The yield of 1,3-butanediol was 39%, whereas that of ethanol, actually isolated, amounted to 15%.

The observation described here clearly suggest that the reduction of aldol might have taken, at least partially, an anomalous course, involving C—C bond cleavage. Of course, the latter reaction might possibly have occurred either prior to or after the carbonyl group was reduced. In an experiment designed toward this establishment, 1,3-butanediol was similarly treated with a molar equivalent of lithium aluminum hydride. It was found that in comparable working conditions the unchanged diol could be recovered in high yield, but no ethanol could be detected.

From this, one can conclude that in the reduction process of aldol a carbon-carbon bond cleavage occurs prior to the hydride attack at the carbonyl group. This indicates that the final product in this reduction is determined by the order in which the groups are attacked. Initial reduction of the carbonyl group leads to the desired diol while prior reaction of the hydroxyl group can subsequently result in diol, or, by reversal of the aldol formation and further reduction, ethanol. In contrast to the reduction reaction, the addition of methyl magnesium iodide to acetaldol in ordinary conditions resulted in 70% yield of the corresponding diol. This reflects the different capacities of the above organometallic complexes of initiating a retrograde reaction of the aldol formation.

An inspection of the literature revealed that, although certain β-hydroxyketones are not affected by the mixed metal hydride complexes,[5] yet C—C bond cleavages have actually been observed in the lithium aluminum hydride reductions of certain 1,3-bifunctional systems, of which at least one was of unsaturated character. Thus, similar C—C bond

(1) Formerly Shalom Israelashvili, to whom inquiries should be sent.

(2) S. Sarel, L. A. Pohoryles, and R. Ben-Shoshan, *J. Org. Chem.*, **24**, 1873 (1959).

(3) Compare K. M. Mann and R. F. Nystrom, *J. Am. Chem. Soc.*, **73**, 5894 (1951).

(4) See L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949).

(5) (a) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **75**, 939 (1953); (b) R. L. Wear, *J. Am. Chem. Soc.*, **73**, 2390 (1951); S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **73**, 4001 (1951).

fissions have been reported in the reductions of cyanohydrines,[6] β-nitro alcohols,[7] β-nitroamines,[7a] β-ketonitriles,[8] and in diaryl ketones.[9]

The reduction of acetylacetone with an excess of lithium aluminum hydride produced a mixture consisting of 70.5% pent-3-en-2-ol, 19% of the starting β-diketone, 2.5% of 2,4-pentanediol, and 8% of yellow solid product. This finding was indicated by the infrared and ultraviolet spectra as well as by chemical evidence. Thus, all liquid fractions gave similar infrared spectrum showing bands (cm.$^{-1}$) at 3450, 1709, 1671, and 1639–1580, in the ultraviolet region of the spectrum, they show the presence of a single absorption band at 272 mμ, which are typical for enolized β-diketones.[10] Accordingly, they responded positively to both alcoholic ferric chloride solution and 2,4-dinitrophenylhydrazine reagent.[11]

It is interesting to note that unlike the reduction of 2-hydroxymethylenecyclopentanone and of 2-hydroxymethylenecyclohexanone, which has been reported to produce the respective mixture of isomeric diols and unsaturated alcohols in a ratio of 1:14 and 1:6,[5a] the ratio between the diol and the unsaturated alcohol in the foregoing reaction is of the order 1:28.

The yellow solid product, which has been isolated in the foregoing reaction, was analyzed as $C_8H_{12}O_4$. The chemical and spectroscopic data now at hand suggest that this compound might be a dimethyldihydroxy derivative of 1,3-cyclohexadione, but it was not investigated any further.

In common with analogous aliphatic and alicyclic enolizable β-dicarbonyls, it appears that the final product of the reduction of acetylacetone is determined by the order in which the groups, in both forms of the tautomeric mixture, are attacked. Initial reduction of the enol form, followed by elimination of an oxygen atom and further reduction, can subsequently result in pent-3-en-2-ol, while normal reduction of the diketone form leads to the desired diol. Accordingly, these results clearly suggest that, at ordinary reaction conditions, acetylacetone reacts predominantly *via* its enolic form,[12] but, unlike analogous alicyclic systems,[5a] the former shows a lesser tendency to lose an oxygen atom to form a C—C double bond. Considering the differences in effectiveness between lithium aluminum hydride and Grignard reagents in promoting an oxygen atom, elimination from the enolic forms of β-dicarbonyls,[13] Freeman's finding,[14] which observed monoaddition of phenyl magnesium bromide to acetylacetone at ordinary conditions and simple double addition on forcing conditions, is consistent with the data presented here.

The preparation of vic-diols by means of hydrolysis of the corresponding dibromides appears to be of limited practical value, and was found particularly valueless for the production of certain 2-alkyl-1,2-alkanediols. Thus, the solvolysis of 2-methyl-2,3-dibromobutane in aqueous sodium carbonate gave the corresponding diol in 51% yield, whereas similar treatment of isobutylene bromide failed to produce the desired 1,2-diol, but gave in part isobutyraldehyde.[15]

EXPERIMENTAL[16]

Materials. Diethyl ethylphenylmalonate (Riedel de Haen, Germany), diethyl ethylisoamylmalonate (Bubeir Dolder, Basel), and ethyl lactate (B.D.H.) were used without further purification. Commercial acetylacetone was fractionated and the cut boiling at 136–137° (680 mm.), λ_{max} 272 mμ, ε 8540 (lit., λ_{max} 270 mμ, ε = 10,000[10]) was used.

β-Hydroxybutyraldehyde (aldol) was prepared in 45% yield by the method of Grignard and Reiff.[17] A fraction boiling at 85° (13 mm.) (lit.,[18] b.p. 72° at 12 mm.) was used.

Benzoin, m.p. 128–129°, was prepared according to Adams and Marvel.[19]

Formation of diols by means of $LiAlH_4$. The general technique described below is typical for the preparation of compounds listed in Table I. To a slurry of lithium aluminum hydride (5 g., 0.13 mol.) in dry ether (100 ml.) was added dropwise with agitation a solution of diethyl ethylisoamylmalonate (25.8 g., 0.10 mol.) in dry ether (100 ml.). After addition was completed, the reaction mixture was refluxed for two hr. and then allowed to stand overnight at room temperature. The excess of $LiAlH_4$ was decomposed with water (ice cooling) and the organo-metallic complex was decomposed by means of an equivalent amount of 25% aqueous phosphoric acid. The organic layer was separated and the aqueous layer was first centrifuged and then continuously extracted with ether. The ethereal extracts were combined, carefully dried, and after solvent removal the

(6) A. W. D. Avison, *J. Appl. Chem.*, 1, 469 (1951); J. D. Roberts and W. F. Gorham, *J. Am. Chem. Soc.*, **74**, 2278 (1952).

(7) (a) A. Dornow and M. Gellrich, *Ann.*, **594**, 177 (1955); (b) A. Dornow and co-workers, *Ber.*, **90**, 1769, 1774, 1780 (1957).

(8) P. Reymand and J. Matti, *Bull. Soc. Chim.* (France) (5), **17**, 720 (1950). For references to latter work see ref. 7(b), p. 1774.

(9) P. Rona and U. Feldman, *J. Chem. Soc.*, 1737 (1958).

(10) R. S. Rassmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).

(11) G. D. Johnson, *J. Am. Chem. Soc.*, **73**, 5888 (1951).

(12) J. B. Conant and A. F. Thompson, *J. Am. Chem. Soc.*, **54**, 4039 (1932) reported that in hexane and alcohol solutions, acetylacetone is about 92% and 83% enolic, respectively. See also W. Strohmeier and I. Hohne, *Z. Naturforsch.*, **7b**, 184 (1952); **8b**, 53 (1953).

(13) J. P. Freeman and M. F. Hawthorne, *J. Am. Chem. Soc.*, **78**, 3366 (1956).

(14) J. P. Freeman, *J. Am. Chem. Soc.*, **80**, 1926 (1958).

(15) C. M. Suter and H. D. Zook, *J. Am. Chem. Soc.*, **66**, 738 (1944).

(16) All melting points were determined using a Dr. Tottoli melting point apparatus, and are uncorrected. Ultraviolet absorption spectra were determined with the aid of a Beckman quartz spectrophotometer, model DU, and were taken in 95% ethanol solution. Infrared spectra were taken with a Baird double beam recording spectrophotometer, model B. Analyses were performed by Mrs. Marika Goldstein at the microanalytical laboratory of the Department of Organic Chemistry, the Hebrew University.

(17) V. Grignard and J. Reiff, *Bull. Soc. Chim.*, (4), **1**, 116 (1907).

(18) L. P. Kyriakides, *J. Am. Chem. Soc.*, **36**, 532 (1914).

(19) R. Adams and C. S. Marvel, *Org. Syntheses*, **Coll. Vol. I**, 94 (1941).

TABLE I

PREPARATION OF 1,2-, 1,3-, AND 1,4-DIOLS BY LITHIUM ALUMINUM HYDRIDE REDUCTION

Diol	Reaction Temp.	B.P.	Mm.	M.P.	n_D^{20}	Yield, %
Mesohydrobenzoin[a]	0			134–136		90
1,3-Butanediol[b]	34	69–70	0.6		1.4445	39
2-Ethyl-2-phenyl-1,3-propanediol[c]	34			79		75
2-Ethyl-2-isoamyl-1,3-propanediol[d]	63	133–135	10		1.4672	72
1,4-Butanediol[e]	34	140–143	27		1.4450	35–40

[a] Recrystallized from benzene. J. S. Buck and S. S. Jenkins, *J. Am. Chem. Soc.*, **51**, 2163 (1929) give m.p. 134° for mesohydrobenzoin. [b] O. J. Schierholtz and M. L. Staples, *J. Am. Chem. Soc.*, **57**, 2710 (1935) give b.p. 207.5° at 760 mm., $n_D^{19.5}$ 1.4425 for pure 1,3-butanediol. [c] Recrystallized from carbon tetrachloride; H. L. Yale, E. J. Pribyl, W. Braker, J. Bernstein, and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 3716 (1950) give m.p. 78–79°. [d] *Anal.* Calcd. for $C_{10}H_{22}O_2$: C, 68.9; H, 12.7. Found: C, 69.0; H, 12.4. [e] W. R. Kirner and G. H. Richter, *J. Am. Chem. Soc.*, **51**, 2505 (1929), give b.p. 108° at 4 mm., n_D^{20} 1.4467 for 1,4-butanediol.

residue was distilled fractionally through an efficient column. The m.p., b.p., and yields of the diols prepared are given in Table I.

The reduction of aldol. Freshly distilled β-hydroxybutyraldehyde (0.6 mol.) was brought to reaction with lithium aluminum hydride (0.37 mol.) in the manner here reported. The organo-metallic complex was decomposed by adding 55 g. of phosphoric acid (85%) and the crystalline insoluble phosphates formed were removed by filtration. The inorganic precipitate was thoroughly washed with ether, the ethereal extracts were combined, dried (Na_2SO_4), and the solvent was removed. The residue, upon fractional distillation through Widmer column gave three cuts: (1) 8.2 g. (15%) of ethanol, boiling at 78–80° (680 mm.), n_D^{20} 1.3700; (2) 1.5 g. of an impure crotyl alcohol, boiling at 30–32° (30 mm.), n_D^{20} 1.3440; (3) 21 g. (39%) of 1,3-butanediol. In the distilling flask a residue (11 g.) remained. It was transferred into a Claisen flask and was distilled at reduced pressure, yielding 5.5 g. of viscous oil boiling at 108–120° (0.5 mm.), leaving behind 4.5 g. of a polymeric material.

Identification of reaction products. The first cut, ethanol, was identified by preparing its 3,5-dinitrobenzoate, colorless needles melting at 94–95° (from ethanol water). Mixed melting point with an authentic specimen of ethyl 3,5-dinitrobenzoate gave no depression. The second cut gave a positive color test with tetranitromethane.

The action of $LiAlH_4$ on 1,3-butanediol. When 0.3 mol. of 1,3-butanediol was treated with 0.17 mol. of lithium aluminum hydride in a fashion described above, only unchanged starting material was recovered from the reaction mixture. The recovery amounted to 80–85%.

The reaction of acetylacetone with lithium aluminum hydride. Acetylacetone (1.0 mol.) was brought to reaction with an excess of lithium aluminum hydride (0.65 mol.) at boiling tetrahydrofuran, in a manner reported here. After the usual work-up, the crude reaction product was subjected to fractional distillation giving two fractions: (1) 36 g. of colorless liquid boiling at 119–121° (690 mm.), n_D^{20} 1.4325, λ_{max} 272 mμ (ε 1830); (2) 10 g. of a liquid of b.p. 122–127° (690 mm.), n_D^{20} 1.4355, λ_{max} 272 mμ (ε 2600).

Fraction 1 was analyzed by its infrared and ultraviolet absorption spectra, showing that it consists of a mixture of 18% acetylacetone and 82% pent-3-en-2-ol.

Anal. Found: C, 67.9; H, 10.3.

In a like manner Fraction 2 was found to consist of a mixture of 30% acetyl acetone, 57% pent-3-en-2-ol, and 13% of 2,4-pentanediol.

Anal. Found: C, 65.45; H, 10.55.

In the distillation flask a residue of a yellow solid product remained (5 g.). It gave upon recrystallization from carbon tetrachloride orange-yellow crystals melting at 192°, λ_{max} 278–282 mμ (ε 15,400).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.8; H, 6.97; mol. wt., 172. Found: C, 55.3; H, 6.94; mol. wt., 160 (Rast).

It gave an immediate red coloration with an alcoholic ferric chloride solution. This product was not investigated any further.

2,4-Pentanediol. This diol was at last prepared in good yields by employing either the Grignard method or the high pressure catalytic reduction of appropriate β-diketone.

(a) *The Grignard method* furnished this diol in 70% yield by reacting methyl magnesium iodide (2.5 mol.) with freshly distilled acetaldol (1.0 mol.), according to Franke and Kohn.[20] (b) *The catalytic reduction* of acetylacetone (1 mol.) was conducted at 70–80 atmospheric pressure and 125° in the presence of Raney nickel (8 g.) during 2 hr., according to Sprague and Adkins,[21] resulting in a 50–70% yield of the desired diol. The cut boiling at 104–105° (17 mm.), n_D^{20} 1.4358 (reported[21] b.p. 97–98° at 13 mm., n_D^{20} 1.4349) was collected.

2-Methyl butanediol-2,3. (a) *By Grignard method.* Into a cooled solution of methyl magnesium iodide (3 mol.) in dry ether (500 ml.) was added, dropwise with stirring, a solution of 1 mol. of ethyl lactate in ether (100 ml.), during 1 hr. The reaction mixture, after being refluxed for 1 hr., was poured into cooled 4*N* sulfuric acid, the aqueous layer was separated and then concentrated to one third of its volume by vacuum distillation. Solid sodium chloride was added and the whole was continuously extracted with ether. The crude diol, after solvent removal, was fractionally distilled at reduced pressure, affording the pure diol, of b.p. 93–95° 24 mm., n_D^{25} 1.4380 (reported[22] b.p. 80–82° at 13 mm., 178° at 760 mm.), in 55% yield.

Anal. Calcd. for $C_5H_{12}O_2$: C, 57.7; H, 11.5. Found: C, 57.4; H, 11.5.

(b) *By solvolysis of 2-methyl-2,3-dibromobutane.* A mixture of 2-methyl-2,3-dibromobutane[23] (b.p. 74° at 31 mm., n_D^{20} 1.5118[24]) (250 gr.) and 2300 ml. of 10% aqueous sodium carbonate solution was heated at 90° under vigorous agitation for 12 hr. The formation of some low boiling liquid is noted during this operation (probably an epoxy derivative). The cooled mixture was then continuously extracted by using ether as solvent. After drying and solvent removal,

(20) A. Franke and M. Kohn, *Monatsh.*, **27**, 1108 (1906).

(21) J. M. Sprague and H. Adkins, *J. Am. Chem. Soc.*, **56**, 2669 (1934).

(22) G. Ciamician and C. Silber, *Ber.*, **43**, 947 (1910); N. A. Milas and S. Sussman, *J. Am. Chem. Soc.*, **58**, 1302 (1936).

(23) F. C. Whitmore, W. L. Evers, and H. S. Rothrock, *Org. Syntheses*, **Coll. Vol. II**, 408 (1943).

(24) J. F. Norris and R. Reuter, *J. Am. Chem. Soc.*, **49**, 2630 (1927), give b.p. 172–173° (760 mm.) n_D^{20} 1.511 for trimethylethylene dibromide.

the residue was fractionated at reduced pressure to yield 120 gr. of starting dibromide (b.p. 70° at 30 mm., n_D^{25} 1.4385) and 30 gr. of 2-methyl-2,3-butanediol, b.p. 93–95° at 24 mm., n_D^{25} 1.4375. The yield based upon 2-methyl-2,3-dibromobutane consumed, was 51%. The yield based upon dibromide used amounted to 27% conversion.

Treatment of isobutylene dibromide with aqueous potassium carbonate at 55° during 5 days resulted in its 40% conversion into isobutylraldehyde (b.p. 62°, n_D^{20} 1.3725), but no diol could be isolated.

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Thermal Rearrangement of Tetraphenyl-*p*-dioxadiene

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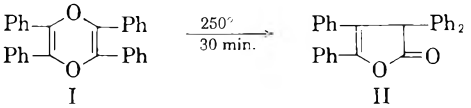
Tetraphenyl-*p*-dioxadiene (I) differs markedly from the analogous sulfur compound, 2,5-diphenyl-*p*-dithiadiene, in that it rearranges on pyrolysis to give a lactone whereas the sulfur compound decomposes to give a thiophene derivative. Similarities in the chemistry of I and *cis*-dibenzoylstilbene (III), which gives the same lactone on pyrolysis, are discussed.

Parham and Traynelis have recently described the thermal decomposition of 2,5-diphenyl-*p*-dithiadiene to give 2,4-diphenylthiophene and free sulfur.[2] With the thought that a similar reaction might occur in the *p*-dioxane series, the pyrolysis of tetraphenyl-*p*-dioxadiene (I) was carried out; the product, obtained in 90% yield, was not the anticipated tetraphenylfuran but was instead a rearrangement product, 2,2,3,4-tetraphenyl-3-buteno-4-lactone (II).



I II

The product (II) was identified by its elemental analysis, its infrared spectrum [very strong band at 5.58 μ, consistent with a β,γ-unsaturated-γ-lactone,[3a] weak absorption at 6.02 μ (—C=C—),[3b] and medium absorption at 8.06 μ, expected for the system —O—C=[3c]], and its melting point.

The rearrangement is not acid-catalyzed. A sample of I which had been carefully freed from traces of acid gave a smoother reaction and better yield of II than did a sample of I which had been crystallized from acetic anhydride. Also, the formation of the lactone does not involve formation and subsequent air oxidation of tetraphenylfuran. Pyrolysis of the furan under the same conditions as pyrolysis of I led only to recovered starting material.

The lactone II was first reported by Zinin[4] in 1872, and some of the chemistry of the compound has been reviewed by Japp and Klingemann.[5] Zinin oxidized tetraphenylfuran to *cis*-dibenzoylstilbene (III), the pyrolysis of which gave the same lactone (II) as is now obtained upon pyrolysis of tetraphenyl-*p*-dioxadiene (I).

The formation of the same lactone on pyrolysis is not the only point of close resemblance between tetraphenyl-*p*-dioxadiene (I) and *cis*-dibenzoylstilbene (III). Many of the recorded properties are so similar that the actual existence of two compounds might be questioned. In fact, Irvine and McNicoll apparently did confuse the two compounds.[6] They reduced their "dibenzoylstilbene" and obtained tetraphenylfuran, citing this reduction as proof that their compound was the same as Zinin's III,[7] but Madelung and Oberwegner have since pointed out[9] that the compound in question was really I. Both compounds have been prepared in this laboratory, and our work confirms the earlier finding that, although very similar, they are not identical. Both are isomers of $C_{28}H_{20}O_2$. The dioxadiene melts at

(1) Present address: The Richardson Co., Melrose Park, Ill.

(2) W. E. Parham and V. J. Traynelis, *J. Am. Chem. Soc.*, **76**, 4960 (1954); see also W. E. Parham and V. J. Traynelis, *J. Am. Chem. Soc.*, **77**, 68 (1955); W. E. Parham, I. Nicholson, and V. J. Traynelis, *J. Am. Chem. Soc.*, **78**, 850 (1956) and H. H. Szmant and L. M. Alfonso, *J. Am. Chem. Soc.*, **78**, 1064 (1956).

(3) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, J. Wiley and Sons, New York, N. Y., 1954. (a) p. 159; (b) p. 31*ff*; (c) p. 102.

(4) N. Zinin, *Ber.*, **5**, 1104 (1872).

(5) F. R. Japp and F. Klingemann, *J. Chem. Soc.*, **57**, 662 (1890).

(6) J. C. Irvine and D. McNicoll, *J. Chem. Soc.*, **93**, 950 (1908).

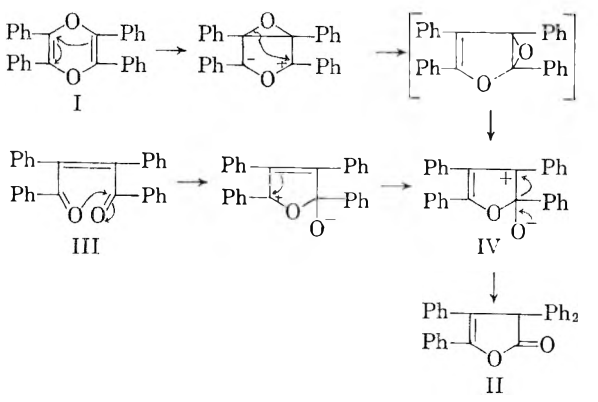
(7) Zinin reduced III to tetraphenylfuran with hydrogen iodide.[8] Irvine and McNicoll[6] state that their sample of I is the same as Zinin's III because of its elemental analysis and conversion to the furan; however, the only reduction of a "dibenzoylstilbene" described in the experimental involves hydrogen chloride rather than the iodide, and it is not clear whether the reaction is actually being performed on I or III. We have been unable to verify the formation of tetraphenylfuran upon treating I with hydrogen chloride in refluxing anhydrous methanol according to the procedure of reference (6); the yellow solution became colorless, but no furan precipitated. (After working up the reaction solution, however, there was obtained a small yield of benzoin, which could form tetraphenylfuran.)

(8) N. Zinin, *Chem. Zent.*, **38**, 373 (1867); *J. prakt. chem.*, [1] **101**, 160 (1867); *Jahresber. Fort. Chemie*, **20**, 417 (1867).

(9) W. Madelung and M. E. Oberwegner, *Ann.*, **490**, 201 (1931).

218–219°, the stilbene at 216–217°. The former gives a dibromide of melting point 226°,[10] the latter forms a dibromide of melting point 222°.[11] Both compounds give the same lactone (II) on pyrolysis, and both compounds have been reported to give tetraphenylfuran on reduction.[7,12,13] Both compounds have previously been described as yellow, although in this laboratory the stilbene III is colorless whereas the dioxadiene I is a bright canary yellow.[14] The infrared spectra of the two solids differ, however, and the mixed melting point is depressed.

The formation of the lactone II from the dioxadiene I or from the stilbene III may be interpreted as occurring through the common intermediate IV by the following paths[15]:



EXPERIMENTAL

Preparation of tetraphenyl-p-dioxadiene (I). 2,5-Bismethoxy-2,3,5,6-tetraphenyl-*p*-dioxane was prepared from benzoin by the method of Irvine and McNicoll[6] who incorrectly described the compound as 2-hydroxy-3,5-dimethoxytetraphenyltetrahydrofuran.[9] The dioxane was heated for 10 min. in boiling acetic anhydride containing one drop of concentrated sulfuric acid; on cooling, yellow crystals of I were formed, m.p. (crude) 214–215° (reported,[9] 214°). The yield of I ranged from 30 to 45%, based on benzoin.

Anal. Calcd. for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.76; H, 5.27.

Infrared absorption bands are as follows (reported as microns in a potassium bromide pellet; s, strong, m, medium, w, weak): 3.31w, 6.03s, 6.22w, 6.34w, 6.68m, 6.91m, 7.28w, 7.60w, 7.90s, 9.08m, 9.33s, 9.72s, 9.97m, 10.08s, 10.92m, 12.97s, 13.17s, 14.5s.

An alternate preparation of I was developed during the course of this work. The yield is not as good as that obtained above, but the method is much faster and does not involve the isolation of an intermediate. A solution of benzoin (3.0 g., 0.0141 mole), *p*-toluenesulfonic acid (0.1 g.) and petroleum hexane (Skellysolve B, 100 ml.) was heated under reflux for 48 hr., using an apparatus designed for azeotropic removal of water as formed.[16] The solvent was evaporated and replaced with ethanol to give, upon cooling, 0.45 g. of product, m.p. 203–209°, identical in the infrared with the tetraphenyl-*p*-dioxadiene prepared as above. A second crop, weighing 0.20 g., melted from 130–145°, and was shown by infrared to be a mixture of I and tetraphenylfuran. The yield of I (0.45 g.) was 16%.

Pyrolysis of tetraphenyl-p-dioxadiene (I). Three grams of I, recrystallized from acetic anhydride to m.p. 214–215°, was held in an open Pyrex test tube for 30 min. at 250°. The resulting red-brown tar was recrystallized, after treatment with Norite, from ethanol-chloroform, to give 2.1 g. of tan crystals, m.p. 136.2–136.6°, for a 70% yield of 2,2,3,4-tetraphenyl-3-buteno-4-lactone (II). Recrystallization from ethanol gave 1.7 g. of colorless platelets, m.p. 137.1–137.6° (reported,[4,5] 136°).

Anal. Calcd. for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.50; H, 5.19.

Infrared absorption bands are as follows (potassium bromide pellet): 3.26m, 5.58s, 6.02w, 6.22m, 6.70s, 6.91s, 7.46m, 8.06m, 8.38m, 8.68s, 9.06s, 9.34s, 9.57s, 9.89s, 9.96m, 10.39s, 10.83m, 11.86w, 12.82s, 13.06s, 13.24s, 13.83s, 14.3s (broad), 15.29w, 15.70w.

In order to determine if acid catalysis was involved, compound I was freed of acid by dissolving in chloroform and washing with 10% aqueous sodium hydroxide. The recovered material, obtained by adding ethanol to the dried (magnesium sulfate) solution, melted at 218–219°. Pyrolysis of 2.0 g. as before gave 1.8 g. (90%) of the same lactone, m.p., without recrystallization, 135.0–136.5°. This time, however, the melt did not form a tar upon cooling, but remained as a clear, yellow liquid, and treatment with Norite was not necessary.

Reaction of compound I with hydrogen chloride according to the method of Irvine and McNicoll[6] did not give tetraphenylfuran as reported. Compound I (1.00 g.) was heated under reflux in 125 ml. of anhydrous methanol, passing hydrogen chloride gas through the solution. There was some yellow solid, but this gradually dissolved; after several hours the solution became colorless. Hydrogen chloride was added for another hour, and the solution was allowed to stand overnight at room temperature.

The solution was neutralized (phenolphthalein) with pellets of sodium hydroxide. The precipitated sodium chloride (which was completely water soluble) was filtered, and the filtrate was concentrated by distillation. Chloroform was added and the distillation was continued until most of the methanol had been removed. A small, light, water soluble layer was removed by use of a separatory funnel. The chloroform solution was dried over magnesium sulfate and concentrated to the point of being an oil. After standing for several weeks partial crystallization occurred; the crystals were washed with ethanol and filtered, m.p. 128–130°. They were identical in the infrared with authentic benzoin; the yield was 0.05 g.

Preparation of tetraphenylfuran. Tetraphenylfuran may be prepared by the method of Zinin,[8] or the following procedure may be used:

Benzoin (50.0 g., 0.236 mole) and 0.1 g. of *p*-toluenesulfonic acid were heated under reflux for 12 hr. in 250 ml. of xylene, using a trap to remove water as it was formed.[16] Two hundred ml. of solvent was then removed by distillation, and the residual oil was added to three times its volume of ethanol. The resulting crystals of tetraphenylfuran were recrystallized from ethanol-chloroform to give 11.0 g. of white needles, m.p. 173.5–175.0° (reported,[8] 175°). The yield was 25%.

Anal. Calcd. for $C_{28}H_{20}O$: C, 90.29; H, 5.41. Found: C, 90.29; H, 5.36.

Pyrolysis of tetraphenylfuran. Tetraphenylfuran (0.15 g.) was pyrolyzed as described above for the pyrolysis of I,

(10) W. Madelung and M. E. Oberwegner, *Ann.*, 526, 195 (1936).

(11) N. Zinin, *Jahresber. Fort. Chemie*, 29, 426 (1876).

(12) E. Berlin, *Ann.*, 153, 130 (1870).

(13) J. Dorn, *Ann.*, 153, 349 (1870).

(14) Madelung and Oberwegner (reference 9) have also reported the stilbene to be colorless.

(15) The mechanism is shown as occurring stepwise for convenience; of course, the analogous concerted and free-radical mechanisms are possible.

(16) E. J. Salmi, *Ber.*, 71, 1803 (1938).

heating to 250° for 1 hr. There was recovered 0.14 g. of starting material, m.p. 174.0–174.9°.

Preparation of cis-dibenzoylstilbene (III). Compound III may be prepared by the method of Zinin,[3] or the following adaptation of his procedure may be used:

Tetraphenylfuran (1.0 g.) was heated to reflux for 1 hr. in 20 ml. of glacial acetic acid containing 0.2 g. of chromium trioxide. The resulting green solution was diluted with 50 ml. of water and washed three times with ether and once with chloroform. The combined extracts were washed twice with saturated aqueous sodium bicarbonate and once with water. The solvent was removed by distillation and replaced with ethanol. Crystallization gave 0.3 g. of III, as white needles, m.p. 216–217° (reported,[3] 220°). The mixed melting point with I was 193–205°.

Anal. Calcd. for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.74; H, 5.37.

Infrared absorption bands are as follows (potassium bromide pellet): 3.26w, 6.02s, 6.22m, 6.31m, 6.71w, 6.90m, 7.57m, 7.70m, 7.91s, 8.06m, 8.38m, 8.47m, 9.08w, 9.19w, 9.61w, 9.71w, 9.82m, 9.98w, 10.90w, 11.68w, 11.87w, 12.14m, 12.96s, 13.40w, 13.61s, 14.40s, 14.68s, 15.60w.

Pyrolysis of cis-dibenzoylstilbene. Compound III (0.1 g.) was heated to 270° for 15 min. Crystallization of the melt from ethanol-chloroform gave a quantitative yield of the same lactone (II), m.p. 135.5–137.0°, as was obtained upon the pyrolysis of I. The identity of the compounds was established by comparison of their infrared spectra.

EVANSTON, ILL.

[CONTRIBUTION FROM ORGANIC CHEMISTRY DEPARTMENT, NATIONAL RESEARCH CENTRE]

Carbonyl and Thiocarbonyl Compounds. II.[1] Reaction of Halogenated *o*-Quinones with Certain Hydrazones and Diazocompounds

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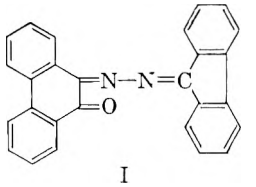
In contrast to other *o*-quinones, tetrachloro- and tetrabromo-*o*-benzoquinone react with fluorenone hydrazone at room temperature to give the cyclic ethers IIa and IIb respectively. With xanthone hydrazone the analogous products IIIa and IIIb are obtained. The mechanism proposed for this reaction suggests the formation of diazo derivatives as intermediate products.

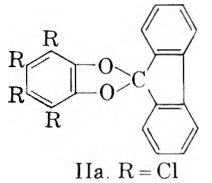
The halogenated cyclic ethers IVa–IVf are obtained by the action of various diazomethane derivatives on tetrachloro- and tetrabromo-*o*-benzoquinone. 3,4-Dichloro-1,2-naphthoquinone reacts with 9-diazoxanthene giving the cyclic ether V. V is easily cleaved with hydrochloric acid in dioxane. An improved procedure for the preparation of 3,4-dichloro-1,2-naphthoquinone is described.

Gerhardt[2] has shown that aromatic ketohydrazones react with *o*-quinones to give ketazines of the type R₂—C=N—N=R=O.[3] For example, when warming phenanthraquinone with fluorenone hydrazone in dry benzene, a 45% yield of the deeply colored phenanthraquinofluorenone ketazine I was obtained. Acenaphthenequinone, camphorquinone, and thianaphthenequinone have been found to react similarly.

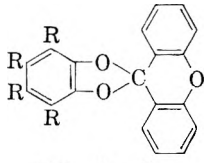
In an attempt to prepare analogous ketazines from halogenated *o*-benzoquinone derivatives, it has been found, however, that the reaction between ketohydrazones and these quinones proceeds in a different manner. Thus, when fluorenone hydrazone is added to a dry ethereal solution of tetrachloro-*o*-benzoquinone, a vigorous reaction with evolution of gas occurs and the colorless cyclic ether IIa is obtained together with tetrachlorocatechol. The reaction proceeds easily at room temperature and the product is obtained in excellent yield. Tetrabromo-*o*-benzoquinone reacts similarly with the formation of the bromo-analogue IIb. IIa and IIb have been previously obtained by the action of 9-diazofluorene on the corresponding quinone:[4]



I



IIa. R = Cl
IIb. R = Br



IIIa. R = Cl
IIIb. R = Br

Xanthone hydrazone reacts similarly, but more vigorously, with these quinones with the formation of the analogous products IIIa and IIIb in almost quantitative yields. IIIa and IIIb have been obtained previously by the action of 9-diazoxanthene on the corresponding quinones.[1] IIIa and IIIb are hydrolyzed easily when boiled with a solution of hydrochloric acid in dioxane to give xanthone and the corresponding tetrahalocatechol.

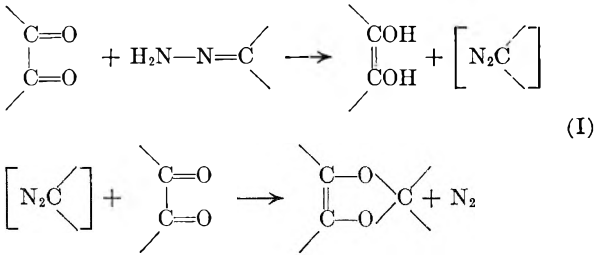
(1) Previous paper in this series, *Can. J. Chem.*, **37**, 863 (1959).

(2) O. Gerhardt, *Monatsh*, **42**, 70 (1921); *Chem. Abstr.*, **15**, 3834 (1921).

(3) G. Rieveschl and F. E. Ray, *Chem. Rev.*, **23**, 304 (1938).

(4) A. Schönberg and N. Latif, *J. Chem. Soc.*, 446 (1952).

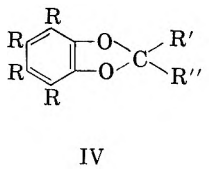
The mechanism of this reaction between the above-mentioned hydrazones and halogenated *o*-quinones involves the dehydrogenation of the hydrazone by the high-potential quinone to give the corresponding diazo derivative. The latter then reacts further with another molecule of the quinone forming the cyclic ether as shown in equation I.



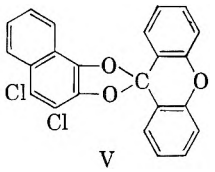
(I)

Dehydrogenation reactions using high-potential *o*-quinones have been frequently studied.[6] However, attention was directed mostly to the study of the dehydrogenation of hydroethylenic and hydroaromatic compounds. Similar dehydrogenations involving N—H linkages have not been described before.

Action of diazo-compounds on halogenated o-quinones. In the course of studies on the molluscacidal activity of halogenated cyclic ethers, the preparation of various methylenedioxy derivatives has been required for biological evaluation. (*p*-Chlorophenyl)phenyl-, bis(*p*-chlorophenyl)-, and (*p*-nitrophenyl)phenyl-diazomethane react with tetrachloro- and tetrabromo-*o*-benzoquinone at room temperature, forming the methylenedioxy derivatives IVa–IVf.



IV



V

IVa. R = Cl; R′ = phenyl; R″ = *p*-chlorophenyl
IVb. R = Br; R′ = phenyl; R″ = *p*-chlorophenyl.
IVc. R = Cl; R′ = R″ = *p*-chlorophenyl.
IVd. R = Br; R′ = R″ = *p*-chlorophenyl.
IVe. R = Cl; R′ = phenyl; R″ = *p*-nitrophenyl.
IVf. R = Br; R′ = phenyl; R″ = *p*-nitrophenyl.

The constitution of the products is based on analogy,[4,6] as well as on the fact that they are colorless and hydrolyzed by concentrated sulphuric acid at room temperature, as exemplified by IVa and IVb, to give the corresponding tetrahalocatechol.

In a previous article[1] the preparation of 9-diazoxanthene and its reaction with phenanthraquinone and *o*-benzoquinone derivatives have been described. 3,4-Dichloro-1,2-naphthoquinone reacts similarly with diazoxanthene to give the cyclic ether V. Its constitution is based on analogy and on the fact that it is colorless and easily hydrolyzed by hydrochloric acid in dioxane to xanthone and 3,4-dichloro-1,2-dihydroxynaphthalene, as usually happens with analogous xanthene cyclic ethers (cf. IIIa). A modification of the method of preparation of the quinone[7] to obviate the formation of resinous by-products[8] is described.

EXPERIMENTAL[9]

Reaction of fluorenone hydrazone with: (a) *Tetrachloro-o-benzoquinone.* To a dry ethereal solution of the quinone (0.02 mole), the hydrazone (0.01 mol.) was added in portions at room temperature. After each addition a vigorous reaction with evolution of gas occurred. After all the hydrazone has been added, the red color of the quinone almost disappeared and on further standing for a few minutes a brownish solid separated. This was filtered off, washed with methyl alcohol and recrystallized from acetone when 9,9-(tetrachloro-*o*-phenylenedioxy) fluorene IIa was obtained in colorless crystals m.p. 281° (not depressed when admixed with an authentic sample prepared by the action of diazofluorene on the quinone), yield about 80%.

Anal. Calcd. for $C_{19}H_8O_2Cl_4$: C, 55.6; H, 1.9; Cl, 34.6. Found: C, 55.22; H, 2.16; Cl, 34.33.

The filtrate was evaporated to dryness, extracted with methyl alcohol and the extract poured onto ice and acidified with hydrochloric acid. The solid separated was dried and added to acetic anhydride and the mixture refluxed for 30 min., then poured onto ice. The solid separated was recrystallized from methyl alcohol and proved to be the diacetate of tetrachlorocatechol (m.p. and mixed m.p.).

(b) *Tetrabromo-o-benzoquinone.* The reaction was carried out as in the case of the chloro analog. The product separated was filtered off and recrystallized from xylene when IIb was obtained in colorless crystals m.p. 338°, yield about 80%.

Anal. Calcd. for $C_{19}H_8O_2Br_4$: C, 38.7; H, 1.3; Br, 54.4. Found: C, 38.39; H, 1.42; Br, 54.25.

Reaction of xanthone hydrazone with: (a) *Tetrachloro-o-benzoquinone.* To a dry ethereal solution of the quinone (0.02 mol.) the hydrazone was added in portions until the color of the quinone disappeared. A vigorous reaction with evolution of gas took place and a crystalline solid separated during the addition. This was filtered off, washed with hot methyl alcohol, and recrystallized from xylene when 9,9-(tetrachloro-*o*-phenylenedioxy) xanthene IIIa was obtained in colorless crystals m.p. 286° (undepressed when admixed with an authentic sample prepared by the action of diazoxanthene on the quinone).[1] Yield almost quantitative.

Anal. Calcd. for $C_{19}H_8O_3Cl_4$: C, 53.52; H, 1.87; Cl, 33.3. Found: C, 53.12; H, 2.13; Cl, 33.08.

Hydrolysis of IIIa. To a solution of concentrated hydrochloric acid (sp. gr. 1.19/1 ml.) in dioxane (5 ml.) was added IIIa (0.15 g.), the mixture boiled for 30 min. and left to cool. It was then poured onto ice and the colorless crystals separated were filtered off and dried. These were dissolved in the least amount of boiling methyl alcohol and the solution was left to cool when xanthone separated (m.p. and mixed m.p.). On addition of dilute hydrochloric acid to the mother liquor, a white precipitate was formed. This was filtered off, dried, and added to acetic anhydride. The mixture was then refluxed for 30 min., left to cool, then poured onto ice. The solid separated was recrystallized from methyl alcohol and proved to be the diacetate of tetrachlorocatechol (m.p. and mixed m.p.).

(5) L. Horner and H. Merz, *Ann.*, **570**, 89 (1950); E. A. Braude, L. M. Jackman, and R. P. Linstead, *J. Chem. Soc.*, 3564 (1954).

(6) A. Schönberg, W. I. Awad, and N. Latif, *J. Chem. Soc.*, 1358 (1951).

(7) Th. Zincke and Engelhardt, *Ann.*, **283**, 341 (1894).

(8) L. F. Fieser and J. T. Dunn, *J. Am. Chem. Soc.*, **59**, 1019 (1937).

(9) Melting points are not corrected.

TABLE I

Diazomethane[a] Derivative	*o*-Benzoquinone Derivative	Product M.p.	Analysis
(*p*-Chlorophenyl)-phenyl-	Tetrachloro-	IVa, 152°	*Anal.* Calcd. for $C_{19}H_9O_2Cl_5$: C, 51.12; H, 2.01; Cl, 39.68. Found: C, 51.65; H, 1.7; Cl, 39.34
(*p*-Chlorophenyl)-phenyl-	Tetrabromo-	IVb, 161°	*Anal.* Calcd. for $C_{19}H_9O_2Br_4Cl$: C, 36.53; H, 1.44. Found: C, 37.1; H, 1.44
bis(*p*-Chlorophenyl)phenyl-	Tetrachloro	IVc, 174°	*Anal.* Calcd. for $C_{19}H_8O_2Cl_6$: C, 47.4; H, 1.66; Cl, 44.28. Found: C, 47.58; H, 1.63; Cl, 43.77
bis(*p*-Chlorophenyl)phenyl-	Tetrabromo-	IVd, 170°	*Anal.* Calcd. for $C_{19}H_8O_2Br_4Cl_2$: C, 34.59; H, 1.21. Found: C, 34.42; H, 1.23
(*p*-Nitrophenyl)-phenyl-	Tetrachloro-	IVe, 190°	*Anal.* Calcd. for $C_{19}H_9O_4NCl_4$: C, 49.98; H, 1.97; N, 3.06; Cl, 31.07. Found: C, 50.35; H, 2.1; N, 3.18; Cl, 29.43
(*p*-Nitrophenyl)-phenyl-	Tetrabromo-	IVf, 208°	*Anal.* Calcd. for $C_{19}H_9O_4NBr_4$: C, 35.9; H, 1.41; N, 2.2; Br, 50.39. Found: C, 36.11; H, 1.37; N, 2.0; Br, 49.45

[a] A. Schönberg, A. Fateen, and A. A. Sammour, *J. Am. Chem. Soc.*, **79**, 6020 (1957).

(b) *Tetrabromo-o-benzoquinone.* The reaction was carried out as in the case of the chloro quinone. The product separated during the reaction was filtered, washed with boiling acetone, and recrystallized from xylene (using charcoal) when the tetrabromo-analogue IIIb was obtained in almost colorless crystals m.p. 280° (decomp.). Its infrared spectrum is identical with that obtained by the action of diazoxanthene on the quinone.

Anal. Calcd. for $C_{19}H_8O_3Br_4$: Br, 52.98. Found: Br, 51.84.

Action of diazoalkanes on tetrachloro- and tetrabromo-o-benzoquinone. General procedure. The quinone (0.01 mol.) was added in portions to a dry ethereal solution of the diazoalkane (0.015 mol.). A vigorous reaction with evolution of gas occurred after each addition. After all the quinone has been added, the reaction mixture was left for 30 min. at room temperature when a crystalline solid separated. This was filtered off, washed with methyl alcohol, and recrystallized from alcohol. The methylenedioxy derivatives IVa–IVf were obtained in colorless crystals in almost quantitative yields (in the case of IVe and IVf, using charcoal was found necessary during crystallization). Results of the experiments are shown in Table I.

Hydrolysis of IVa. The substance (0.1 gm.) was mixed well with concentrated sulfuric acid (10 ml.), left overnight at room temperature then poured onto ice. The solid formed was filtered off, dried, refluxed for 30 min. with acetic anhydride, left to cool, and poured onto ice. The precipitate formed was recrystallized from methyl alcohol when the diacetate of tetrachlorocatechol was obtained (m.p. and mixed m.p.). When IVb was similarly treated the diacetate of tetrabromocatechol was obtained.

Preparation of 3,4-dichloro-1,2-naphthoquinone. Freshly prepared 1-amino-2-naphthol hydrochloride (2 gm.) was suspended in glacial acetic acid (20 ml.). A vigorous stream of dry chlorine (free of HCl) was allowed to pass in the suspension until all the aminonaphthol went into solution with a red color. The solution was then poured onto ice, and the solid separated filtered off, washed with petroleum ether and recrystallized from benzene in orange red crystals m.p. 184° (undepressed when admixed with an authentic sample).[7]

Reaction of 3,4-dichloro-1,2-naphthoquinone with 9-diazoxanthene. The quinone (1 g.) was added in very small portions of a dry ethereal solution of diazoxanthene[1] (1.4 g.). A new portion was only added when the reaction from a previous addition had subsided. When all the quinone was added, the reaction mixture was kept at room temperature for 15 min. The yellowish product formed was filtered off, washed with hot acetone and recrystallized from benzene when 9,9-(3,4-dichloro-1,2-naphthylenedioxy)xanthene V was obtained in colorless crystals m.p. 268°, yield about 80%.

Anal. Calcd. for $C_{23}H_{12}O_3Cl_2$: C, 67.81; H, 2.94; Cl, 17.44. Found: C, 67.4; H, 2.90; Cl, 17.0.

Hydrolysis of V. Hydrolysis and separation of xanthone were carried out as in the case of IIIa. To the mother liquor left after the separation of xanthone, water (acidified with a few drops of hydrochloric acid) was added. The precipitate obtained was filtered, dried, added to acetic anhydride and the mixture refluxed for 30 min. then poured onto ice. The solid separated was recrystallized from methyl alcohol in colorless crystals m.p. 156° which are believed to be the diacetate of 3,4-dichloro-1,2-dihydroxynaphthalene.

Anal. Calcd. for $C_{14}H_{10}O_4Cl_2$: C, 53.67; H, 3.19. Found: C, 53.85; H, 3.24.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

Conformational Analysis of Disubstituted Cyclohexanes by Proton Resonance Spectroscopy

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Received April 27, 1959

It is shown that the stereochemistry of a disubstituted cyclohexane may be determined from its proton resonance spectrum provided that the positions of the substituents on the ring are known.

Proton magnetic resonance spectroscopy has been found useful in studying conformations of polysubstituted six-membered ring compounds.[2-4] In many cases it has been shown that rapid conformational interconversion of the ring causes averaging of the magnetic environment of the ring protons so that only a single resonance peak is observed. This happens when there are two types of ring protons which exchange identity when the ring goes from one chair conformation to the other. As the effect of a substituent upon a distant ring proton depends primarily upon the bulk of the substituent and the geometry of the compound, it was thought that in disubstituted cyclohexanes the spectra of the methylene ring protons should not depend appreciably upon the substituent but only upon the stereochemistry of the compounds provided the substituents are not too bulky.

EXPERIMENTAL

The proton resonance spectra were obtained in a manner described previously using a Varian Associates nuclear magnetic resonance spectrometer at a frequency of 40 mc. per second.[5] The side band modulation[6] was generated by a Heathkit Square Wave Generator, Model SQ1. After the frequency was adjusted for superposition of a side-band from the solvent at various positions on the spectra the pulses from the square wave generator were counted on an Instrument Development Laboratories Model 161 Scaling Unit. The modulating frequency could be adjusted to within 1 c.p.s. and its value determined within 0.1 c.p.s. It was assumed that the sweep of the magnetic field was linear between the locations determined by sideband modulation. Peak widths were measured at half the peak height. In those cases where overlap occurred between the methyl and methylene peaks the methylene peak was extended symmetrically for the determination of its half width. Although positions are quoted to 0.1 c.p.s., instrumental irregularities and the discrete width of the sideband signals make it unlikely that the accuracy is better than 0.3 c.p.s. These effects however are small compared with the differences between the various spectra.

cis and trans 3-Methylcyclohexanol and trans 4-methylcyclohexanol were obtained from Professor E. L. Eliel[7] and their purity confirmed by infrared spectroscopy. *trans*-2-Methylcyclohexanol was prepared according to the literature.[7] *cis*-2-Methylcyclohexanol and *cis*-4-methylcyclohexanol were separated by fractional distillation with a spinning-band column from the Eastman 2-, and 4-methylcyclohexanol. The infrared spectra corresponded to those of the pure isomers.

cis-1,2-Diacetoxycyclohexane was prepared by a reported method.[8] *cis*- and *trans*-1,2-Cyclohexanediol and the trans acetate and benzoate were obtained from the stockrooms of Cornell University. The spectra of all samples were obtained in methylene chloride solution, except the diols which were dissolved in water. The data on the dimethylcyclohexanes had been reported previously.[9]

RESULTS

It was found that the width of the resonance absorption peak due to the ring protons was always considerably greater in the isomer which would have the diequatorial conformation than in the one with an axial-equatorial conformation. These observations are listed in Table I and representative spectra are shown in Fig. 1.

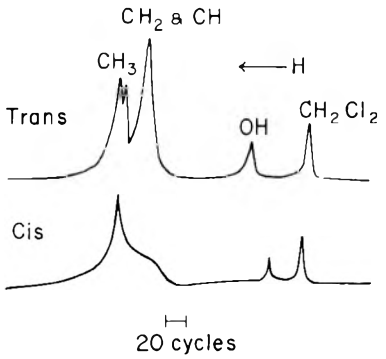


Fig. 1. 3-Methylcyclohexanol in CH_2Cl_2 solution

Although the proton attached to a ring carbon atom bearing a substituent is normally shifted relative to those on an unsubstituted ring carbon atom, this was not observed for the methyl cyclohexanols, nor for most of the dimethylcyclohexanes. The

(1) Present address: Division of Applied Chemistry, National Research Council, Ottawa, Canada.

(2) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, 79, 1005 (1957); 80, 6098 (1958).

(3) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Am. Chem. Soc.*, 80, 2237 (1958).

(4) S. Brownstein, *J. Am. Chem. Soc.*, 81, 1606 (1959).

(5) S. Brownstein, *J. Am. Chem. Soc.*, 80, 2300 (1958).

(6) J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, 19, 1608 (1951).

(7) E. L. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, 79, 5986 (1957).

(8) F. V. Brutcher and G. Evans, *J. Org. Chem.*, 23, 618 (1958).

(9) N. F. Chamberlain, *Anal. Chem.*, 31, 56 (1959).

TABLE I

RING PROTON PEAK WIDTHS

Compound	Conformation	Peak Width, Cycles/Sec.
Methylcyclohexanols		
cis-1,2	a, e	8.4
trans-1,2	e, e	22.0
cis-1,3	e, e	37.8
trans-1,3	a, e	12.5
cis-1,4	a, e	14.3
trans-1,4	e, e	38.4
Dimethylcyclohexanes		
cis-1,2	a, e	4.8
trans-1,2	e, e	14.1
cis-1,3	e, e	12.8
trans-1,3	a, e	8.6
cis-1,4	a, e	4.8
trans-1,4	e, e	19.2
Cyclohexanediols		
cis-1,2	a, e	7.1
trans-1,2	e, e	20.2
Cyclohexanediacetates		
cis-1,2	a, e	10.3
trans-1,2	e, e	35.0
Cyclohexanedibenzoates		
trans-1,2	e, e	16.0

effect of conformation on the chemical shift of the methyl group in the methylcyclohexanols is shown in Table II.

TABLE II

CHEMICAL SHIFT OF METHYL PROTONS

Methylcyclohexanol	Conformation	$\delta_{int.}^{CH_2Cl_2}$[a]
cis-1,2	a, e	4.33
trans-1,2	e, e	4.10
cis-1,3	e, e	4.33
trans-1,3	a, e	4.60
cis-1,4-	a, e	4.55
trans-1,4	e, e	4.43

[a] The separation is in parts per million of the applied field from the protons of the solvent, CH_2Cl_2. This notation is fully explained in *Chem. Revs.*, **59**, 463 (1959).

DISCUSSION

It has been shown that spin-spin coupling is greater between two protons that are axial than between axial-equatorial protons, which is in turn greater than for two equatorial protons (I). This results in a broad spin-spin multiplet for ring protons which are restrained in an axial position.[10] A compound in which both substituents must be either equatorial or axial will exist primarily in the diequatorial conformation. This restrains to axial positions the protons which are on the same carbon atoms as the substituents, and consequently there is considerable spin coupling between these and the other ring protons. If the resolution is not sufficient to observe the individual lines of the multiplets, a comparatively broad envelope is observed due to the proton resonance of the ring hydrogens.

In a compound where one substituent is axial and the other is equatorial there will be rapid interconversion between the two possible conformations and their populations will be similar provided that the size of the substituents is not too different. This will result in the protons attached to the substituent bearing carbon atoms having an equatorial position about half the time. There will be smaller spin coupling constants with the other ring protons and the envelope of resonance absorption due to the ring protons will be narrower. Therefore, if the position of the substituents on the cyclohexane ring is known, one can determine from the proton resonance spectrum of a compound whether the substituents are cis or trans.

The chemical shift of the methyl protons in the methylcyclohexanols should be the weighted average of the shift for a purely axial methyl group and a purely equatorial one since there is rapid conversion between the two possible conformations. A greater contribution from the axial positions would be expected when one substituent is axial and the other equatorial rather than when both substituents must be either axial or equatorial. It is found that the methyl protons occur at higher field in the axialequatorial isomer than the diequatorial isomer for the various methylcyclohexanols.

Acknowledgment. This work was supported in part by a research grant No. A-2172 from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

ITHACA, N. Y.

(10) E. L. Eliel, *Chem. and Ind. (London)*, 568 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF FLORIDA]

Fluoroolefins. VII. The Synthesis of 2-Trifluoromethyl-1,3-butadiene[1]

PAUL TARRANT AND ROBERT EDWARD TAYLOR

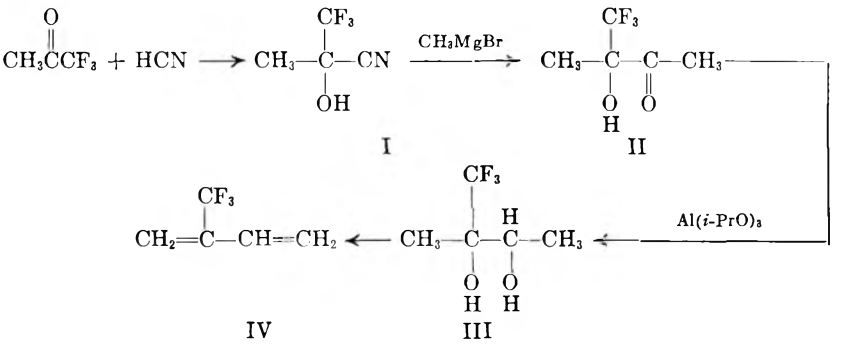
Received May 1, 1959

The synthesis of 2-trifluoromethylbutadiene by two new methods is described. The better method involves the reaction of trifluoroacetone with malonic acid and the reduction of the resulting β-trifluoromethylcrotonic acid to the carbinol and its dehydration.

Previous work in our laboratory has shown that 2-trifluoromethylbutadiene cannot be prepared in a simple manner from acetylene and trifluoroacetone because of the ready formation of 2,5-bis-(trifluoromethyl)-3-hexyne-2,5-diol.[2]

Henne and Hinkamp[3] prepared trifluoromethylbutadiene by a procedure involving the reaction of trifluoroacetone with ethylmagnesium bromide, dehydration to the olefin, reaction with *N*-bromosuccinimide, and, finally, dehydrobromination to the desired compound. The over-all yield of the diene was low.

An investigation of the synthesis of trifluorobutadiene in our laboratory followed a different route and two synthetic methods were developed. The first of these involved the following steps:



The addition of hydrogen cyanide was carried out under the conditions described by Darrall *et al.*[4] and a 70% yield of I was obtained. The Grignard reaction was carried out without difficulty and gave a 70% yield of 2-trifluoromethyl-2-hydroxy-3-butanone (II). Reduction of II by aluminum isopropoxide afforded only a 24% yield of the glycol (III). However, the use of lithium aluminum hydride gave III in 66% yield. Sodium borohydride reduction of II was even less successful than aluminum isopropoxide reduction. The dehydration step was accomplished by heating III with phosphoric oxide; the yield of diene was 37% but this value could undoubtedly be improved on a larger scale because handling losses were large. No carbonyl compounds were isolated after dehydration of the glycol indicating that a pinacol-pinacolone type rearrangement had not occurred.

It will be noted that good yields of products were obtained in all reactions except the dehydration step. Difficulty in dehydrating carbinols with a hydroxyl and a trifluoromethyl group on the same carbon atom has been noted previously.[5] It was anticipated that a better method for the synthesis of the desired diene could be developed by carrying out the dehydration step involving the trifluoromethyl carbinol as early as possible. Consequently, a study was made of the dehydration of trifluoroacetone cyanohydrin (I). Efforts to duplicate the results shown in the patent literature with thionyl chloride as the dehydrating agent[6] were unsuccessful. However, pyrolysis of the acetate of the cyanohydrin was realized, although the yields of 2-trifluoromethylacrylonitrile were not so high as those reported by Buxton, Stacey, and Tatlow.[7] The acetate was not pyrolyzed appreciably at temperatures below 450° while much carbonization occurred above 550°. Several experiments were carried out at 500 ± 5° but reproducibility of results was difficult to obtain.

(1) Paper VI. *J. Am. Chem. Soc.*, **76**, 2343 (1954). This research was supported by Contract DA44-109 qm-1469 between the Office of the Quartermaster General and the University of Florida with Dr. J. C. Montermoso as the Project Officer. From the Ph.D. dissertation of R. E. Taylor, January 1955.

(2) P. Tarrant and D. A. Warner, *J. Am. Chem. Soc.*, **76**, 1624 (1954).

(3) A. L. Henne and P. E. Hinkamp, *J. Am. Chem. Soc.*, **76**, 5147 (1954).

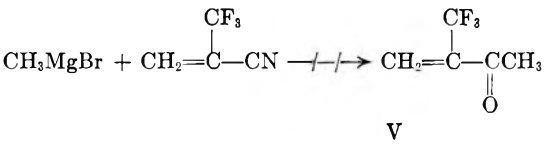
(4) R. A. Darrall, F. Smith, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 2329 (1951).

(5) K. N. Campbell, J. O. Knobloch, and B. K. Campbell, *J. Am. Chem. Soc.*, **72**, 4380 (1950).

(6) J. B. Dickey, U. S. Patent **2,472,812** (1949).

(7) M. W. Buxton, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 366 (1954).

The reaction between 2-trifluoromethylacrylonitrile and methylmagnesium bromide did not give the desired ketone (V).



V

Instead, a constant boiling fraction was obtained which contained 9% nitrogen. Infrared analysis indicated the presence of the nitrile group. Apparently addition occurred largely to the carbon-carbon double bond, although analytical data do not fit the requirements for $CH_3CH_2CH(CF_3)CN$. Examples of 1,4- addition of RMgX to α-substituted, α,β-unsaturated nitriles have been reported.[8]

The second method developed for the preparation of 2-trifluoromethylbutadiene made use of the activating effect of the carboxylic acid group to overcome the influence of the trifluoromethyl group in the dehydration step. Trifluoroacetone was condensed with malonic acid to give β-hydroxy-β-trifluoromethylbutyric acid according to the method of Walborsky *et al.*[9] The acid was dehydrated to β-trifluoromethylcrotonic acid by refluxing with sulfuric acid. The unsaturated acid was reduced to $CH_3C(CF_3)=CHCH_2OH$ (VI), by lithium aluminum hydride in 38% yield. The conversion of the crotonic acid to VI with lithium aluminum hydride *via* the acid chloride gave a 49% yield of the carbinol. Dehydration of VI gave 2-trifluoromethylbutadiene in 60% yield.

It will be seen that the dehydration of VI to IV occurred 1,4- and improved yields are attributed to the less difficult operation of removing the hydroxyl group from a carbon atom which did not bear a trifluoromethyl group.

The infrared spectra of 2-trifluoromethylbutadiene prepared by the two methods were identical.

EXPERIMENTAL

3-Trifluoromethyl-3-hydroxy butanone (II). A 2-l. flask equipped with a stirrer, addition funnel, gas inlet tube, and ice water cooled condenser was charged with magnesium (48.6 g.) and flame dried under nitrogen. Ether and methyl bromide were added to form the Grignard reagent. Trifluoroacetone cyanohydrin[4] (139 g., 1.0 mol.) was added slowly and the mixture allowed to stand overnight. Hydrolysis was accomplished with 10% sulfuric acid. The organic layer and ether extracts were dried and distilled to give 110 g. (70.5% yield) of II boiling over a 4° range. A center fraction had the following properties: b.p. 118.0°, n_D^{25} 1.3581, d_4^{25} 1.2701.

Anal. Calcd. for $C_5H_7F_3O$: C, 38.47; H, 4.52; MR_D 26.53. Found: C, 38.3; H, 5.00; MR_D 26.99.

2-Trifluoromethyl-2,3-butanediol (III). (a) Reduction with aluminum isopropoxide. A solution of aluminum isopropoxide (140 g., 0.68 mol.) in 2-propanol was reacted in the usual manner with II (83 g., 0.55 mol.). After hydrolysis with 6*N* sulfuric acid and distillation, 21 g. of (24%) III, b.p. 58° at 5.5 mm., n_D^{25} 1.3866, d_4^{25} 1.3282, was obtained.

Anal. Calcd. for $C_5H_9F_3O_2$: C, 38.0; H, 5.74; MR_D 28.04. Found: C, 38.16; H, 5.84; MR_D 28.00.

(b) Reduction with lithium aluminum hydride. A slurry of the hydride (16 g., 0.42 mol.) in ether was treated with II (39 g., 0.25 mol.). Fractionation of the organic material gave 26 g. (66%) of III, b.p. 41–43° at 2 mm.

(c) Reduction by a water solution of sodium borohydride yielded 16% (5 g.) of III while III was obtained (66 g., 55%) under anhydrous conditions.

β-Hydroxy-β-trifluoromethylcrotonic acid. A solution of malonic acid (240 g., 2.3 mol.) in 370 ml. of pyridine was prepared in a 2-l. flask equipped with a gas-inlet tube, stirrer, and ice water reflux condenser. The flask was cooled in ice. Trifluoroacetone (224 g., 2.0 mol.) was distilled into the solution which became pasty. The mixture was heated slowly to 90° and maintained at that temperature for 14 hr. The solution was heated to 130° until the evolution of carbon dioxide stopped. After removal of pyridine, 212 g. (62%) of β-hydroxy-β-trifluoromethylbutyric acid, b.p. 100–115° at 8 mm., was obtained.

β-Trifluoromethylcrotonic acid. The acid from above (212 g., 1.23 mol.) was refluxed with 50% sulfuric acid. The unsaturated acid was removed as it formed *via* a water separator. After 14 hr. no further acid was isolated. The crude acid was dried over sodium sulfate to give 134 g. (71%) of β-trifluoromethylcrotonic acid, b.p. 160–166°. Walborsky[9] used phosphoric acid for this dehydration.

β-Trifluoromethylcrotonyl chloride. Freshly distilled thionyl chloride (11.9 g.) was refluxed with β-trifluoromethylcrotonic acid (15.4 g., 0.1 mol.) in an appropriate flask until no further hydrogen chloride was evolved. The residue was distilled to give 12 g. (69.8%) of trifluoromethylcrotonyl chloride, b.p. 99.5–100.5°, n_D^{23} 1.3916, d_4^{23} 1.3037.

Anal. Calcd. for $C_5H_4ClF_3O$: Cl, 20.6; MR_D 31.47. Found: Cl, 20.2; MR_D 29.71.

β-Trifluoromethylcrotyl alcohol. (a) Reduction of trifluoromethylcrotonic acid. A slurry of lithium aluminum hydride (17 g., 0.447 mol.) in 1 l. of dry ether was prepared in a 5-l. flask equipped as previously described, cooled in an ice bath, and treated with 3-trifluoromethylcrotonic acid (78 g., 0.5 mol.) at such a rate as to produce an internal temperature of 5–10°. After 1 hr., 150 ml. of water was added followed by 1.5 l. of 10% sulfuric acid. The ether was separated, the water extracted with ether, and the extracts were dried thoroughly over sodium sulfate. Fractionation gave 24.0 g. (38.4%) of β-trifluoromethylcrotyl alcohol, b.p. 144–145°, n_D^{22} 1.3761, d_4^{22} 1.2021.

Anal. Calcd. for $C_5H_7F_3O$: C, 42.8; H, 5.04; MR_D 26.36. Found: C, 42.61; H, 5.44; MR_D 26.75.

(b) Reduction of β-trifluoromethylcrotyl chloride. The procedure was the same as described above for the 3-trifluoromethylcrotonic acid. The use of lithium aluminum hydride (22 g., 0.58 mol.) and 3-trifluoromethylcrotonyl chloride (82 g., 0.477 mol.) gave 47 g. (70.0%) of β-trifluoromethylcrotyl alcohol, b.p. 141–146°, n_D^{22} 1.3762, d_4^{22} 1.202.

2-Trifluoromethylbutadiene. (a) By dehydration of 2-trifluoromethyl-2,3-butanediol. A 500-ml. three-neck flask equipped with a 6-in. column and ice-water cooled variable take-off head, stirrer, and addition funnel was charged with phosphoric oxide (14.2 g., 0.1 mol.). One-tenth mol. (15.8 g.) of 2-trifluoromethylbutanediol-2,3 was added dropwise and slowly heated. A relatively high temperature (200–250°) was required before decomposition to the intermediate began. Thirteen g. of crude product was obtained up to a head temperature of 76°. Fractionation of the crude material gave 4.5 g. (36.9%) of very volatile 2-trifluoromethylbutadiene-1,3, b.p. 35.0–35.5°, n_D^{22} 1.3431, d_4^{22} 1.037. The literature values are b.p. 34–35°, n_D^{20} 1.3485, d_D^{20} 1.064.

Anal. Calcd. for $C_5H_5F_3$: C, 49.3; H, 4.13; MR_D 24.36. Found: C, 49.51; H, 4.34; MR_D 24.87.

(8) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, pp. 782–3, Prentice-Hall, Inc., 1954.

(9) H. M. Walborsky, M. Baum, and D. F. Loncrini, *J. Am. Chem. Soc.*, **77**, 3637 (1955).

(b) By dehydration of 3-trifluoromethyl-2-buten-1-ol. 2-Trifluoromethyl-2-buten-1-ol (45 g., 0.32 mol.) was added slowly with external cooling to phosphoric oxide (42.6 g., 0.3 mol.) in a 500-ml. flask equipped as above in part (a) above and stirred without heating until a uniform paste was formed. Heat was then applied and 23 g. of crude product obtained. Fractionation gave 22 g. (60.3%) of 2-trifluoromethylbutadiene-1,3, b.p. 36°, n_D^{22} 1.3434. Infrared spectra of this sample were identical with that of the sample prepared by the dehydration of 2-trifluoromethylbutadiol-2,3.

α-Trifluoromethylacrylonitrile. The equipment used for pyrolysis of trifluoroacetone cyanohydrin acetate consisted of the following: A flowmeter for measuring the volume of nitrogen and a dropping funnel for the acetate were connected to one end of a 1 × 12 in. Pyrex tube packed with borosilicate beads. The Pyrex tube was heated by a combustion furnace to 500 ± 5° and the internal temperature automatically controlled by a thermocouple and pyrometer. Pyrolyzed material was led directly from the furnace into an ice-water cooled receiver equipped with a reflux condenser. A tube connected the top of the reflux condenser to two cold traps in Dry Ice and acetone.

A typical reaction was carried out as follows: Acetate (45 g.) was added in 57 min. Nitrogen was added at the rate of 10 l. per hour. The crude product (37.5 g.) was fractionated to give 14.0 g. (46.6%) of 2-trifluoromethylacrylonitrile, b.p. 73–85°.

Trifluoromethylacrylonitrile has the following physical properties: b.p. 78–79°, $n_D^{26.4}$ 1.3261, $d_D^{26.4}$ 1.1753.

Anal. Calcd. for $C_4H_2F_3N$: MR_D 20.79. Found: MR_D 19.96. Lit.,[4] b.p. 75.9–76.2°, n_D^{20} 1.3239.

Reaction of methylmagnesium bromide with α-trifluoromethylacrylonitrile. Two mol. of methylmagnesium bromide was prepared in a 2-l., three-neck flask from 2.00 mol. (48.6 g.) of magnesium and enough methyl bromide to react completely with it in 1 l. of dry ether. To this cold solution was added trifluoromethylacrylonitrile (212 g., 1.75 mol.) dissolved in 200 ml. of dry ether. After refluxing for 4 hr., during which time a wax-like precipitate formed, 10% sulfuric acid was added and the precipitate dissolved. The ether solution was separated and the water layer extracted with additional ether. After drying and removal of the ether, fractionation gave 15 g. of material with the following properties: b.p. 127–127.5°, n_4^{27} 1.4108, d_4^{27} 0.9350.

Anal. Found: C, 49.7; H, 5.99; N, 9.13.

GAINESVILLE, FLA.

[CONTRIBUTION NO. 158 FROM THE CENTRAL RESEARCH LABORATORIES OF MINNESOTA MINING AND MANUFACTURING CO.[1]]

The Chemistry of Xylylenes. IV. The Stabilization of Benzyl Radicals in Solution

L. A. ERREDE AND J. P. CASSIDY[2]

Received May 11, 1959

Solutions of benzyl radicals, in concentrations as high as 10^{-4} molar, were prepared by fast flow pyrolysis of toluene at low pressure and subsequent condensation of the pyrolyzate into a solvent kept at −78°. Solvated radicals were still present 1.5 hr. after termination of pyrolysis. Surprisingly, an equal amount of *p*-xylylene was also accumulated during the reaction. Apparently this was formed by dehydrogenation of *p*-xylene produced *via* methylation of toluene. The unusual stability of solvated benzyl radicals at −78° may be a manifestation of complex formation with toluene thereby decreasing their rate of coupling.

It has been reported by one of us[3] that solutions of extremely reactive compounds such as *p*-xylylene can be prepared by instantaneous condensation of its low pressure stream into a suitable solvent kept at low temperature. This technique was also applied successfully to the preparation of solutions of benzyl radicals, albeit in low concentration. Thus, 500 g. toluene, metered at the rate of 0.03 mol./min., was pyrolyzed at 1000°, 4 mm. pressure, and 0.004 sec. residence time, and the pyrolyzate was condensed at −78° into 4.5 l. toluene. Iodometric titration of an aliquot sample indicated that about 1.5×10^{-3} equivalents of active species had accumulated in the final solution. The concentration of titratable species decreased steadily at −78° from 3×10^{-4} molar to 3×10^{-5} molar over a period of 90 min. and thereafter decreased very slowly to 1×10^{-5} molar over a period of 28 hr.

Apparently this was a mixture of two active compounds. The more stable species, despite the fact that it decolorized test solutions of diphenylpicrylhydrazyl, was not a free radical since negative results were obtained when an aliquot of this solution, that had been aged for 20 hr., was analyzed in an electron spin spectrometer.[4]

Gas chromatography and infrared analysis indicated that the pyrolysis feed stock (b.p. 110–111°) used in these experiments was 99.8% toluene, 0.1% benzene, and 0.1% aliphatic hydrocarbon. The presence of xylenes was not detected in even a trace amount. The composition of the condensate obtained as a result of its pyrolysis at 970° and 0.02 sec. residence time was 97.2% toluene, 1.1% dibenzyl, 0.7% benzene, 0.4% ethylbenzene, 0.4%

(1) A portion of this work was carried out in the laboratories of the M. W. Kellogg Co. The data were acquired by the Minnesota Mining and Manufacturing Co. with the purchase of the Chemical Manufacturing Division of the M. W. Kellogg Co. in March 1957.

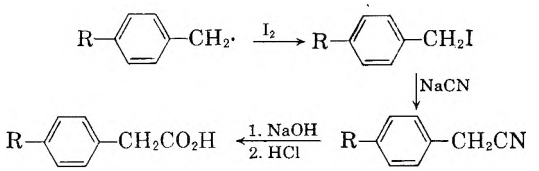
(2) Present address: The M. W. Kellogg Co., Jersey City, N. J.

(3) L. A. Errede and B. F. Landrum, *J. Am. Chem. Soc.*, 79, 4952 (1957).

(4) The authors are indebted to Professor John Wertz of the University of Minnesota for use of the electron spin spectrometer.

diphenylmethanes, 0.2% anthracene, <0.1% aliphatic hydrocarbon, a trace amount of xylenes, which was mostly *o*-xylene, and a trace amount of stilbene. Hydrogen and methane were also produced during the pyrolysis as noncondensable gases. None of the above compounds react with diphenylpicrylhydrazyl and with iodine at −78°.

In order to identify the two active species, a second solution, prepared as described above and containing about 10^{-3} mol. titratable product, was quenched at −78° with excess iodine to convert the reactive molecules to the corresponding iodides. Since these are unstable compounds and are present as only minor components in a complex mixture of pyrolysis products, no attempt was made to isolate them as such. Instead the iodides were converted to the corresponding cyanides and these, in turn, were saponified to afford the corresponding carboxylic acids. In this experiment 0.5 g. phenylacetic

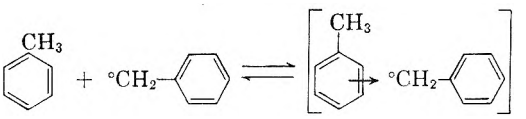


acid and 0.3 g. *p*-phenylenediacetic acid were isolated from the reaction mixture whereas no acidic products were isolated in a control experiment starting with 0.2*N* iodine in toluene solution. These results demonstrate that the active species present in the original solution were benzyl radical and *p*-xylylene in amounts at least as great as those of the mono and dibasic acids isolated.

p-Xylylene is a very reactive diamagnetic compound[5] and is known to exist for many hours in solution at −78°.[3] This undoubtedly was the more stable transient species. It must have formed pyrolytically in gas phase *via* methylation and subsequent thermal dehydrogenation,[6] since methane, benzene and xylenes were identified as products of toluene pyrolysis. No significant increase in yield of acids was realized when the pyrolyzate was condensed at −78° directly into hexane saturated with iodine. This indicates that virtually all the benzyl radicals couple in gas phase to afford dibenzyl before they reach the quench solution.

Solutions of benzyl radicals in extremely viscous solvents at room temperature have been prepared photochemically by Porter and Windsor.[7] The decay time was measured in milliseconds, whereas it was too rapid to follow in a nonviscous solvent such as hexane. This difference in reactivity was attributed to the radical's relative mobility in the two solvents.

The present observation, however, cannot be explained on this basis, since the solvents used were nonviscous liquids. This is clearly a case of decreased reactivity of the solvated radical at low temperature which can best be interpreted in terms of π-complex formation as postulated by Russell[8] and Walling[9] or in terms of σ-complex formation as postulated by Wheland.[10]



Dissociation of such a complex should increase markedly with temperature, and hence coupling of the "liberated" radicals is extremely rapid at room temperature whereas it is relatively slow at −78°. Assuming that the decay time of a 10^{-4} molar solution of benzyl radicals at room temperature is only a matter of milliseconds as reported by Porter and Windsor,[7] then the activation energy for the over-all reaction is about 14 kcal. Actually this thermal dependence may be a direct measure of the stability of the complex, since it is known that the activation energy for coupling of radicals in gas phase is almost zero.

EXPERIMENTAL

Pyrolysis of toluene. In all these experiments chemically pure toluene (b.p. 110–111°) purchased from Merck and Co., Inc., was used as the pyrolysis feed stock. Gas chromatography and infrared analysis indicated that its composition was 99.8% toluene, 0.1% benzene, and 0.1% aliphatic hydrocarbon. No evidence for the presence of even trace amounts of xylenes (or higher aromatic hydrocarbons) was detected despite deliberate attempts to identify these components. Five hundred g. of this feed stock (5.4 mol.) was subjected to fast flow pyrolysis at 970° C., 5 mm. pressure, and 0.02 sec. residence time as described previously.[3] The pyrolyzate was condensed at −78°. The volatile components (480 g., b.p. <140°) were separated by distillation at atmospheric pressure. Its composition was determined by gas chromatography and infrared analysis to be 98.9% toluene, 0.7% benzene, 0.4% ethylbenzene, <0.1% aliphatic hydrocarbon, and a trace amount of xylenes, most of which was *o*-xylene. The residue (2 3 g., b.p. >140°C.) was separated by distillation at 1 mm. Hg. pressure. The first fraction (1.9 g., b.p. 85–100°) was recrystallized from methanol at −78° to afford 1.5 g. crude dibenzyl which, when recrystallized from fresh methanol, was obtained as white crystals (m.p. 49–50°). The methanol mother liquors were evaporated to dryness leaving 0.4 g. oil as residue. This was identified by infrared analysis as a mixture of diphenylmethane and 2-methyldiphenylmethane with a small amount of stilbene also present. The second fraction (0.25 g.; b.p. >100°) was identified by infrared analysis as impure anthracene. This was purified by sublimation and subsequent recrystallization from methanol to afford a sample of pure anthracene in the form of white platelets (m.p. 210–212°).

Thus, 5.4 mol. toluene were metered to the system and 5.1 mol. were recovered. The rest was converted to 0.04 mol. benzene, 0.02 mol. ethylbenzene, 0.007 mol. dibenzyl, 0.002 mol. diphenylmethane, 0.001 mol. anthracene, and trace amounts of xylenes and stilbene. The materials balance

(5) L. A. Errede and J. M. Hoyt, *J. Am. Chem. Soc.*, in press.

(6) M. Szwarc, *J. Chem. Phys.*, 16, 128 (1948).

(7) G. Porter and M. W. Windsor, *Nature*, 180 187 (1957).

(8) G. A. Russell, *J. Org. Chem.*, 24, 300 (1959).

(9) C. Walling and M. W. Mayahi, *J. Am. Chem. Soc.*, 81, 1485 (1959).

(10) G. W. Wheland, *J. Am. Chem. Soc.*, 64, 900 (1942).

accounts for 96% of the phenyl groups metered into the furnace. No attempt was made to isolate quantitatively the noncondensable gases since we and others[6] have shown previously that these are mostly hydrogen and methane.

Preparation and disappearance of active species in solution. Toluene (500 g.) was vaporized at atmospheric pressure and the gas was metered at the rate of 0.03 mol./min. to the evacuated pyrolysis system described previously.[3] The gas was pyrolyzed at 1000°, 4 mm. pressure, and 0.004 sec. residence time, and the pyrolyzate was condensed at −78° in 4.5 l. toluene. The disappearance of accumulated titratable species was followed iodometrically at −78°. Two 100-cc. aliquot samples were removed periodically by means of a prechilled pipette. The first was used as a blank. This was warmed to room temperature and then added to 20 cc. of 0.01*N* iodine. The second was added at −78° to the same volume of 0.01*N* iodine. The excess iodine in each flask was back titrated with 0.0192*N* aqueous $Na_2S_2O_3$, and the difference noted was a measure of titratable species. The results are summarized below:

Time (Hr.)		0	1	1.5	2	10	20	30
Concentration mol./l.	10^4	2.6	1.3	0.3	0.2	0.1	0.1	0.08

Identification of benzyl radical and p-xylylene. A second 4-l. solution of pyrolyzate in hexane was prepared as described above via fast flow pyrolysis of 500 g. toluene. The solution contained about 10^{-3} mol. of titratable species when it was quenched at −78° with excess iodine. The resulting solution was warmed to room temperature and the excess iodine was reduced with aqueous sodium thiosulfate. The organic solvent was removed by evaporation and 11 g. dark oil was obtained as residue. This was made to react at 50° with 10 g. NaCN in 200 cc. water methanol solution (1 to 1) over a period of 4 hr. The mixture was separated by extraction with ether. The ether extract was evaporated to dryness leaving a dark oil. This was leached with hot aqueous NaOH for 4 hr. The aqueous solution was acidified and extracted with ether. Infrared analysis indicated that the dark alkali insoluble oil was essentially a mixture of the usual products of fast flow pyrolysis of toluene, namely dibenzyl, and diphenylmethanes. The ether extract was evaporated to dryness leaving 1.1 g. of acidic material as residue. This was separated by vacuum sublimation. The more volatile acid fraction (0.5 g.) was recrystallized from hexane in the form of white needles (m.p. 74.5–76.0°). Its mixed melting point and its infrared spectrum identified the compound as phenylacetic acid. The less volatile fraction (0.3 g.) was recrystallized from hot water in the form of long white needles (m.p. 243–245°). This was identified as *p*-phenylenediacetic acid since its mixed melting point and its infrared spectrum were identical with that of the authentic sample. In another experiment the pyrolyzed toluene stream was condensed at −78° directly into 4 l. hexane saturated with iodine and thereafter the procedure was followed as described above. Again only 1.5 g. acidic material was obtained. Its infrared spectrum indicated that this was a mixture of phenylacetic acid and *p*-phenylenediacetic acid. As a control experiment, 4 l. of 0.2*N* I_2 in toluene solution was treated as described above and no acidic products were isolated. The above results indicate therefore that benzyl radical and *p*-xylylene were present in the original solution in at least the amounts of corresponding acids isolated.

St. Paul, Minn.

[Contribution of the Fulmer Chemical Laboratory, Washington State University]

Nonbasic Character of Some Aminotrifluoromethyldiphenyl Sulfones Synthesis of 3-Amino-5-trifluoromethyldiphenyl Sulfone[1]

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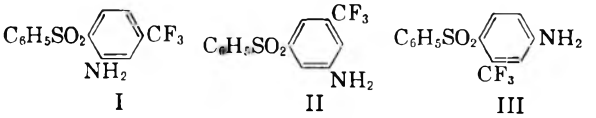
2-Amino-4-trifluoromethyldiphenyl sulfone (I) and the corresponding bis sulfone IV exhibit extreme nonbasic character by their insolubility in hot 30% hydrochloric acid and lack of reactivity with typical amino group reagents. Such behavior is explained by the strong inductive effect of the sulfone group on an *ortho*-amino group and by enhancement through hydrogen bonding of the resonance interaction involving amino and sulfone groups. Derivative formation in this unreactive series of amino sulfones was accomplished by reaction with acetic anhydride in the presence of a catalytic amount of sulfuric acid to give acetamido compounds. Several studies involving synthesis and structure confirmation of 3-amino-5-trifluoromethyldiphenyl sulfone (II) are described.

It has been found that 2-amino-4-trifluoromethyldiphenyl sulfone (I) exhibits some surprisingly nonbasic properties. It is virtually insoluble in 30% hydrochloric acid and fails to react with acetyl chloride, benzenesulfonyl chloride, or phenyl isothiocyanate to give amino derivatives.[3] Because of these observations, it became of interest to study a group of aminotrifluoromethyldiphenyl sulfones, and especially the isomers of I, 3-amino-5-trifluoromethyldiphenyl sulfone (II) and 4-amino-2-trifluoromethyldiphenyl sulfone (III).



The basicity of these amines was evaluated qualitatively by relative solubility in hot or cold hydrochloric acid of varying concentrations, and the results are summarized in Table I. It is to be

(1) Presented in part at the 1956 Northwest Regional Meeting of the American Chemical Society, Seattle, Wash., June 12.

(2) In part abstracted from a thesis submitted by C. Richard Bresson in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Washington State University, June 1958.

(3) In part, these experiments were carried out by Richard C. Thamm, Senior in Chemistry, 1952–53.

noted that II and III are far more basic than I, thus indicating a special significance to the *ortho*-orientation of the amino and sulfone groups. This effect was observed again in respect to the bis sulfones IV and V. In the case of the *o*-amino isomer IV, solubility in hot 30% hydrochloric acid is negligible; however, in contrast, the *p*-amino isomer V is completely soluble in cold 10% hydrochloric acid.

TABLE I

SOLUBILITY OF AMINOTRIFLUOROMETHYLDIPHENYL SULFONES IN HYDROCHLORIC ACID

Sulfone	Temp.	HCl Conc., %	Solubility, Wt., Mg.
2-Amino-4-trifluoromethyldiphenyl (I)	H[a]	30	10[b]
3-Amino-5-trifluoromethyldiphenyl (II)	C	10	I
	H	10	60
4-Amino-2-trifluoromethyldiphenyl (III)	C	10	I
	H	10	20
Bis(2-amino-4-trifluoromethylphenyl) (IV)	H	30	I
Bis(4-amino-2-trifluoromethylphenyl) (V)	C	10	S
2,4′-Diamino-4-trifluoromethyldiphenyl (VI)	C	10	I
	H	10	S
4,4′-Diamino-2-trifluoromethyldiphenyl (VII)	C	10	S

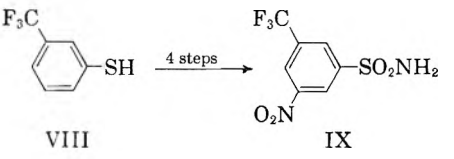
[a] Solubility determinations involved 100 mg. of the sulfone and 10 ml. of hydrochloric acid of the indicated concentration: H, hot—*i.e.*, near boiling; C, cold—*i.e.*, room temperature; I, insoluble; S, soluble. [b] Indicates that 10 mg. dissolved in 10 ml. of hot 30% hydrochloric acid. In each instance the substance was less soluble or insoluble in acid of lesser concentration. In all cases the insoluble material was the amino sulfone rather than the hydrochloride salt.

Fehnel and Carmack[4] have also observed the minimal basicity of an *o*-aminophenyl sulfone, noting that *p*-methylsulfonylaniline is more basic than its *ortho*- isomer. These authors proposed that in the case of *o*-methylsulfonylaniline, the tendency of the aminophenyl chromophore to assume a planar configuration by interaction with the sulfonyl group is augmented by intramolecular hydrogen bonding, thus enhancing the electron deficiency of nitrogen. As an explanation of the nonbasic character of *o*-aminophenyl sulfones, we share the opinion of these authors, but would add that the strong inductive effect of the sulfone group no doubt also plays a part in contributing to the nonbasic character. It also is to be noted that the trifluoromethyl group would exercise an effect in depressing the basicity of the amino group; however, this can be essentially neglected in the present discussion because the trifluoromethyl group occupies the same relative position to the amino group in all isomers.

By reference to sulfones V, VI and VII, it is to be noted that introduction of another amino group in a *para*- position of a second benzene ring mitigates the effect of the sulfone group in decreasing basicity (the electron withdrawing effect of the sulfone group is now distributed over two amino groups). However, as indicated in IV, if both amino groups are in *ortho*- positions, no mitigating effect is observed. Both amino groups here are in position to participate in a system involving resonance and hydrogen bonding. In comparing the isomers II and III, the greater basicity of II would be anticipated since no resonance effect is possible as in the case of the *ortho*- (I) and *para* - (III) orientations.

The difficulties in forming amino derivatives, described above for I, were observed generally for the other amino sulfones studied. It was finally found that acetylation could be accomplished by a procedure employing acetic anhydride and a catalytic amount of sulfuric acid.[5] Information concerning these derivatives is summarized in Table II. It is interesting to note that the *o*-aminodiphenyl sulfones gave the lowest yields. To a degree, these data might be interpreted as a further measure of nonbasic character; however, differences in yields also would most certainly reflect steric factors.

The aminodiphenyl sulfones discussed here have been reported previously[6] with the exception of 3-amino-5-trifluoromethyldiphenyl sulfone (II). Synthetic and structure studies relating to II are now presented in the following account. An initial attempt at synthesis led from *m*-trifluoromethylbenzenethiol (VIII). The thiol group was converted to a sulfonic acid group, a nitro group was introduced, and subsequently a sulfonyl chloride group was formed. Although the sulfonyl chloride was not readily purified, it was characterized by the corresponding sulfonamide IX. This attempted synthesis of II failed, however, because the sulfonyl chloride did not react successfully with benzene in a Friedel-Crafts procedure to form a sulfone.



VIII IX

The desired amino sulfone II finally was obtained by a synthesis starting with 3-amino-5-nitrobenzo-

(4) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **72**, 1292 (1950).

(5) A. I. Vogel, *A Text-Book of Practical Organic Chemistry*, 2nd. ed., Longmans, Green and Co., New York, 1951, p. 556.

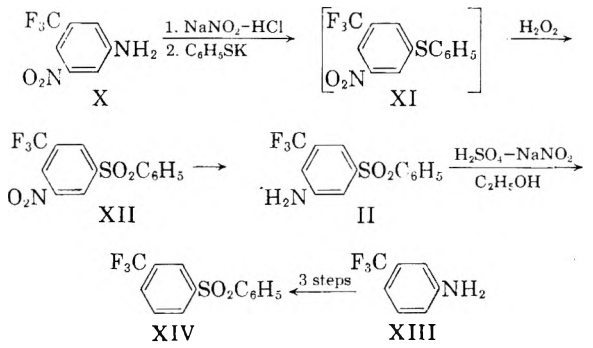
(6) G. W. Stacy, C. R. Bresson, R. E. Harmon, and R. C. Thamm, *J. Org. Chem.*, **22**, 298 (1957).

TABLE II

ACETYL DERIVATIVES OF AMINOTRIFLUOROMETHYLDIPHENYL SULFONES

Corresp. Sulfone	Yield, %[a]	Appearance[b]	M.P.[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
I	49	Long needles	147.5–148	$C_{15}H_{12}F_3NO_3S$	52.47	52.36	3.52	3.65	9.34	9.18
II	64	Needles	160–160.5	$C_{15}H_{12}F_3NO_3S$	52.47	52.30	3.52	3.47	9.34	9.20
III	81[d]	Plates	177–178	$C_{15}H_{12}F_3NO_3S$	52.47	52.48	3.52	3.55	9.34	9.56
IV	33	Fine plates	242–243	$C_{18}H_{14}F_6N_2O_4S$	46.16	46.18	3.01	3.21	6.85	6.68
V	65	Fine needles	263–264	$C_{18}H_{14}F_6N_2O_4S$	46.16	46.12	3.01	3.24	6.85	7.05
VI	8[e]	Plates	215–216	$C_{17}H_{15}F_3N_2O_4S$	51.00	51.20	3.78	3.81	8.01	7.79
VII	50	Fine plates	262–262.5	$C_{17}H_{15}F_3N_2O_4S$	51.00	51.01	3.78	3.96	8.01	8.07

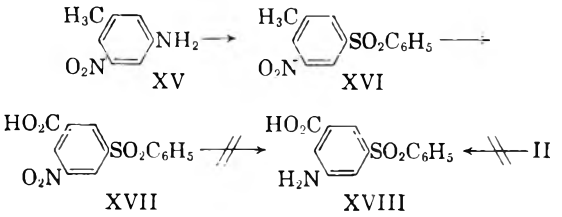
[a] Yields reported are those of the recrystallized products. [b] Analytical samples were recrystallized several times in each instance from 60% ethanol unless otherwise stated; colorless crystals were obtained in all cases. [c] M.p. of analytical sample. [d] Recrystallized from 95% ethanol. [e] This substance was obtained in a quantitative crude yield, but substantial losses were sustained in recrystallizing the material from 95% ethanol.



trifluoride (X). By way of the Ziegler procedure,[7] the amine X reacted to give a mixture from which the anticipated sulfide XI could not be isolated. Other workers[7,8] have reported similar difficulties in isolating sulfides formed by this method. Isolation of XI was, therefore, bypassed, and the crude reaction mixture was treated with hydrogen peroxide to oxidize any sulfide present to the corresponding sulfone XII. Although the product could be isolated by tedious fractional crystallization, chromatography produced the desired XII more conveniently in a 21% over-all yield. The final step, involving a stannous chloride–hydrochloric acid reduction, afforded II in a 77% yield.

The *meta*- orientation of the sulfone and trifluoromethyl groups and hence indirectly the *meta*- orientation of these two groups to the amino group in II was established in the following manner. The sulfone II was deaminated to *m*-trifluoromethyldiphenyl sulfone (XIV), which in turn was prepared in an unequivocal manner from the known amine XIII. The preparation again involved the Ziegler method for introducing a sulfide group at the site of an amino function, and again the sulfide was not isolated but oxidized to the sulfone XIV, which was shown by a mixed melting point determination and infrared spectrum to be identical with the sample of XIV formed by the deamination of II.

A further structure study of II was pursued unsuccessfully, but because several new intermediates and observations of interest were made in the course of this work, it is presented. As it is known that the trifluoromethyl group can frequently be converted to a carboxyl group,[9] interrelationship of a sample obtained from II with that formed by



synthesis from XV was undertaken. In turn, the preparation of known 3,5-dinitrotoluene in route to the prerequisite XV encountered findings that deserve brief comment. In our hands, procedures involving hypophosphorous acid[10] proved unsatisfactory in the deamination of 3,5-dinitro-*p*-toluidine. A method by Cohen and McCandlish,[11] which had been presented incompletely, has been reinvestigated, and a definitive procedure giving yields of 92% was developed. The fact that this procedure employs ethanol is of interest, as ordinarily hypophosphorous acid is the reagent of choice in deaminations. 3-Amino-5-nitrotoluene (XV) was converted to the new sulfone XVI by the Ziegler sulfide preparation, followed by hydrogen peroxide oxidation. The methyl group of XVI was oxidized by the action of sodium dichromate–sulfuric acid to give a 41% yield of 3-carboxy-5-nitrodiphenyl sulfone (XVII).

Although it was found that isomeric 2-amino-4-trifluoromethyldiphenyl sulfone (I) on treatment with fuming sulfuric acid gave 2-amino-4-carboxydiphenyl sulfone (XIX) in 60% yield, it was not

(7) (a) J. H. Ziegler, *Ber.*, **23**, 2469 (1890); (b) C. Graeber and C. Schultess, *Ann.*, **263**, 1 (1891); W. S. Weeden and H. W. Doughty, *Am. Chem. J.*, **33**, 386 (1903); (c) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 1526 (1929).

(8) D. A. Shirley and E. A. Lehto, *J. Am. Chem. Soc.*, **79**, 3481 (1957).

(9) G. M. Le Fave, *J. Am. Chem. Soc.*, **71**, 4148 (1949).

(10) N. Kornblum, *Org. Reactions*, **Vol. II**, 296 (1944).

(11) J. B. Cohen and D. McCandlish, *J. Chem. Soc.*, **87**, 1271 (1905).

possible to carry out a parallel formation of XVIII from II. Concurrent difficulties in this connection and in carrying out the reduction of XVII led us to discontinue this phase of the work.

EXPERIMENTAL[12]

Acetamido derivatives. A mixture of 500 mg. of the aminotrifluoromethyldiphenyl sulfone, 3–4 ml. of acetic anhydride, and two drops of concentrated sulfuric acid was allowed to stand 1–3 days. Yields of only about 10% were obtained with the *o*-amino compounds after 1 day, so that a 3-day period was employed in these cases. The reaction mixture finally was poured into 50 ml. of cold water, and the product was recrystallized from 60 or 95% ethanol. Results for the individual products are summarized in Table II.

m-Trifluoromethylbenzenethiol (VIII).[13] To a stirred mixture of 30 ml. of concentrated hydrochloric acid and 50 g. of ice was added 16.1 g. (0.10 mol.) of *m*-aminobenzotrifluoride,[14] the amine hydrochloride separating. While the temperature was maintained below 5° by cooling in an ice bath, a solution of 7.60 g. (0.11 mol.) of sodium nitrite in 16 ml. of water was added dropwise with stirring. This diazonium salt solution was added with stirring while the temperature was maintained at 40° to a solution of 22.0 g. (0.37 mol.) of potassium hydroxide and 20.0 g. (0.12 mol.) of potassium ethyl xanthate. After the mixture had been stirred for an additional 0.5 hr., cooled, and extracted with ether, the ether was removed, and the residual oil was taken up in 100 ml. of 95% ethanol. While this solution was being heated under reflux, 30.0 g. of potassium hydroxide was added slowly. After the mixture had been heated an additional 5 hr., cooled, and made strongly acidic with 6*N* sulfuric acid, it was steam distilled in the presence of zinc powder. The distillate was extracted with ether, and the ether solution was dried over anhydrous magnesium sulfate. The solvent was removed, and the product was distilled under reduced pressure to give a foul smelling liquid; yield, 9.58 g. (54%), b.p. 55–59° (13–14 mm.), n_D^{25} 1.4882, lit.[15] b.p. 84–86° (40 mm.).

Anal. Calcd. for $C_7H_5F_3S$: C, 47.19; H, 2.83; S, 17.94. Found: C, 47.36; H, 3.06; S, 18.04.

3-Trifluoromethyl-5-nitrobenzenesulfonamide (IX). Treatment of 3.44 g. (0.02 mol.) of the thiol VIII with 20 ml. of 30% hydrogen peroxide in 5 ml. of acetic acid converted it (after refluxing for 5 hr.) to the corresponding sulfonic acid; this was isolated as the sodium salt in a yield of 4.30 g. (87%). To this was added 19 ml. of fuming nitric acid and .17 ml. of 30% fuming sulfuric acid, resulting (after being heated at 90° for 6 hr. and neutralization of the reaction mixture) in the formation of 3.50 g. (68%) of crude sodium 3-nitro-5-trifluoromethylbenzenesulfonate. A mixture of 6.0 g. (0.02 mol.) of this crude sodium salt, 3.20 g. (0.016 mol.) of phosphorus pentachloride, and 20 ml. of phosphorus oxychloride was heated at 140°. This gave 3.40 g. (58%) of a crude sulfonyl chloride, which could not be purified or converted to the corresponding sulfone in a Friedel Crafts reaction with benzene.

However, it was possible to convert the crude sulfonyl chloride to the corresponding sulfonamide IX by adding 500 mg. of the crude oil to 20 ml. of concentrated ammonium hydroxide. The solution was allowed to evaporate to dryness at room temperature to yield 600 mg. of a light yellow solid. This was recrystallized from 95% ethanol, resulting in 100 mg. (22% yield) of 3-trifluoromethyl-5-nitrobenzenesulfonamide (IX), m.p. 140.5–141°.

Anal. Calcd. for $C_7H_5F_3O_4N_2S$: C, 31.11; H, 1.87; S, 11.87. Found: C, 31.20; H, 1.79; S, 11.63.

3-Amino-5-nitrobenzotrifluoride (X). This procedure is adapted from one reported by Finger and Reed[16]; their original procedure employed a two-fold excess of *ethanolic* ammonium sulfide. We obtained a somewhat better result using *methanol* as solvent and a three-fold excess. A solution of 11.8 g. (0.05 mol.) of 3,5-dinitrobenzotrifluoride[17] in methanolic ammonium sulfide [prepared from 36.0 g. (0.15 mol.) of sodium sulfide nonahydrate, 32.0 g. (0.60 mol.) of ammonium chloride, and 150 ml. of methanol] was heated under reflux for 5 hr. The reaction mixture was concentrated by evaporation, cooled, and filtered. The residue was purified by dissolving the amine in hot 20% hydrochloric acid. The resulting solution was cooled, and the 3-amino-5-nitro benzotrifluoride (X) was precipitated by the addition of 20% sodium hydroxide solution; yield 7.62 g. (74%), m.p. 78–79°, lit.[16] m.p. 80–81.5°.

3-Trifluoromethyl-5-nitrodiphenyl sulfone (XII). To 3.05 g. (0.015 mol.) of X was added 30 ml. (0.36 mole) of concentrated hydrochloric acid, the mixture being heated to effect solution. This was filtered and cooled in an ice bath, and a cold solution of 1.04 g. (0.015 mole) of sodium nitrite (dissolved in 5 ml. of water) was added dropwise. After 0.5 hr. the diazonium salt solution was added to a cold, stirred mixture of 3.30 g. (0.03 mol.) of thiophenol, 39.0 g. (0.70 mol.) of potassium hydroxide, 50 ml. of water, and 2.0 g. of copper powder. Stirring was continued for 2 hr. at an ice bath temperature and then for 2 hr. at 60°. The mixture was extracted with ether (3 × 30 ml.), and the ether then was removed by evaporation leaving a reddish black oil. This residue was dissolved in 50 ml. of glacial acetic acid, the solution was heated to 90°, and 40 ml. of 30% hydrogen peroxide was added over a period of 4 hr. The reaction mixture was heated under reflux overnight, cooled, and poured into water; it was then neutralized with 10% sodium hydroxide solution and extracted with ether. The ether was removed by evaporation, and the residue was chromatographed on alumina. The sulfone XII was isolated from the benzene ether eluents and was recrystallized from 85% ethanol to give 1.07 g. (21% yield), m.p. 128–129°.

Anal. Calcd. for $C_{13}H_8F_3NO_4S$: C, 47.13; H, 2.43; S, 9.68. Found: C, 46.98; H, 2.49; S, 9.48.

3-Amino-5-trifluoromethyldiphenyl sulfone (II). From 500 mg. (1.50 mmol.) of XII, which was reduced with stannous chloride–hydrochloric acid solution,[6] 460 mg. of crude II was obtained; this was recrystallized from 60% ethanol and yielded 350 mg. (77%), m.p. 161–162°.

Anal. Calcd. for $C_{13}H_{10}F_3NO_2S$: C, 51.82; H, 3.35; S, 10.64. Found: C, 51.82; H, 3.35; S, 10.49.

m-Trifluoromethyldiphenylsulfone (XIV). To 20 ml. of 10% hydrochloric acid was added 4.04 g. (0.025 mole) of *m*-aminobenzotrifluoride (XIII).[14] The mixture was cooled to 0° in an ice bath, and a solution of 1.73 g. (0.025 mol.) of sodium nitrite in 10 ml. of water was added dropwise. After standing for 0.5 hr. at 0°, the clear diazonium solution was added dropwise to a stirred, cooled (ice bath temperature) mixture of 5.60 g. (0.10 mol.) of potassium hydroxide, 5.50 g. (0.05 mol.) of thiophenol, and 2 g. of copper powder in 50 ml. of water. The mixture was stirred for 1 hr. at 0° and then at 70° for 2 hr. After the reaction mixture had cooled to room temperature, a red oil was extracted with ether (3 × 25 ml.). The solvent was evaporated from the ether extracts,

(12) All melting points are corrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn., and by Weiler and Strauss Laboratories, Oxford, England.

(13) Adapted to this preparation from a procedure reported by D. S. Tarbell and D. K. Fukushima, *Org. Syntheses*, Coll. Vol. III, 809 (1955).

(14) Obtained from Halogen Chemicals Inc., 616 King Street, Columbia 5, S. C.

(15) Prepared previously by a Grignard method by Soper, C. W. Whitehead, O. K. Behrens, J. C. Corse, and R. G. Jones, *J. Am. Chem. Soc.*, **70**, 2849 (1948).

(16) G. C. Finger and F. H. Reed, *J. Am. Chem. Soc.*, 66, 1972 (1944).

(17) Prepared by the method of Finger and Reed in a 55% yield (ref. 16).

and the residual dark oil was dissolved in 50 ml. of a 1:5 solution of acetic anhydride–glacial acetic acid. The mixture was heated to 90°, and 30 ml. of 30% hydrogen peroxide was added over a 4-hr. period. The mixture was heated under reflux, an additional 10 ml. of 30% hydrogen peroxide was added, and the mixture was heated for 1 hr. The solution was poured into 1 l. of ice water, and the mixture was made basic with 20% sodium hydroxide solution. The yield of red-brown semisolid, obtained after filtering and drying, was 5.23 g. (73%). This was purified by chromatography using alumina and the customary sequence of solvents, followed by recrystallization from 95% ethanol to give 3.53 g. (49%), m.p. 77–78°.

Anal. Calcd. for $C_{13}H_9F_3SO_2$: C, 54.54; H, 3.17. Found: C, 54.33; H, 3.16.

Conversion of 3-amino-5-trifluoromethyldiphenyl sulfone (II) *to m-trifluoromethyldiphenyl sulfone* (XIV). A mixture of 300 mg. (0.99 mmol.) of II, 6 ml. of absolute ethanol, and 1.5 ml. of concentrated sulfuric acid was heated to the reflux temperature. Then 0.90 g. of sodium nitrite was added in small portions over a period of 1 hr., and the mixture was heated for an additional 1-hr. period. When the mixture was poured onto 100 g. of ice, a red oil separated. After the supernatant liquid had been decanted, the oil was taken up in benzene, and the solution was dried over anhydrous sodium sulfate. Chromatography followed by recrystallization from ethanol gave a yield of 150 mg. (53%), m.p. 77–78°. Admixture of this sample with the material formed from *m*-aminobenzotrifluoride (XIII) resulted in no depression in melting point (mixed m.p. 77–78°), and the infrared absorption spectra[18] of the two samples were identical.

3,5-Dinitrotoluene. To 21.2 g. (0.11 mol.) of 3,5-dinitro-*p*-toluidine[19] in 400 ml. of absolute ethanol was added 100 ml. of concentrated sulfuric acid with swirling and cooling. After the resulting mixture had been heated to the reflux temperature, 63.6 g. (0.92 mol.) of sodium nitrite was added through the condenser in small portions during a period of 2.5 hr. It was necessary to wash down the condenser frequently with absolute ethanol to prevent the sodium nitrite from accumulating on the condenser walls. After effervescence had ceased, the mixture was diluted with water and poured into a 1-l. mixture of ice water. The mixture was filtered, and the residue was washed and dried; yield of deaminated product, 18.0 g. (92%), m.p. 89–90°, lit.[11] m.p. 93°. A small portion was recrystallized from aqueous ethanol, m.p. 92–93°; however, the crude product was satisfactory for the present work.

3-Methyl-5-nitrodiphenyl sulfone (XVI). The details of this procedure are similar to those described for XII and XIV. A solution of 1.90 g. (0.013 mol.) of 3-amino-5-nitrotoluene[20] in 38 ml. of concentrated hydrochloric acid and 10 ml. of water was diazotized by the dropwise addition of 89.7 mg. (0.013 mol.) of sodium nitrite in 7 ml. of water. The resulting solution was added to a mixture of 2.84 g. (0.026 mol.) of thiophenol, 40.0 g. (0.71 mol.) of potassium hydroxide, and 1.5 g. of copper powder in 50 ml. of water. The reaction mixture was extracted with ether, and after the solvent had been removed by evaporation, the residual oil was taken up in 40 ml. of glacial acetic acid. The resulting solution was heated to 90°, and 25 ml. of 30% hydrogen peroxide was added. After the reaction was complete, the mixture was poured into ice water and was neutralized with 20% sodium hydroxide solution. The mixture was extracted with ether, the solvent was distilled from the combined extracts, and the residue was chromatographed over alumina using the customary sequence of solvents. The sulfone was isolated from the benzene ether fractions, and after recrystallization from 85% ethanol, the yield was 560 mg. (16%), m.p. 133.5–134.5°.

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; S, 11.56. Found: C, 56.30; H, 4.04; S, 11.54.

3-Carboxy-5-nitrodiphenyl sulfone (XVII). In an adaptation of a procedure reported by Kamm and Mathews,[21] 1.44 g. of concentrated sulfuric acid in 0.1 ml. portions was added over a period of 15 min. to a stirred mixture of 200 mg. (0.72 mmol.) of XVI and 290 mg. (0.97 mmol.) of sodium dichromate dihydrate in 1.2 ml. of water. The mixture was heated at 120° for 0.5 hr., cooled, and diluted with 20 ml. of water. The green residue obtained after filtering the mixture was treated with 20 ml. of 20% sodium hydroxide solution; the resulting mixture was filtered, and the filtrate was acidified with dilute sulfuric acid. The crude product obtained amounted to 110 mg. (55% yield), m.p. 163–164°. The sodium hydroxide–insoluble residue from above was starting material; 70 mg. (40% recovery), m.p. 130–131° (mixed m.p. 133–134°). Recrystallization of crude XVII from aqueous acetic acid resulted in 90 mg. (45% yield), m.p. 167.5–168.5°.

Anal. Calcd. for $C_{13}H_9NO_6S$: C, 50.81; H, 2.95; S, 10.43. Found: C, 51.06; H, 2.86; S, 10.31.

2-Amino-4-carboxydiphenyl sulfone (XIX). To 200 mg. (0.66 mmol.) of 2-amino-4-trifluoromethyldiphenyl sulfone (I) was added 1.0 ml. of concentrated sulfuric acid, and the solution was heated at 200° for 15 min. Then 0.4 ml. of 15% fuming sulfuric acid was added, and heating was continued for 0.5 hr. The solution was cooled and poured onto 20 g. of ice; the resulting solution was made basic and extracted with ether (3 × 10 ml.) to remove colored impurities. The aqueous phase was made acidic with dilute sulfuric acid, and the precipitate was removed by filtration; yield, 120 mg. (66%), m.p. 283° (dec.). Recrystallization from 85% ethanol afforded colorless needles, 110 mg. (60% yield), m.p. 286–287° (dec.).

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; S, 11.56. Found: C, 56.10; H, 3.88; S, 11.78.

Acknowledgment. This investigation was supported in part by research funds of Washington State University, Project 234. We are indebted to Mr. David L. Frasco of the Division of Industrial Research of Washington State University for determination of infrared absorption spectra.

PULLMAN, WASH.

(18) The infrared absorption spectra were determined by means of a Perkin-Elmer double beam infrared spectrometer, model 21. The samples were prepared by sublimation onto a sodium chloride plate.

(19) This substance and other prior intermediates were prepared by methods reported by R. A. Morton and A. McGookin, *J. Chem. Soc.*, 901 (1934).

(20) Prepared in 79% yield by an alcoholic ammonium sulfide reduction of 3,5-dinitrotoluene (*cf.* ref. 19).

(21) O. Kamm and A. O. Mathews, *Org. Syntheses*, Coll. Vol. I, 392 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, THE HEBREW UNIVERSITY]

Preparation of Monomeric Fructose Nitrates

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The nitration of fructose by means of nitrogen pentoxide–sodium fluoride, yielded a mixture consisting of a crystalline product (I) and sirupy monomeric nitrated products. The isolation, characterization, and elucidation of the structure of I as 1,4,6-tri-*O*-nitro-2,3-anhydrofructofuranose is described.

Unlike the nitration of aldoses, which proved to undergo a smooth *O*-nitration (esterification) reaction by a variety of reagents,[1] the nitration of ketoses attracted considerably less attention. Back in 1898, Will and Lenze[2] studied the nitration of both fructose and sorbose by means of the powerful nitrating agent, nitric acid–sulfuric acid mixture. However, they could not obtain the expected fully nitrated products. In both cases they were able only to isolate products which according to analyses were formulated as the respective anhydroketose-trinitrates. This nitration of fructose has lately been reinvestigated by Schwager and Leibowitz[3] who showed that the crude reaction product consisted exclusively of a mixture of dimeric fructose nitrates. Among the several products isolated, at least two were identified as hexanitrates of the known difructose-dianhydrides.[4]

Since no monomeric fully nitrated fructose has yet been prepared, it was thought desirable to investigate conditions by which such nitrates could be obtained.

Fructose is known to undergo dimerization reactions quite easily under the influence of a variety of protonic acids.[5] In view of this, it seems reasonable to assume that because of the strongly acidic character of the nitrating agent mentioned above, fructose undergoes a rapid dimerization reaction prior to its *O*-nitration. It was therefore suggested that the desired nitration of fructose could successfully be effected by means of nitrating agents of low acidic properties. In this consideration, the use of nitrogen pentoxide in chloroform solution seemed worthy of investigation. This reagent, although a moderate nitrating agent, has successfully been used by the modification of Caesar and Goldfrank,[6] using the mixture N_2O_5-NaF in chloroform, for nitration of sugars which are sensitive to acids, or sugars that could not otherwise be successfully nitrated.[7]

As expected, the nitration of fructose under the Caesar and Goldfrank conditions, led to the formation of a mixture of monomeric fructose derivatives. The crude reaction product could be separated into (1) a crystalline compound, and (2) a sirupy fraction. This paper describes the isolation, characterization and elucidation of structure of the crystalline product. The nature of the products of which the sirup consists will be described in a subsequent paper.

The dextrorotatory crystalline product (I), which was isolated from the nitrating mixture through fractional crystallization, was analyzed as $C_6H_9O_{11}N_3$ and proved to be a non-reducing compound. It shows three characteristic absorption bands at 1665 cm.$^{-1}$, 1306 cm.$^{-1}$ and 1280 cm.$^{-1}$ in the O-NO_2 regions of the infrared spectrum[8] (symmetric and asymmetric covalent nitrate frequencies), but none at the hydroxyl region. This clearly suggests that I is a trinitrate of an anhydrofructose. For the purpose of its characterization, I was first converted into its parent dextrorotatory anhydrosugar (II), by means of catalytic hydrogenation. This method was chosen not only because of its smoothness but also because it does not involve any configurational changes in the course of reaction.[9] The fact that I could be obtained by renitration of II fully confirms the reliability of the method chosen. Acetylation of II yielded beautiful hexagonal crystals of a triacetate (III), thus further confirming the number of free hydroxyl groups in II. Likewise, III is nonreducing, and does not show any absorption in the hydroxyl region of the infrared spectrum.

II is a non-reducing compound, but undergoes facile acid hydrolysis, yielding fructose quantitatively. It may, therefore, be assumed that the anomeric hydroxyl group at C-2 is not free, but probably is a member of the anhydro-ring.

II could not be identified with any known compound. Seven structural formulas, which do not take into consideration possible inversion of con-

(1) J. Honeyman and J. W. W. Morgan, *Advances in Carbohydrate Chemistry*, **12**, 117 (1957).

(2) W. Will and F. Lenze, *Ber.*, **31**, 68 (1898).

(3) A. Schwager and J. Leibowitz, *Bull. Res. Counc. of Israel*, **5a**, 266 (1956).

(4) R. F. Jackson and S. M. Goergen, *Bur. Standards J. Research*, **5**, 733 (1930).

(5) (a) A. Pictet and J. Chavan, *Helv. Chim. Acta*, **9**, 809 (1926); (b) H. S. Schlubach and C. Behre, *Ann.*, **508**, 16 (1934); (c) L. Sattler and F. W. Zerban, *Ind. Eng. Chem.*, **37**, 1133 (1945); (d) M. L. Wolfrom, H. W. Hilton, and W. W. Binkley, *J. Am. Chem. Soc.*, **74**, 2867 (1952).

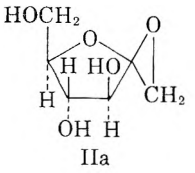
(6) G. V. Caesar and M. Goldfrank, *J. Am. Chem. Soc.*, **68**, 372 (1946).

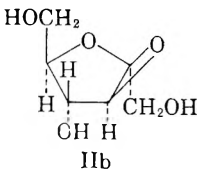
(7) H. L. Wolfrom and A. Rosenthal, *J. Am. Chem. Soc.*, **75**, 3662 (1953).

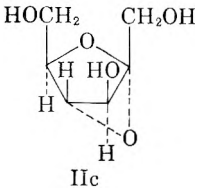
(8) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., 1958, p. 301.

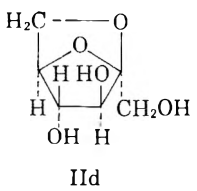
(9) L. P. Kuhn, *J. Am. Chem. Soc.*, **68**, 1761 (1946).

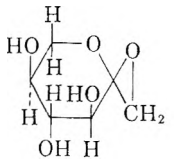
figuration in the course of anhydro-ring formation, are possible, as represented in formulas IIa–IIg.

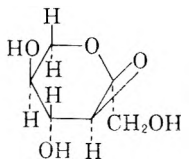

IIa

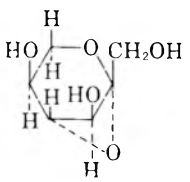

IIb


IIc


IId


IIe


IIf

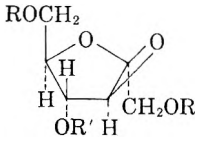

IIg

Formulas (IIc) and (IIg), both having the 1.3-propylene oxide ring structure, were ruled out because of the ease of hydrolysis of II in acid solution, as the hydrolytic cleavage of such systems is known to occur with considerable difficulty.[10] It seems probable, therefore, that II contains an epoxy ring which is known to be very easily hydrolyzed. Nevertheless, all five remaining structures were taken into consideration.

Formulas IIa and IIe, containing an 1,2-anhydro-ring were considered next. An anhydride corresponding to formula IIa has already been described,[11] having entirely different properties from those of II. Nevertheless, this formula could not be excluded on the ground that II might be an anomer of that anhydride. The properties recorded for an anhydride having the formula of IIe[5c] are also quite different from those of II. Moreover, serious doubts have been raised regarding the existence of such an anhydride.[12] Therefore this formula could not be excluded. Formulas IIa and IIg were definitely ruled out on the ground that exhaustive methylation of II followed by acid hydrolysis, gave a sirup which did not react with phenylhydrazine.

Since of the remaining three formulas, two, namely, IId and IIf, have at least two vicinal hydroxyl groups, the periodate oxidation of II was carried out. II proved to be totally resistant to Malaprade reagent. Thus, only formula IIb conforms with the data presented. Since the resistance to periodate oxidation could not be regarded as conclusive evidence for the lack of vicinal hydroxyl groups,[13] more direct evidence was sought. Advantage was taken of the fact that only IIb has two primary hydroxyl groups. II formed easily the corresponding dityrityl (IV) and ditosyl (V) derivatives. Since the treatment of V with sodium iodide in acetone afforded two moles of sodium tosylate in quantitative yield, it follows that II contains two primary hydroxyl groups. The latter can therefore be formulated as an 2,3-epoxy-fructofuranose. This formulation is in line with our spectroscopic data. In the ultraviolet absorption spectrum, I shows a band at 220 mμ which is characteristic for the furanose system.[14] Furthermore, II and all its derivatives show a single band at 1263 $\pm$ 2 cm.$^{-1}$ in the epoxide region of the infrared spectrum.[15]

From the data presented here, the absolute configuration of II could not be adduced with certainty. Only if the epoxy-ring is oriented above the furanose ring, could the anhydrosugar be regarded as a true anhydrofructofuranose. In the reverse case, it should be formulated as an anhydro-psicofuranose. This point could be clarified by studying the mechanism of formation of I. A clue to this problem could be derived from the observation that I is not formed in the course of the nitration but rather at the washing stage of the crude reaction product. As will be shown in a subsequent paper, I is probably being produced from 1,2,4,6-tetra-*O*-nitrofructofuranose, involving a base-catalyzed trans-elimination of a molecule of nitric acid. This clearly permits the assignment of 2,3 anhydrofructofuranose structure for II:



I. R = R′ = NO_2. II. R = R′ = H. III. R = R′ = Ac. IV. R = Tr; R′ = H. V. R = Ts; R′ = H.

A preliminary account of this research has already been published.[16]

EXPERIMENTAL[17]

Preparation of the nitrating mixture. Nitrogen pentoxide was prepared according to the method of Caesar and Gold-

(10) R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, 63, 2241 (1941).

(11) H. H. Schlubach and H. Elsmer, *Ber.*, 61, 2358 (1928).

(12) M. L. Wolfrom, W. W. Binkley, W. L. Schilling, and H. W. Hilton, *J. Am. Chem. Soc.*, 73, 3553 (1951).

(13) R. J. Dilmer, H. A. Davis, and G. E. Hilbert, *J. Am. Chem. Soc.*, 68, 1377 (1946); B. H. Alexander, R. J. Dilmer, and C. L. Mehltratter, *J. Am. Chem. Soc.*, 73, 4658 (1951).

(14) H. Bredereck, G. Hoschele, and W. Huber, *Ber.*, 86, 1271 (1953).

(15) Ref. (8), p. 118.

(16) M. Sarel-Imber and J. Leibowitz, *J. Org. Chem.*, 24, 141 (1959).

(17) Melting points were taken on a Fisher-Jones apparatus and are uncorrected. Nitrogen determinations were carried out by a micro-Kjeldahl method with an apparatus described by A. J. Kuck, A. Kingsley, D. Dinsey, F. Sheehan, and G. F. Swigert, *Anal. Chem.*, 22, 604 (1950). Sulfur and iodine analyses by Drs. G. Weiler and F. Strauss, Microanalytical Laboratory, Oxford. Infrared spectra were taken with a Baird double beam recording spectrophotometer, model B.

frank,[6] using 96% nitric acid (*d* 1.51) with the exception that the solid nitrogen oxides were first washed with small amounts of ethanol-free chloroform.[18] Chloroform fractions containing more than 10% of low nitrogen oxides were discarded. The rest of the oxides were dissolves in chloroform to a concentration of 20 g. nitrogen pentoxide in 100 ml. solvent, and kept overnight at −10°.[7]

Nitration of fructose. A chloroform solution containing nitrogen pentoxide (73 g., 0.67 mol.) and nitrogen tetroxide (5.3 g.) was mixed with sodium fluoride (12 g.) and cooled to −5°. To this mixture, finely powdered dry fructose (9 g.) was added slowly with vigorous stirring. The cooling bath was then removed and the stirring was continued for an additional 40 min. while the temperature was not allowed to rise above 14°. After the precipitated inorganic salts were removed by filtration, the filtrate was thoroughly washed with tap water (*p*H 7.5–8) until washings were free of nitric acid as shown by the diphenylamine reagent. This required numerous washings but it proved to be quite essential, as otherwise the reaction product tended to decompose spontaneously. It was observed that the addition of small quantities of *p*-benzoquinone (0.1 g.) has a remarkable stabilizing effect. The chloroformic solution was dried by sodium sulfate and the solvent was removed by distillation at reduced pressure, leaving behind 15 g. of a viscous sirup with a content of 14–15% nitrogen. The specific optical rotations of different batches ($[\alpha]_D^{25}$) ranged between −19 and −24°. It is significant to note that these values become less negative as the solution of the crude nitration product was more thoroughly washed.

2,3-Anhydrofructofuranose trinitrate (I). When a concentrated methanolic solution of the crude sirupy reaction product was cooled to −10°, only partial freezing occurred, giving, after decanting of supernatant liquor, a solid material. The supernatant liquor fraction was further concentrated and again fractionated by partial freezing. To the combined solid fractions methanol was added and it was again processed in a like fashion. These operations were repeated several times with each fraction, until the solid fractions became crystalline. Recrystallization from methanol yielded a total of 1.5 g. of white needles melting at 80.5°; $[\alpha]_D^{25}$ +34.5° (*c* 1.1, ethanol), +40° (*c* 1.4, methanol); λ_{max}^{EtOH} 220 mμ (log ε 3.28).

Anal. Calcd. for $C_6H_7O_9N_3$: N, 14.14; mol. wt. 297. Found: N, 14.02; mol. wt. 300 (benzene). The infrared spectrum shows strong absorption bands (cm.$^{-1}$) at 1306, 1280, 1665, (—O—NO_2).

I does not reduce Fehling solution. It is readily soluble in methanol, ethanol, and dioxane and insoluble in water. It is stable towards light and strong inorganic acids, but readily decomposes by alkali.

2,3-Anhydrofructofuranose (II). Denitrification of I could easily be effected by means of catalytic hydrogenation in the presence of 10% palladium over charcoal, at atmospheric pressure. For preparative purposes this reduction was conveniently accomplished by the use of a Parr apparatus. The reduction of I (2 g.) in the presence of the catalyst (8 g.),[9] using ethanol as solvent (100 ml.), was complete within 30 min., at atmospheric pressure. After removal of the catalyst by centrifugation, it was necessary to pass the supernatant alcoholic solution through a Kieselguhr column to get rid of colloidal materials. The solvent was then removed by distillation at reduced pressure and the colorless sirupy residue left in the flask was dried *in vacuo* over phosphorous pentoxide. Yield: 1 g. (92%). It could not be induced to crystallize from the common solvents. $[\alpha]_D^{25}$ +79.4° (*c* 0.5, ethanol). The infrared spectrum shows strong absorption bands (cm.$^{-1}$) at 3366 (free OH); 1073, 1064, 1027 (—C—O—). II does not reduce Fehling solution. It is soluble in methanol, ethanol, and the corresponding aqueous alcohols, and insoluble in benzene and petroleum-ether. Treatment of II with *N* inorganic acids in the cold, causes hydrolysis within 10 min. with the appearance of reducing power.

Acid catalyzed conversion of II *into fructose.* II (1 g.) was dissolved in 40% aqueous methanol (100 ml.) containing hydrochloric acid (*N*) and heated under reflux for 90 min. The resulting solution was divided into 2 parts, one was used for chromatographic analysis, while the second was employed for the preparation of an osazone after being neutralized with sodium acetate. The osazone thus obtained was identical with an authentic specimen of glucosazone as to melting point, mixed m.p., and crystallographic form under the microscope.

Chromatographic identification of II *and its hydrolysis product.* Paper chromatography was carried out with Whatman paper No. 1, using a mixture of butanol–acetic acid–water in the ratio of 4:1:5 as developer. Spraying was done with a solution of 3% *p*-anisidine hydrochloride in butanol. Paper chromatography of II and of its hydrolysis product gave the following R_f values: 0.44 for II and 0.23 for the hydrolysis product, identical with the R_f value of a sample of authentic fructose.

The denitration of the crude nitration product. When the catalytic hydrogenation was carried out under 3 atm. pressure, the ratio catalyst/substrate was reduced to 1:1 (w./w.) and the reaction was complete in 20 min. The reaction product was then treated in a manner described for the preparation of II, giving a sirupy product with a negative optical rotation. Paper chromatography of this product as described, showed only 2 spots on the chromatograms, with R_f values of 0.23 and 0.44, corresponding to fructose and II, respectively. This clearly indicates that the crude nitration product is composed exclusively of monomeric fructose nitrates.

Chromatographic separation of the denitration product. The separation of the reaction product into its components was effected by chromatography over a column containing Florex XXX[19]–Celite[20] (5:1 by weight) of 80-mesh.

The ratio substrate/absorbent expressed in w./w. is 1:100. The column was washed first with 95% ethanol and then with 10 ml. of 80% methanol. The product (2.5 g.) was absorbed on the column from a 50% aqueous methanol solution and was then eluted with 90% methanol and collected in a series of 10 ml. fractions. The first fractions were dextrorotatory, followed by laevorotating ones. The combined dextrorotating fractions, after removal of the solvent, gave a residue which was purified as described. The purified product was obtained as a dry sirup in 30% yield and was shown by specific optical rotation and R_f value to consist entirely of II. The laevorotatory fractions were identified as pure fructose, both by osazone and R_f value.

This technique furnishes an alternative route for the isolation of pure 2,3-anhydrofructofuranose from the crude nitration product, and avoids the difficulties sometimes encountered in the isolation of crystalline I from the crude nitration product by fractional crystallization.

2,3-Anhydrofructofuranose triacetate (III). A solution of 2 ml. acetic anhydride, 3 ml. pyridine and 200 mg. of II was kept at 0° for 24 hr. Crushed ice was then added with shaking, and the white crystals obtained, after standing a few hours, were separated by centrifugation. Two recrystallizations from ethanol yielded 80 mg. of hexagonal crystals, melting at 112°, $[\alpha]_D^{25}$ +57.4 (c 0.68, ethanol).

Anal. Calcd. for $C_{12}H_{16}O_8$: C, 50.00; H, 5.55; mol. wt., 288. Found: C, 49.93; H, 5.05; mol. wt., 289 (benzene).

The infrared spectrum shows bands (cm.$^{-1}$) at 1750 (C=O), 1240 (—C—O). The triacetate (III) is soluble in ordinary organic solvents, but slightly soluble in water. It does not reduce Fehling solution.

(18) Purified by a method described by L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath & Co., New York, N. Y., 1941, p. 365.

(19) A fuller's earth type of clay produced by the Floridin Company.

(20) No. 503, Johns-Manville Products.

Oxidation of II by potassium periodate. Due to the sensitivity of II towards acids, the Malaprade reaction was carried out by 0.038*M* potassium periodate solution at *p*H = 6.5. The anhydrofructose (II) was added to the oxidizing system at room temperature, and the amount of the oxidant consumed was estimated by titration of aliquots with arsenic acid and iodine standard solutions. Actually no reaction could be detected, even after 2 days, as was also shown by optical rotation measurements.

2,3-Anhydrofructofuranose ditrityl ether (IV) was prepared by the method used for the tritylation of fructose.[21] To a solution of II 0.5 g. (0.003 mol.) in pyridine (5 ml.) was added trityl chloride (1.7 g., 0.006 mol.). The solution was kept at room temperature for 48 hr., then poured into crushed ice and shaken several times during 4 hr. The solid which separated was filtered, dissolved in a small amount of methanol, and reprecipitated by adding water. Several recrystallizations from ethanol yielded 100 mg. of elongated prismatic rods of IV, melting at 165°.

Anal. Calcd. for $C_{44}H_{38}O_5$: C, 81.88; H, 5.88. Found: C, 81.74; H, 5.74.

The infrared spectrum shows bands (cm.$^{-1}$) at 3420 (free OH), 3030 (C—H), 1590, 1080 (phenyl).

2,3-Anhydrofructofuranose ditosylate (V). A solution of II (1.1 g., 0.007 mol.) in pyridine (8 ml.) was mixed at 0° with a solution containing tosyl chloride (2.6 g., 0.015 mol., m.p. 67°) in pyridine (8 ml.) and allowed to stand at 0° for 3 hr. The temperature was then allowed to rise to 25° and remained so for 20 hr. After the reaction mixture was poured into crushed ice it was allowed to stand overnight, and the brown amorphous precipitate was separated by centrifugation. It was recrystallized first from aqueous methanol and then twice from absolute ethanol, yielding white cubes (500 mg.) of V, melting at 155°.

(21) B. Helferich, *J. prakt. Chem.*, **147**, 60 (1936).

Anal. Calcd. for $C_{20}H_{22}O_9S_2$: C, 51.48; H, 4.68; S, 12.86. Found: C, 51.52; H, 4.86; S, 12.5. The infrared spectrum shows bands (cm.$^{-1}$) at 3546 (free OH), 1184 (O—SO_2).

Recrystallization of V from methanol afforded microcrystals of m.p. 147° containing one mole of methanol of crystallization which could not be removed easily.

Anal. Calcd. for $C_{20}H_{22}O_9S_2 \cdot CH_3OH$: C, 50.19; H, 5.17; S, 12.74. Found: C, 50.22; H, 4.86; S, 12.75.

This, upon recrystallization from absolute ethanol, again gave the ditosylate of melting point 156°.

Increasing the molar ratio of II/TsCl from 1:2 to 1:3 had no effect either upon the composition or on the yield of the reaction product. V was invariably produced.

Reaction of V with sodium iodide in acetone. A solution of V (820 mg.) in 10 ml. of dry acetone was mixed with a solution of sodium iodide (1.7 g.) in dry acetone (10 ml.). The resulting homogeneous mixture was placed in a Pyrex ampule, sealed, and then was heated for 48 hr. at 100°. After a few hours, yellowish crystals separated from the reaction system, the amount of which increased while the reaction progressed. At the end, the precipitate of sodium tosylate was filtered, washed several times with acetone, and its weight determined.

Anal. Calcd. for $C_7H_7O_4SNa$: C, 39.60; H, 4.25. Found: C, 39.46; H, 4.14.

From the filtrate, the solvent was removed by evaporation *in vacuo*, and the residue was dissolved in a chloroform-water mixture, washed with sodium thiosulphate and dried over anhydrous sodium sulphate. After removal of solvent under reduced pressure, the residue was crystallized from benzene, yielding an amorphous product, melting at 126–128°. It contained iodine, but could not be further purified by the usual methods.

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Mechanism of Carbene Formation from *t*-Butyl Dichloroacetate[1]

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Received May 29, 1959

A mechanism is proposed for the formation of dichlorocarbene from the reaction of *t*-butyl dichloroacetate and potassium *t*-butylate, involving a chlorination step with the formation of the intermediate *t*-butyl trichloroacetate.

In a previous communication[2] the reaction of *t*-butyl dichloroacetate(I) and potassium *t*-butylate in the presence of isobutylene was described and reaction (a) was suggested as a possible route for the formation of dichlorocarbene. The final product, 1,1-dichloro-2,2-dimethylcyclopropane(V), was isolated in 13% yield. Further experiments have furnished data which required that the simple mechanism (a) be replaced by the mechanism illustrated by steps (b) to (f), inclusive.

$$\underset{\text{I}}{Cl_2CHCO_2R} + RO^- \rightleftharpoons Cl_2\bar{C}CO_2R \longrightarrow Cl_2C + CO + RO^- \quad (a)$$

$$Cl_2CHCO_2R + RO^- \rightleftharpoons Cl\bar{C}H{-}CO_2R + ROCl \quad (b)$$

$$ClCHCO_2R + ROH \rightleftharpoons \underset{\text{II}}{ClCH_2CO_2R} + RO^- \quad (c)$$

$$Cl_2CHCO_2R + RO^- \rightleftharpoons Cl_2\bar{C}CO_2R + ROH \quad (d)$$

$$Cl_2\bar{C}CO_2R + ROCl \longrightarrow \underset{\text{III}}{Cl_3CCO_2R} + RO^- \quad (e)$$

$$Cl_3CCO_2R + RO^- \longrightarrow Cl_2C + \underset{\text{IV}}{ROCOR} + Cl^- \quad (f)$$

$$Cl_2C + (CH_3)_2C{=}CH_2 \longrightarrow \underset{\text{V}}{(CH_3)_2C(CH_2)(CCl_2)} \quad (g)$$

It is proposed that *t*-butyl dichloroacetate is converted, in the presence of *t*-butylate, into a mixture of *t*-butyl monochloroacetate(II) and *t*-butyl tri-

(1) This work was supported by a grant (G-7382) from the National Science Foundation.

(2) W. E. Parham and F. C. Loew, *J. Org. Chem.*, **23**, 1705 (1958).

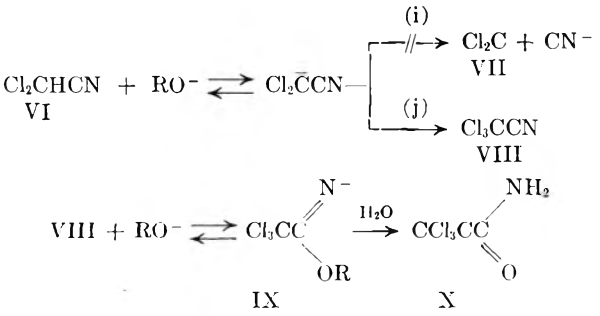
chloroacetate(III). The authors[2] have previously shown that compound II is converted into higher molecular weight condensation products in the presence of potassium *t*-butylate, whereas compound III is converted into dichlorocarbene and di*tert*-butyl carbonate(IV). Thus, if such a shift of chlorine occurs, the maximum yield of 1,1-dichloro-2,2-dimethylcyclopropane(V), obtained from compound I, would be less than one half of that obtained from pure compound III under the same conditions.

The reaction of equimolar ratios of pure *t*-butyl dichloroacetate(I), potassium *t*-butylate and *t*-butyl hypochlorite in the presence of isobutylene and pentane yielded 1,1-dichloro-2,2-dimethylcyclopropane (V, 45%) and di-*t*-butyl carbonate (IV, 55%), analyzed by gas chromatography. *t*-Butyl trichloroacetate(III) was also isolated in 5% yield. The yield of compound V was thus comparable to that obtained previously[2] from the reaction of *t*-butylate with *t*-butyl trichloroacetate(III) (see step f and g, i.e. 55% of compound V), establishing that chlorination of the initial *t*-butyl dichloroacetate(I) may be accomplished by positive halogen, and lending support for step e. Step b has not been substantiated because of the authors' inability to isolate any *t*-butyl hypochlorite; however, the intermediate formation of *t*-butyl hypochlorite as the chlorinating agent seems more feasible than chlorination of the *t*-butyl dichloroacetate carbanion by *t*-butyl dichloroacetate (h). Chlorination of carbanions by

$$Cl_2\bar{C}CO_2R + Cl_2CHCO_2R \longrightarrow Cl_3CCO_2R + Cl^-CHCO_2R \quad (h)$$

t-butyl hypochlorite is well established.[3]

More compelling evidence for reactions of the type shown in equations b–e was obtained by a study of the reaction of dichloroacetonitrile(VI) and potassium *t*-butylate in the presence of isobutylene.



A considerable amount of tarry material resulted; no cyanide ion was formed, and trichloroacetamide (X, 10% yield) was isolated from the reaction mixture upon subsequent hydrolysis. The starting material was pure (vaporphase chromatography), thus the isolation of trichloroacetamide establishes a chlorination step in the above reaction analogous to that postulated earlier for the reaction with *t*-butyl dichloroacetate(I).

While the evidence at hand strongly supports the chlorination mechanism discussed (b–e), the results do not, of course, rule out Equation (a) as a possible source for the formation of dichlorocarbene from *t*-butyl dichloroacetate(I). However, attention was called earlier[2] to the fact that dichlorocarbene and *t*-butyl alcohol do react to form carbon monoxide; consequently, there are no data currently available supporting equation (a).

EXPERIMENTAL

Vapor-phase chromatography was carried out as previously described.[4]

The Reaction of t-Butyl Dichloroacetate (I) *with Potassium t-Butylate and t-Butyl Hypochlorite in the Presence of Isobutylene.* A mixture of *t*-butyl dichloroacetate[5] (46.25 g., 0.25 mole) and *t*-butyl hypochlorite[6] (27.14 g., 0.25 mole) was added over a 1.5-hr. period to a cold (−15°) mixture of powdered potassium *t*-butoxide[7] (0.25 mole), isobutylene (75 ml. at −80°, ca. 1 mole), and olefin-free pentane (125 ml.). The resulting mixture was stirred for an additional 1.5-hr. period at −10°. The Dry Ice condenser and cooling bath were removed, and the isobutylene was allowed to evaporate overnight. Water (150 ml.) was added, the organic layer was separated and the water phase was extracted with three 75-ml. portions of pentane. The organic layer and the pentane extracts were combined and dried ($MgSO_4$). The mixture was filtered and the filtrate was concentrated. The residue was distilled and two fractions were collected: (1) 65.34 g., boiling below 82° (55 mm.); (2) 4.7 g., b.p. 82° (55 mm.) to 59° (7 mm.). Analyses of fraction (1) by vapor-phase chromatography showed that it consisted mainly of 1,1-dichloro-2,2-dimethylcyclopropane (15.8 g., 45%) and di-*t*-butyl carbonate (24.0 g., 55%). Distillation of fraction (2) yielded 2.81 g. (5%) of *t*-butyl trichloroacetate, b.p. 54–55° (7 mm.), n_D^{25} 1.4392 (reported[8] b.p. 37° (1 mm.), n_D^{25} 1.4398). The material had an infrared spectrum essentially identical with that of an authentic sample.

Dichloroacetonitrile (VI) used was obtained from L. Light and Co., Ltd., England. This material (95–99% pure) was redistilled, b.p. 112–114° (735 mm.) (reported[9] b.p. 112–113°). The vapor-phase chromatogram of the distilled material showed only one symmetrical peak—there was no evidence of impurity.

The Reaction of Dichloroacetonitrile with Potassium t-Butylate in the Presence of Isobutylene. Dichloroacetonitrile (55 g., 0.50 mole) was added over a 1-hr. period to a cold (−15°) mixture of powdered potassium *t*-butylate (0.60 mole), isobutylene (150 ml. at −80°, ca. 2 mole), and olefin-free pentane (100 ml.). The resulting black mixture was stirred for an additional two hours at −15°; the Dry Ice condenser and cooling bath were removed, and the isobutylene was allowed to evaporate overnight. Water (200 ml.) and pentane (300 ml.) were added to the mixture, and

(3) (a) M. Anbar, I. Dostrovsky, D. Samuel, and A. P. Yoffee, *J. Chem. Soc.*, 3603 (1954); (b) M. Mousseron and P. Froger, *Bull. soc. chim. France*, 12, 69 (1945); (c) The referee suggests that reaction *h* is more probable than reaction *b*, in view of the greater bond energy of the carbon-chlorine bond compared to the oxygen-chlorine bond. *Cf.* K. S. Pitzer, *J. Am. Chem. Soc.*, 70, 2140 (1948).

(4) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, 24, 1733 (1959).

(5) W. E. Parham and R. R. Twelves, *J. Org. Chem.*, 22, 730 (1957).

(6) *Org. Syntheses*, 32, 20 (1952).

(7) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, 76, 6162 (1954).

(8) W. E. Scovill, R. E. Burk, and H. P. Lankelma, *J. Am. Chem. Soc.*, 66, 1039 (1944).

(9) L. Bisschopinck, *Ber.*, 6, 732 (1873).

the organic layer was separated. The water layer was washed once with pentane. The organic layers were combined and dried ($MgSO_4$). A significant amount (20 g., dried) of black amorphous material remained, which was insoluble in both water and pentane. The composition of this amorphous material was not determined.

Concentration of the dried organic solution yielded a dark, solid residue which was sublimed under vacuum (150°, 0.1 mm.). The sublimate (6.5 g.) was crystallized from benzene, affording 6.0 g. (10%) of trichloroacetamide, m.p. 142–143° (m.p., mixture m.p. and infrared spectra identical with an authentic sample).

Acidification (dil. HNO_3) of the remaining aqueous layer and subsequent precipitation with silver nitrate solution yielded silver chloride. An infrared spectrum of the dried precipitate showed no absorption in the 2000–2300 $cm.^{-1}$ region (silver cyanide absorbs[10] strongly at 2178 $cm.^{-1}$), thus it was concluded that no cyanide ion was formed in the reaction.

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(10) W. D. Stallcup and D. Williams, *J. Chem. Phys.*, **18**, 199 (1942).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Migration of Aryl Groups in the Deamination of Amines

J. C. MARTIN AND W. G. BENTRUDE

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The evidence on aryl group migration in the nitrous acid deamination of amines has been examined insofar as it bears on the problem of the mechanism by which nitrogen is lost in the reaction. It has proved possible to reconcile the results of Curtin[8,18] on the migration aptitudes of aryl groups in the 1,1-diaryl-2-amino-1-propanols with the scheme proposed by Collins[5] to explain results using C^{14} labeling experiments in the same system. The relative rates of aryl migration and interconversion of rotational isomers of the open carbonium ion intermediates have been calculated.

The concept of the phenonium ion[1] has become quite firmly established in organic chemistry in recent years. The study of limiting solvolysis reactions of systems yielding carbonium ions which could be expected to gain energetically by the bridging of a neighboring phenyl[2] has yielded much good evidence for this bridged ion as an intermediate. Phenyl participation to give a phenonium ion has come to be expected in such cases, although modification of the molecule in a manner calculated to stabilize the open (nonbridged) carbonium ion may decrease the importance of such bridging.[3]

It is of interest, in this context, that recent studies[4,5,6] of the nitrous acid deaminations of amines with neighboring aryl groups has produced evidence that open carbonium ions are important intermediates in such reactions, even in systems which give only bridged ions in ordinary solvolysis reactions.

The deamination reaction is closely related to other solvolysis reactions with the principal difference being that the leaving group, a nitrogen molecule, is unusually stable, compared to the usual leaving groups in solvolysis reactions.

Because of the driving force for the deamination reaction, which originates in this great stability of one of the products, the diazonium ion is a very unstable intermediate which may lose a nitrogen molecule as an integral part of the mechanism of any one of several exothermic reactions. The exothermic nature of these reactions would be expected to cause all of the reactions of the diazonium ion (rearrangement, solvolysis, elimination) to have activation energies not only smaller but more closely similar than those of related reactions of the alkyl halides or sulfonate esters.[7]

Such reasoning was used by Curtin and Crew[8] to explain the small size of the increase in migration aptitude of a neighboring phenyl when it is substituted by a *p*-methoxy group in the semipinacolic deaminations of the 2-amino-1,1-diarylethanols. If the loss of nitrogen is exothermic, the transition state resembles starting material[7] and the small substituent effect results from the limited amount of bonding in the transition state between the migrating aryl group and the developing carbonium ion center.

Streitwieser[9a,b] and Huisgen[10] have explained the products observed in a variety of deamination reactions on the basis of a similar argument, the high energy diazonium ion reacting rather indiscriminately in the various possible modes.

If, indeed, activation enthalpy terms are monotonously constant and small in reactions involv-

(1) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3863, 3875, 3883 (1949).

(2) S. Winstein and K. S. Schreiber, *J. Am. Chem. Soc.*, **74**, 2165 (1952).

(3) D. J. Cram and J. Allinger, *J. Am. Chem. Soc.*, **79**, 2858 (1957).

(4) D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, **79**, 2866 (1957).

(5) B. M. Benjamin, H. S. Schaeffer, and C. J. Collins, *J. Am. Chem. Soc.*, **79**, 6160 (1957).

(6) C. J. Collins, W. A. Bonner, and C. T. Lester, *J. Am. Chem. Soc.*, **81**, 466 (1959).

(7) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(8) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **76**, 3718 (1954). See also D. Y. Curtin and M. von Wilhelm, *Helv. Chim. Acta*, **40**, 2129 (1957).

(9) (a) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2888 (1957). (b) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957).

(10) R. Huisgen and C. Ruchardt, *Ann.*, **601**, 1 (1956).

ing the loss of nitrogen molecules, the entropy of activation becomes correspondingly more important. It is not surprising to find that the reaction expected to have the most favorable entropy of activation, namely the loss of nitrogen to give an open carbonium ion without participation of solvent or of neighboring groups, is much more important than in dissociation reactions involving leaving groups other than nitrogen.

This view of the deamination reaction pictures the formation of a highly energetic carbonium ion, not necessarily stabilized by bridging to neighboring groups, by optimum solvation, or by any resonance interation requiring a particular orientation in space. The postulated formation of such a "hot" carbonium ion has been used to explain many observations in various deamination reactions.[4,11–13]

Ciereszko and Burr[11] have proposed such a high energy primary carbonium ion as an intermediate in the deamination of the 2-amino-1,1-diarylethanols. The small spread in migration aptitudes for *p*-anisyl and phenyl is explained to result from an indiscriminate attack on the neighboring aryl groups by the carbonium ion.

The first reported experimental demonstration of such open carbonium ions in systems which give bridged ions in ordinary solvolysis reaction was by Cram and McCarty.[4] They studied the stereochemical results of the deaminations of the optically pure diastereoisomeric 3-phenyl-2-butylamines and obtained results which they explained to result from "conformational control of the migrating group." In the scheme advanced here a particular rotational isomer of the open carbonium ion is produced depending on which rotational isomer of the diazotized amine loses nitrogen.[14] The fate of this open carbonium ion then depends upon its rotational isomerism and upon the solvent.[15] Any rearrangement occurs by a very rapid attack of this carbonium ion on the neighboring aryl group which is geometrically most favorably situated in that particular rotational isomer of the carbonium ion. Such attack is considered fast compared to the interconversion of rotational isomers.

Collins[5,6] has carried out isotopic labelling experiments on the semipinacolic deaminations of 1,1-diphenyl-2-amino-1-propanols (Ia). It had been established earlier[16,17] that phenyl migration in this series proceeded principally with inversion at the migration terminus to give V from I. Collins[5,6] showed that open ions were important intermediates in this series since an appreciable portion of the phenyl rearrangement went to give retention of configuration at the terminus (VIa from Ia). In this case the results are explained without postulating any important contribution of phenonium ion intermediates in the reaction scheme.

It is of interest to determine the extent to which the reaction scheme deduced by Benjamin, Schaeffer, and Collins[5,6] to explain the results of their isotopic labeling experiments will accommodate the migration aptitudes observed earlier in such reactions by Curtin and Crew.[8,18] Fortunately both groups of workers have studied the semipinacolic deamination of 1,1-diaryl-2-amino-1-propanols. Collins[5] studied the aryl migration by following the movement of stereospecifically C^{14}-labeled phenyl rings in optically active Ia. Curtin[18] determined the products when the aryl groups were variously substituted phenyl rings in racemic Ib and Ic.

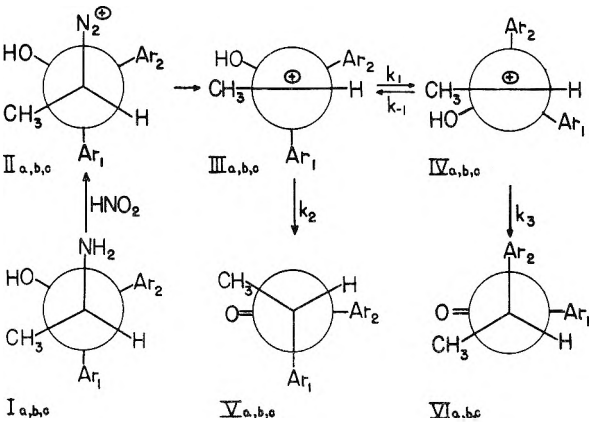

Fig. 1.

Ia, IIa, IIIa, IVa, Va, and VIa. $Ar_1 = C_6{}^{14}H_5$, $Ar_2 = C_6H_5$
Ib, IIb, IIIb, IVb, Vb, and VIb. $Ar_1 = C_6H_5$, $Ar_2 = p$-anisyl
Ic, IIc, IIIc, IVc, Vc, and VIc. $Ar_1 = p$-anisyl, $Ar_2 = C_6H_5$

When optically active Ia was treated[5] with nitrous acid the product mixture of ketones consisted of 88% Va, in which the carbon to which the labeled phenyl moved showed an inversion of configuration, and 12% VIa, the product resulting from a migration of unlabeled phenyl with retention of configuration at the migration terminus. On the basis of these results the reaction scheme outlined above was postulated for Ia.

The assumption is made here that all of the reaction occurs through molecules in the thermodynamically most favored conformation, IIa. This yields the open carbonium ion, IIIa, which may either rearrange to Va, with migration of labeled phenyl, or in a step of comparable rate undergo rotation

(11) L. S. Ciereszko and J. G. Burr, *J. Am. Chem. Soc.*, **74**, 5431 (1952).
(12) D. Semenow, C. Shih, and W. G. Young, *J. Am. Chem. Soc.*, **80**, 5472 (1958).
(13) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954).
(14) See P. I. Pollack and D. Y. Curtin, *J. Am. Chem. Soc.*, 72, 961 (1950) for a closely related idea.
(15) See W. A. Bonner and D. D. Tanner, *J. Am. Chem. Soc.*, **80**, 1447 (1958).
(16) A. McKenzie, R. Roger, and G. O. Wills, *J. Chem. Soc.*, **779** (1926).
(17) H. I. Bernstein and F. C. Whitmore, *J. Am. Chem. Soc.*, **61**, 1324, (1939).
(18) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **77**, 354 (1955).

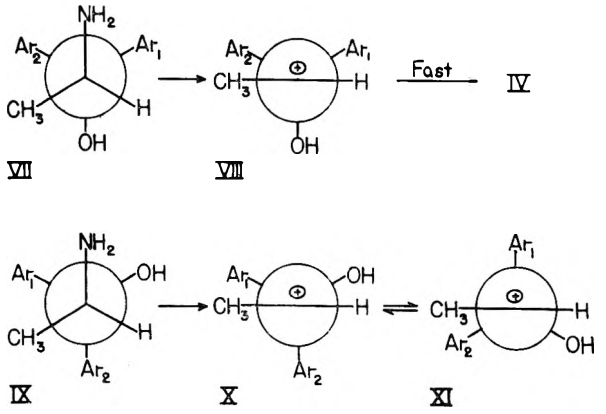

Figure 2.

about the C—C bond to yield carbonium ion IVa. Rearrangement of IVa to VIa, involving migration of configuration at the migration terminus, is considered to occur with a rate comparable to that of reversion to IIIa. The observation of a product mixture containing 88% of Va and 12% of VIa demands, within this framework of assumptions, that $k_1 < k_2$. The symmetry of the starting material demands in this case that $k_2 = k_3$ (ignoring kinetic isotope effects) and $k_1 = k_{-1}$.

Applying the steady state approximation[19] to the intermediate present in lowest concentration, carbonium ion IVa, we may obtain relative values of k_1, k_{-1}, k_2 and k_3.

$$\frac{d[Va]}{dt} = R_2[IIIa]; \frac{d[VIa]}{dt} = k_3[IVa] \quad (1)$$

$$\frac{d[IVa]}{dt} = k_1[IIIa] - k_{-1}[IVa] - k_3[IVa] = 0 \quad (2)$$

Combining (1) and (2) and integrating we get

$$[VIa] = \frac{k_1 k_3}{k_2(k_{-1} + k_3)} [Va] \quad (3)$$

Since, in this case, $k_3 = k_2$ and $k_1 = k_{-1}$ and we know that [VIa]/[Va] = 12/88 we can calculate from (3) that

$$k_2 = k_3 = 6.3k_1$$

Any important contribution of IX to the reaction scheme is ruled out by the failure to observe any appreciable amount (<2%) of product with inverted terminal configuration in which unlabelled phenyl (Ar_2) had migrated. (Such a product would result from rearrangement of ion X derived from amine IX.)

The experimental facts of ref. (5) are equally well explained, however, by postulating an importance of amine conformation VII in the reaction scheme. Reaction of VII with nitrous acid would give carbonium ion VIII, which could not give aryl migration but would be expected to be quickly converted to IV, as such a conversion would involve eclipsing only of hydrogen with Ar_1. Postulating 12% of the reaction to take this path we could accommodate the observed product composition in a scheme in which aryl migration is much faster than the interconversion of rotational isomers IIIa and IVa.

It is possible to choose between these two explanations by considering the results of Curtin and Crew[18] on ratios for *p*-anisyl and phenyl migration in the diastereoisomeric forms of 1-*p*-anisyl 1-phenyl-2-aminopropanol (Ib and Ic). The *erythro* isomer (Ib) gave 88% phenyl migration (Vb) and 12% *p*-anisyl migration (VIb). If we make the reasonable assumption that *para* substitution affects neither conformational equilibria nor rates of interconversion of IIIb and IVb, we may use the same kinetic treatment in this case as we used for Ia.

We would expect the electronic effect of the *p*-methoxy group to increase the rate of *p*-anisyl migration over that for phenyl migration, so the ratio k_3/k_2 in Equation 3 would not be expected to be unity. A reasonable value for this ratio may be derived from the migration ratios observed[5] in the pinacolic deamination of 2-amino-1-*p*-anisyl-1-phenylethanol (XII). In this compound the carbon from which nitrogen is lost is symmetrically substituted with two hydrogen atoms. One would, therefore, expect the migration ratio to express only the electronic effects of the remote *para* substituents in this case. The ratio of $k_{p\text{-anisyl}}/k_{phenyl}$ was found[20] to be 1.56.

In the reaction of Ib the ratio k_3/k_2 in Equation 3 may be set equal to 1.5 and we calculate:

$$k_2 = 7.0\ k_1 \text{ and } k_3 = 10.5\ k_1 \quad (5)$$

We may apply these calculated ratios of rate constant [equations (5)] to predict the product composition for the reaction of the diastereoisomeric amine (Ic). Recognizing that this compound is the same as Ib except that the phenyl and *p*-anisyl are exchanged, we may write for Ic:

$$k_2 = 10.5\ k_1 \text{ and } k_3 = 7.0\ k_1 \quad (6)$$

Then from Equation 3 we predict:

$$[Vc]/[VIc] = 0.084; [Vc] = 7.7\%; [VIc] = 92.3\%$$

The experimentally determined composition of the reaction product in this case was 6% of Vc and 94% of VIc. The close agreement between the calculated and actual percentage compositions may be considered as confirmation of the postulated reaction scheme.

It is of interest to note that from the data on C^{14}-labeled phenyl migration in Ia the migration rate was 6.3 times as fast as interconversion of IIIa and IVa ($k_2/k_1 = 6.3$). The rate of phenyl migration

(19) A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, J. Wiley and Sons, Inc., New York, 1953, p. 159.

(20) Curtin[8] has calculated this same ratio, 1.5, to represent the purely electronic component of the migration ratios observed in the deaminations of Ib and Ic. This compares with ratios of up to 500 in other reactions. [W. E. Bachmann and F. H. Moser, *J. Am. Chem. Soc.*, **54**, 1124 (1932).]

when the group left behind is *p*-anisyl (in Ib) is 7.0 times as fast as interconversion of IIIb and IVb ($k_2/k_1 = 7.0$). Again assuming that the remote *para* substituent has no effect on rates of rotation (*i.e.*, the value of k_1 is the same for each reactant), we conclude that phenyl migration, leaving behind a carbonium ion stabilized by a hydroxyl group and a *p*-anisyl group, is faster by 10% than the migration of phenyl in a system in which the developing carbonium ion center is stabilized by the hydroxyl group and an unsubstituted phenyl group.

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[CONTRIBUTION FROM EASTERN RESEARCH LABORATORY, THE DOW CHEMICAL COMPANY]

Addition of Hydrogen Cyanide to Aromatic Schiff Bases

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Details are presented on the synthesis of *N,N'*-alkylenebis[(2-substituted) glycinonitriles] by the addition of hydrogen cyanide to aromatic bis-Schiff bases. Where thermally stable, the nitriles may be hydrolyzed to the *N,N'*-alkylenebis-2-arylglycines.

In previous publications[2] we have reported on the properties of a novel chelating agent, *N,N'*-ethylenebis[2-(*o*-hydroxyphenyl)] glycine[3] and we wish now to report the synthesis of this and of related compounds. In essence, our method consists of the addition of 2 mol. of anhydrous hydrogen cyanide to a bis-Schiff base derived from an aromatic aldehyde and a diamine, and subsequent hydrolysis of the resulting glycinonitrile to an *N,N'*-alkylenebis-2-arylglycine. Though bis-glycinonitriles have been prepared from diamine dihydrochlorides, carbonyl compounds and potassium cyanide in aqueous solution,[4,5] little data is available on the addition of anhydrous hydrogen cyanide to Schiff bases, a reaction originally discovered by Plöchl.[6]

Inasmuch as the aromatic Schiff bases are readily prepared and purified, this method offers an alternate to the usual processes for the preparation of 2-substituted amino acids. However, the reaction sequence is limited severely by the lack of reactivity of certain of the aromatic Schiff bases with hydrogen cyanide and the thermal instability of the bis-glycinonitriles. Thus, of the twenty-seven Schiff bases reported in Table I, seven (19–27) did not react at all with hydrogen cyanide and a number of the others yielded intractable oils. Attempts to catalyze the cyanide addition were not successful and the use of solvents of varied polarity, other than liquid hydrogen cyanide, offered little advantage in the case of the non-reactive Schiff bases, but was of some advantage in moderating the reaction for the more reactive compounds. The electronic nature of the substituent on the aromatic ring seems to have little or no effect on the formation of these adducts. Thus, while the *ortho*-hydroxyphenyl derivative affords product in almost quantitative yield, the corresponding 2,4-dihydroxyphenyl counterpart yields no glycinonitrile whatsoever, and is recovered unchanged.

A characteristic property of the glycinonitriles listed in Table II is their thermal instability. This undesirable feature greatly limited the number of compounds which were successfully hydrolyzed to the corresponding amino acids. Even those nitriles which could be successfully hydrolyzed had a limited stability; *N,N'*-ethylenebis[2-(*o*-hydroxyphenyl)]glycinonitrile though almost white when stored in the cold, slowly decomposed at room temperatures to give an orange brown solid which could not be characterized. A second mode of decomposition, which was typical of the heterocyclic derived Schiff bases, was their reversion to starting compounds with evolution of hydrogen cyanide. Thus, it is not surprising that only the most stable of the glycinonitriles were successfully hydrolyzed whereas the majority afforded only intractable highly colored tars. The *N,N'*-alkylenebis-2-substituted glycines are listed in Table III and some details of their preparation are given in the experimental section.

EXPERIMENTAL

Schiff bases. These were synthesized in the usual manner by reaction of the appropriate aldehyde with the proper anhydrous diamine in alcohol in a 2:1 molar ratio. Purification was accomplished by recrystallization from alcohol. In the case of the 2-pyridine aldehyde- and 6-methyl-2-pyridinealdehyde-derived Schiff bases, reaction was conducted under a blanket of nitrogen using a few drops of glacial acetic acid to expedite reaction. Ligroin (66–75°)

(1) Present address: Chas. Pfizer and Co., Inc., Brooklyn, New York.

(2) H. H. Freedman, A. E. Frost, S. J. Westerback, and A. E. Martell, *Nature*, **179**, 1020 (1957); *J. Am. Chem. Soc.*, **80**, 530 (1958).

(3) Concurrent with our initial publication, a communication appeared by H. Kroll, M. Knell, J. Powers, and J. Simonian, *J. Am. Chem. Soc.*, **79**, 2024 (1957), which reported the synthesis of this compound by a method substantially identical to ours.

(4) N. Schlesinger, *Ber.*, **45**, 1486 (1912).

(5) H. Zahn and H. Wilhelm, *Ann.*, **579**, 1 (1953).

(6) J. Plöchl, *Ber.*, **13**, 2118 (1880).

TABLE I

BIS-SCHIFF BASES R—CH=N—Y—N=CHR

	R	Y	M.P.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	Phenyl	Ethylene	52[a]	75.8						
2	*o*-Hydroxyphenyl	Ethylene	126–127[b]	Quant.						
3	*o*-Hydroxyphenyl	1,2-Propylene	Oil[c]	75.0						
4	*o*-Hydroxyphenyl	Trimethylene	54–55[d]	91.3						
5	*o*-Hydroxyphenyl	*o*-Phenylene	164–169[e]	36.4						
6	*m*-Hydroxyphenyl	Ethylene	198–200[f]	68.7						
7	*p*-Hydroxyphenyl	Ethylene	222–226	68.3	57.8	56.8	4.9	6.2	8.4	11.0
8	*o*-Methoxyphenyl	Ethylene	117–119[g]	68.5						
9	*p*-Methoxyphenyl	Ethylene	112–114[h]	79.5						
10	*o*-Chlorophenyl	Ethylene	88–89	76.4	63.0	62.7	4.6	4.6	9.2	9.2
11	*o*-Toluyl	Ethylene	55–56	41.7						
12	*p*-Toluyl	Ethylene	158–160	72.0	81.8	81.5	7.6	7.8	10.6	10.7
13	1-Naphthyl	Ethylene	136.5–138	83.2	85.7	85.7	6.0	6.0	8.3	8.4
14	2-Thienyl	Ethylene	91.5–93[i]	34.0						
15	2-Furyl	Ethylene	53–54[j]	60.0						
16	2-Pyridyl	Ethylene	67–68[k]	67.2						
17	2-Lutidyl	Ethylene	69–72	—	72.2	72.4	6.8	6.8	21.0	20.7
18	*o*-Hydroxyphenyl	Iminobis-ethylene	Oil							
19	2,5-Dihydroxyphenyl	Ethylene	248 (dec.)	Quant.	64.0	64.0	5.4	5.4	9.3	9.3
20	2,4-Dihydroxyphenyl	Ethylene	192 (dec.)	—	64.0	63.6	5.4	5.4	9.3	9.2
21	2-Hydroxy-5-chlorophenyl	Ethylene	183–185	66.4	57.0	57.0	4.2	4.2	8.3	8.3
22	2-Hydroxy-5-nitrophenyl	Ethylene	260	Quant.	53.6	53.9	3.9	4.2	15.7	15.9
23	1-(2-Hydroxynaphthyl)	Ethylene	311 (dec.)[d]	—						
24	1-(4-Hydroxynaphthyl)	Ethylene	250 (dec.)	—	78.2	77.8	5.5	5.5	7.6	7.8
25	2-(3-Hydroxynaphthyl)	Ethylene	285	64.0						
26	1-(2-Methoxynaphthyl)	Ethylene	292–294	90.0	78.8	78.6	6.1	5.9	7.1	7.4
27	*o*-Hydroxyphenyl (H=CH_3)	Ethylene	202–203	Quant.	73.0	72.8	6.8	6.7	9.5	9.6

[a] Mason, *Ber.*, 20, 267 (1887) reports m.p. 53–4°. [b] Ref. a, reports m.p. 125–126°. [c] Strache, *Ber.*, 21, 2358 (1888) reports a yellow oil. [d] Pfeiffer, *et al.*, *J. Prakt. Chem.*, 149, 217 (1937) report a yellow oil. [e] Ref. d, m.p. 163°. [f] Bogoslovskii, *J. Gen. Chem.* (*U.S.S.R.*), 14, 995 (1944), m.p. 189–191.5°. [g] Ref. a, m.p. 113°. [h] Ref. a, m.p. 110–111°. [i] Eichhorn and Bailar, *J. Am. Chem. Soc.*, 75, 2905 (1953). [j] Ramceau, *Rec. trav. chim.*, 57, 194 (1938). [k] Busch and Bailar, *J. Am. Chem. Soc.*, 78, 1137 (1956).

TABLE II

N,N'-ALKYLENEBIS[(2-SUBSTITUTED)GLYCINONITRILES]

Compd.[d]	M.P.	Yield, %	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	118–123 dec.[a]	75.8	74.5	74.2	6.3	6.2	19.3	19.3
2	125–126 dec.[b]	99.0	67.1	67.1	5.7	5.6	17.4	17.2
3	Oil	—						
4	Oil	—	(Crude oil hydrolyzed without purification)					
5	Oil	—						
6	Oil	—						
7	130 dec.	83.4	67.1	67.6	5.6	6.6	17.4	16.6
8	Oil	—						
9	95–97 dec.	81.4	68.6	68.5	6.3	6.5	16.0	15.5
10	80–99 indef.	—						
11	Amorphous	—	75.4	75.2	7.0	7.0	17.6	17.5
12	127–132 dec.	Quant.	75.4	75.3	7.0	7.1	17.6	17.3
13	152 dec.	Quant.	80.0	79.8	5.7	5.6	14.4	14.1
14	87–90 dec.	—						
14[c]			—	—	—	—	14.9	14.9
15	87–91 dec.	—	62.2	58.7	5.2	5.0	20.7	20.5
15[c]			48.0	47.4	4.7	4.6	16.3	15.9
16	96–102 dec.	—	65.7	65.6	5.5	5.8	28.7	27.9
17	Oil	—	72.2	72.4	6.8	6.8	21.0	20.7
18	Oil	—	65.9	65.0	6.4	7.3	19.2	18.6

[a] Ref. 4 gives m.p. 122–123°. [b] Ref. 3 gives m.p. 113–115°. [c] Dihydrochloride. [d] The numbers refer to the parent compounds as given in Table I.

TABLE III

N,N-ALKYLENEBIS[(2-SUBSTITUTED)GLYCINES]

Compd.[a]	M.P.	Yield, %	Hydrolysis Method	Analyses					
				Carbon		Hydrogen		Nitrogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
1	>280[a]	Quant.	II	65.8	65.1	6.2	6.2	8.5	8.6
2	234–235 (dec.)[b]	75	I	60.0	59.8	5.6	5.8	7.8	7.9
4	234–238 (dec.)	53	I	60.9	60.6	6.5	6.2	7.5	7.6
7	240–245 (dec.)	29	II	60.0	58.2	5.6	5.9	7.8	7.5
9	246 (dec.)	25	I	61.8	59.7	6.23	6.0	7.2	7.0
10	202–207 (dec.)	10	II	54.4	52.9	4.6	4.6	7.1	6.4
18[c]	—	17[c]	I	47.0	46.8	5.3	5.8	8.2	9.4

[a] Ref. 4 reports m.p. >250°. [b] Ref. 3 gives no m.p. [c] As the trihydrochloride, Cl, Calcd. 20.7, Found 20.7. [d] See footnote d, Table II.

was used as recrystallizing solvent. Pertinent data are reported in Table I.

Reaction with liquid hydrogen cyanide: Preparation of N,N'-alkylenebis(2-substituted)glycinonitriles. The general procedure consisted in adding to the Schiff base at 5–10° with efficient stirring, a 4 to 5 molar excess of liquid hydrogen cyanide or an amount sufficient to give a good slurry.[7] When reaction took place, solution of the Schiff base occurred within a few min., followed in some instances, by precipitation of the adduct. In such cases separation was affected by filtration followed by air drying or by adding a ten-fold volume of water and stirring thoroughly, followed by filtration and further washing with water. When precipitation did not occur, the excess liquid hydrogen cyanide was removed by aspiration or by evaporation at room temperature since the application of heat usually caused decomposition of the adducts. The adducts were generally analytically pure requiring no further purification. Pertinent data are listed in Table II. For convenience, reaction was conducted in a flask fitted with a sintered glass disc and stop-cock arrangement to minimize handling of the liquid hydrogen cyanide.

Hydrolysis of adducts. Preparation of N,N'-alkylenebis(2-substituted)glycines. Method I. The first general procedure involved adding 4–5 ml. of cold concentrated hydrochloric acid per gram of nitrile and, once the initial exothermic reaction had subsided, heating the mixture on a steam bath for a few min. The acids often separated as their hydrochlorides from which the free acids were obtained by neutralization. When separation did not occur, the free acids were isolated by neutralization with 30% sodium hydroxide to *p*H 4–5 followed by filtration and thorough washing with water, in which most were insoluble. Recrystallizations were effected from methanol.

Method II. The second general procedure was that of Schlesinger.[4] This consisted in adding 10 ml. of a concentrated hydrochloric acid-concentrated sulfuric acid mixture (1–5 by volume) per gram of nitrile at a temperature below 35°. After three days at room temperature, an equal volume of water was added, the mixture heated to reflux for one hour, and the acid isolated as above. Data on the various acids are summarized in Table III.

Acknowledgment. We are grateful to A. A. Carlson for preparing many of the Schiff bases.

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(7) Inasmuch as the reaction may be vigorously exothermic after passing through an induction period, it is strongly recommended that all the usual precautions for working with liquid hydrogen cyanide be observed and that the reaction be limited to a 0.1 mol. scale.

[CONTRIBUTION FROM THE POLYMER RESEARCH LABORATORY, THE DOW CHEMICAL CO.]

Organic Chemistry of α-Methylstyrene. I. Reactions Leading to *N*-(α,α-Dimethyl-substituted-benzyl)acrylamides

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The reactions of α-methylstyrene, *p*-chloro-α-methylstyrene, *p*-bromo-α-methylstyrene, and *m*-trifluoromethyl-α,α-dimethylbenzyl alcohol with acrylonitrile have been investigated and three of the corresponding *N*-substituted acrylamides prepared. α-Methylstyrene or *p*-substituted-α-methylstyrenes (*p*-substituent *ortho-para* directing) under the above reaction conditions preferentially dimerize rather than react with acrylonitrile. The carbonium ion from *m*-trifluoromethyl-α,α-dimethylbenzyl alcohol or the dehydration product appears to be less reactive with another *m*-trifluoromethyl-α-methylstyrene than with the nitrogen of acrylonitrile; the product obtained in good yield is *N*-(*m*-trifluoromethyl-α-α-dimethylbenzyl)-acrylamide.

The reaction of 2-phenyl-2-propanol with acid leads to the formation of 2-phenylpropene (α-methylstyrene) as the major product. If 2-phenylpropene is let stand in an acid medium under various conditions of solvent, acid strength, and temperature, three dimeric products result: 2,4-diphenyl-4-methylpentene-1 (II), 2,4-diphenyl-4-methylpentene-2 (III), and 1,1,3-trimethyl-3-phenylindane (IV). These products may be considered to arise from the reaction of a cumyl carbonium ion with 2-

phenylpropene to give initially the dimeric ion (I), which may lose a proton at either of two positions to give either the pentene-1 (II) or pentene-2 (III), a mixture of II and III, or I may intra-alkylate to give the indane (IV) (Fig. I).

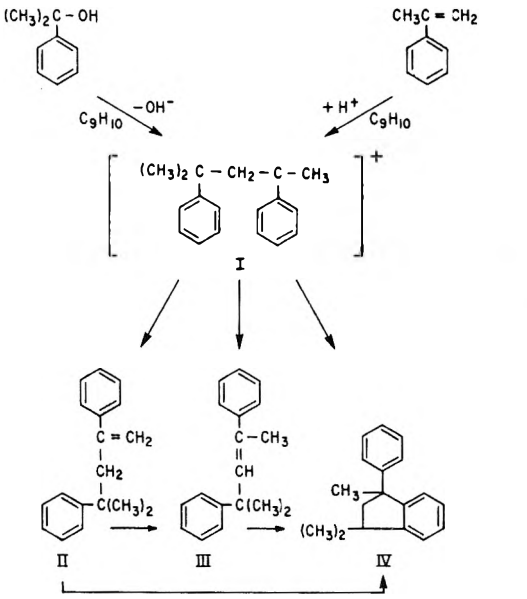
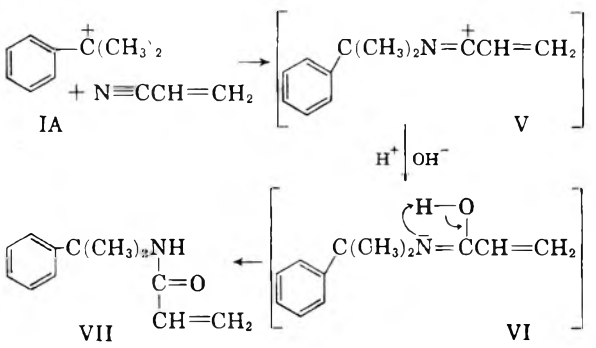


Figure 1

Bergmann and Weizmann[1] have reported the preparation of several ring substituted α-methylstyrenes, and Petropoulos[2,3] has reported an interesting series of experiments where the indane dimers of ring-substituted α-methylstyrenes are described. In a recent paper Overberger[4] reports that α-ethylstyrene reacts with stannic chloride at 0° for 1 hr. to give a mixture of dimers and trimers. The initial dimer was shown to be 3,5-diphenyl-5-methyl-2-heptene. If the reaction were prolonged, the indane-type dimer, 1,3-diethyl-1-methyl-3-phenylhydrindane was isolated. As there has been reasonable evidence for the existence of a protonated double bond in styrene or α-methylstyrene in the presence of a strong acid, it appeared reasonable to assume that a carbonium ion intermediate such as $C_6H_5(CH_3)_2C^+$(IA)[5] would react with nucleophilic reagents to give intermediates which might then be hydrolyzed to give useful and interesting products. There has been one reference to the preparation of an *N*-substituted acrylamide using the Ritter type reaction with styrene[9] and acrylonitrile.

Discussion. It was postulated that the reaction of α-methylstyrene with acrylonitrile under acidic conditions should proceed by way of a cumyl carbonium ion (IA), which could, in turn, attack the nitrogen of the acrylonitrile to give an intermediate (V), which would extract hydroxyl from the water present to give VI; this would tautomerize to give



the desired product, *N*-cumylacrylamide (VII). When the original Ritter solvent and catalyst conditions—sulfuric acid in glacial acetic acid—were employed, little or no acrylamide was obtained. When tetrahydrofuran replaced the acetic acid and acrylonitrile was used in as much as a 10 mol. excess, as high as a 30% yield of *N*-cumylacrylamide was achieved. In the experiments using sulfuric and glacial acetic acids as reaction medium, little or no α-methylstyrene was recovered; most of the α-methylstyrene was converted to a mixture of the two liquid dimers and the solid indane dimer. When sulfuric acid–tetrahyrofuran was used as reaction medium, some α-methylstyrene was recovered but most of it was converted to a mixture of the liquid dimers (II and III); when the reaction was run for a relatively short time, only the pentene-1 dimer was found.[10]

(1) E. Bergmann and A. Weizmann, *Trans. Faraday Soc.*, **32**, 1327 (1936).

(2) J. C. Petropoulos, U. S. Patent, 2,754,285 (July 10, 1956).

(3) J. C. Petropoulos and J. J. Fisher, *J. Am. Chem. Soc.*, **80**, 1938 (1958).

(4) C. G. Overberger, E. M. Pearce, and D. Tanner, *J. Am. Chem. Soc.*, **80**, 1761 (1958).

(5) In work reported after initiation of this program, Deno[6,7] utilized the Ritter reaction[8] of isobutylene and *t*-butyl alcohol with acrylonitrile (reaction leads to *N*-*t*-butylacrylamide) to study the kinetics of this acid-catalyzed reaction in various solvents. He concluded that the reaction proceeds by a mechanism which precludes, under the conditions used, the formation of an ion which we have chosen to consider as a free (or loosely solvated) carbonium ion.

(6) N. C. Deno, T. Edwards, and C. Perizzolo, *J. Am. Chem. Soc.*, **79**, 2108 (1957).

(7) N. C. Deno and C. Perizzolo, *J. Am. Chem. Soc.*, **79**, 1345 (1957).

(8) J. J. Ritter and co-workers, *J. Am. Chem. Soc.*, **70**, 4045–4048 (1948); **71**, 4128–4130 (1949); **73**, 4076 (1951); **74**, 763 (1952).

(9) A. L. Miller, U. S. Patent 2,790,789 (April 30, 1957).

(10) It was reasoned that if sulfuric and acetic acids not only gave the liquid dimers but a quantity of indane, and if in reducing the acid strength of the medium by using sulfuric acid–tetrahydrofuran no indane formed, then it should be possible to design a reaction where conditions would favor the competitive reaction of the cumyl carbonium with acrylonitrile (amide formation) rather than with itself (dimer formation). Originally it was thought that if the reactive species were the cumyl carbonium ion, then by starting with α,α-dimethylbenzyl alcohol, as soon as the alcohol was converted to the cumyl carbonium ion this would react with acrylonitrile because no α-methylstyrene would be present.

TABLE I

EFFECT OF FORMIC ACID AS CATALYST ON THE FORMATION OF REACTION PRODUCTS OF α-METHYLSTYRENE (118 G., 1 MOL.) AND ACRYLONITRILE

Run No.	Formic Acid %	Formic Acid Ml.	Acrylonitrile Moles	Conditions[d] Time, hr.	Conditions[d] T., °C.	N-Cumylacrylamide Isolated Yield G.	Yield %	M.p.,[e] °C.	Pentene-1 Dimer[f] G.	Pentene-1 Dimer[f] %	Recovered α-Methylstyrene[f] G.	Recovered α-Methylstyrene[f] %
1	85	1000	2	18	25	1.6	0.85	112–112	93	84	6.1	5.5
2	85	1000	2	2.5	55	1.5	0.85	103–104	99	90	5.5	5.0
3	98	500	3	4.5	50	0.16	0.30	95–97	66	65	1.5	1.5
4	98	250	4	4.0	50	3.4	1.8	86–89	87	85	2.6	2.5
5	98	250	4	20	70	3.3	1.7	97–99	45	45	2.1	2.0
6	98	250	6	16	70	4.8	2.54	107–112	74	70	4.8	4.5
7	98	250	6	2(16)	85(25)	4.4	2.33	110–113	81	80	5.1	5.0
8	98	250	6	20	25	0.5	0.26	88–92	48	65	11.0	14.0
9	90	250	6	2(16)	85(25)	5.8	3.07	113–114	73	70	7.0	7.5
10	90	250	10	1.5	83	7.2	3.8	108–113	46	65	17.1	24.0
11	90	250	10	1.5	83	8.1	4.29	112–113	47	75	11.6	18.0
12[a]	98	46	2	4.0	70	No product			—	—	—	—
13[a]	80	54	2	4.0	70	No product			—	—	—	—
14[a]	85	108	2	4.0	70	No product			—	—	—	—
15[a]	90	250	6	4.0	70	2.4	1.27	113–114	—	—	—	—
22[b]	90	250	10	1.5	83	5.7	3.0	113–114	—	—	—	—
23[c]	90	250	10	1.2(60)	82(25)	7.4	3.9	113–114	—	—	—	—

[a] Experiments 12–15 contained 200 ml. of tetrahydrofuran. [b] In experiment 22 the acrylonitrile and water were placed in flask and the α-methylstyrene–formic acid mixture added dropwise during 30 min. [c] In experiment 23 the acrylonitrile and α-methylstyrene were mixed in the flask and the formic acid added dropwise during 30 min. [d] Figures in brackets indicate times and temperatures after initial reaction before experiment was worked up. [e] Melting points below the 113–114 figure are crude products which, on recrystallization, gave material having the proper melting points. [f] Infrared analysis by Dr W. Potts.

TABLE II

REACTION OF 2-PHENYL-2-PROPANOL WITH ACRYLONITRILE IN A TETRAHYDROFURAN SOLUTION OF SULFURIC ACID. RATE STUDY

Run No.	Time, Hr.	Wt., G.	Yield, %	M.P. °C.	Monomer, %	α-Methylstyrene Reaction Products, % in Sample[a]: 4-Methyl-2,4-diphenyl-pentene-1	4-Methyl-2,4-diphenyl pentene-1
1	1	0.5	1.0	111	3.5	1.5	0.0
2	2	0.7	1.4	111	5.0	1.5	0.0
3	3	0.9	1.8	110	5.0	2.0	0.0
4	4	0.8	1.6	110	5.0	2.0	0.0
5	20	1.5	3.0	103	2.0	3.0	0.0
6	23	1.3	2.6	104	2.5	3.0	Trace
7	28	1.5	3.0	104	1.5	3.5	Trace
8	93	Oily residue; no			1.0	1.5	2.5
9	99	isolable solid			Trace	1.0	3.5
10	117	product			—	Trace	4.0
11	The residue from the reaction mixture was worked up in the standard fashion to give 176 g. of oily product; distillation of this gave pure pentene-2 dimer of α-methylstyrene, b.p. 144°/2.4 mm.						

[a] By infrared analysis, Dr. W. Potts.

Two parallel and nearly identical experiments were run, one using α,α-dimethylbenzyl alcohol (Table II) and the other using α-methylstyrene (Table III). At set times (see Experimental) samples were withdrawn from each reaction. Each sample was treated to isolate *N*-cumylacrylamide with the liquid residue being analyzed (infrared) for the various possible by-products α-methylstyrene, liquid dimers (II and III), and indane dimer (IV). Starting with either α-methylstyrene or α,α-dimethylbenzyl alcohol in sulfuric acid–tetrahydrofuran with an equivalent of acrylonitrile, both reactions gave measurable amounts of α-methylstyrene after 1 hr. A maximum yield of *N*-cumylacrylamide was in the neighborhood of 2 to 3% in either experiment. Both experiments gave an interesting set of results so far as dimerization of α-methylstyrene is concerned. The initial dimer formed under these conditions is the 4-methyl-2,4-diphenylpentene-1 (III) until after 20 hr. As the time of reaction increased, the pentene-1 disappeared and the percentage of the pentene-2 isomer increased. The residue from each reaction mixture gave *pure* pentene-2 isomers with no pentene-1 or indane isomer.

On the basis of a report that α-methylstyrene could be dimerized[11] to the liquid or solid dimers i n

(11) J. Hukki, *Acta Chem. Scand.*, **3**, 279–296 (1949).

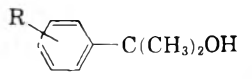
TABLE III

REACTION OF α-METHYLSTYRENE WITH ACRYLONITRILE IN A TETRAHYDROFURAN SOLUTION OF SULFURIC ACID. RATE STUDY

Run No.	Sample Time, hr.	Sample Wt., g.	N-Cumylacrylamide Yield, %	N-Cumylacrylamide M.p., °C.	Monomer, %	α-Methylstyrene Reaction Products 4-Methyl-2,4-diphenyl pentene-1, %	α-Methylstyrene Reaction Products 4-Methyl-2,4-diphenyl-pentene-2, %
1	1	0.2	0.4	103–107	3.5	1.0	0.0
2	2	0.2	0.4	111	4.5	1.5	0.0
3	3	0.3	0.6	111	3.0	2.0	0.0
4	4	0.5	1.0	111	2.5	3.0	0.0
5	20	0.9	1.8	108	1.0	3.0	1.0
6	23	1.1	2.2	108	1.0	2.0	5.0
7	28	1.0	2.0	103	1.0	2.0	4.5
8	93	Oily residue; no isolable product			0.0	Trace	6.0
9	99	Oily residue; no isolable product			0.0	0.0	6.0
10	117	Oily residue; no isolable product			0.0	0.0	6.0
11	The residue from the reaction mixture was worked up in the standard fashion to give 255.6 g. of oily product; distillation of this gave pure pentene-2 dimer of α-methylstyrene, b.p. 144°/2.4 mm.						

TABLE IV

RING-SUBSTITUTED-α,α-DIMETHYLBENZYL ALCOHOLS



Substituent R	Yield G.	Yield %	Reported Constants B.p., °C.	Pres., mm.	n_D^{25}	B.p., °C.	Pres. mm.	n_D^{25}
H	100	60	45–47	0.8	1.5300	202[a]	760	1.5314[19°]
p-Br	No pure product isolated; olefin formation on distillation[b]							
p-Cl	20	52	M.p. 31–32°		—	M.p. 43.2[a,b]		—
p-CH_3O	Only olefin isolated under any conditions used							
p-$(CH_3)_3C$	150	80	M.p. 78.5°		—	M.p. 79[c]		—
m-CF_3	120	59	73.5	2.5	1.4572	91.5[d]	10	1.4572

[a] *Cf.* E. Bergmann and A. Weizmann, *Trans. Faraday Soc.*, 32, 1327 (1936). [b] H. C. Brown, Y. Okamoto, and G. Ham, *J. Am. Chem. Soc.*, 79, 1906 (1957). [c] L. Walther, *J. Pharm. Chim.*, 27, 476 (1938); *cf.*, *Chem. Abstr.*, 32, 6237 (1938). [d] G. B. Bachman and L. L. Lewis, *J. Am. Chem. Soc.*, 69, 2022 (1947).

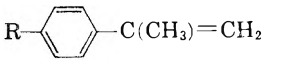
formic acid, it was hoped that by using a modification of his procedure and by adding either an excess or equivalents of acrylonitrile, the formation of *N*-(α,α-dimethylbenzyl)acrylamide would be the preferred course of the reaction. When more concentrated formic acid was used with either α-methylstyrene or the tertiary carbinol, the yield of liquid dimers was higher and the concentration of polymers was lower. When equivalents of α-methylstyrene, acrylonitrile, and formic acid were mixed and heated, only a trace of the *N*-cumylacrylamide was obtained (Table I). In no experiment, even with a ten-fold excess of acrylonitrile, was there isolated a reasonable yield of the desired product, *N*-(α,α-dimethylbenzyl)acrylamide.

Further experiments made it possible to prepare the *N*-cumylacrylamide in as high as 30% yield using 10 mol. excesses of acrylonitrile and the sulfuric acid–tetrahydrofuran mixture as reaction medium. Other ring-substituted α-methylstyrenes, where the substituent was *p*-Cl, *p*-Br, *p*-CH_3O-, and *p*-*t*-butyl, were utilized in a standardized procedure in attempts to prepare the corresponding *N*-(*p*-substituted α,α-dimethylbenzyl)acrylamides. The α-methylstyrenes were prepared (see Table V) from the corresponding tertiary alcohols (see Table IV) either by dehydration as a separate reaction or spontaneously during attempted distillation of the intermediate tertiary alcohol. From the data presented, it would appear that an *ortho-para* directing substituent in the *para*-position did little to improve the competition of the cumyl carbonium ion with its corresponding α-methylstyrene *vs.* reaction with acrylonitrile. It would appear that, as nucleophilic reagents, the α-methylstyrenes are stronger than the nitrogen in acrylonitrile.[12]

(12) In discussing the reaction of precursors of α-methylstyrene or ring-substituted α-methylstyrenes, it should be noted that Brown[13–17] has published an extensive series of papers where it can be seen that the reactive intermediates, the cumyl carbonium ions may be envisioned as being identical with those described here.

TABLE V

PARA-SUBSTITUTED-α-METHYLSTYRENES

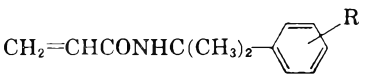


Substituent R	Method[a]	Yield G.	Yield %	B.P., °C./Mm.	n_D^{25}	Literature B.p., °C.	Literature n_D^{20}	Percentage Composition Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
H	DA	Plant matl.		50–51/12	1.5350	48.5/10	1.5358[b]	—	—	—	—
Cl	IDA	86	41	80–81/0.8	1.5808	228	1.5835[c,h]	54.57	59.94	4.58	4.63[f]
Br	DA, IDA	80	52	86/5	1.5558	88/15	1.5543[d,h]	70.82	68.80	5.94	5.61[g]
CH_3O	IDA	68	40	70–74/1 M.p. 32	—	99.5/101/4.5[e,h] M.p. 33	—	81.04	80.96	8.16	8.10

[a] DA, dehydration of the corresponding alcohol; IDA, instantaneous dehydration of the corresponding alcohol during purification of the alcohol. [b] R. R. Driesbach, *Physical Properties of Chemical Compounds, Adv. in Chem. Ser.* No. 15, 1955; page 160. [c] K. Ziegler and P. Zimmermann, *Ber*, **55B**, 3406 (1922). [d] D. T. Mowry, W. F. Huber, and E. L. Ringwald, *J. Am. Chem. Soc.*, **69**, 851 (1947). [e] Y. Okamoto and H. C. Brown, *J. Am. Chem. Soc.*, **79**, 1909 (1957). [f] Bromine. Calcd., 40.35; found; 40.29. [g] Chlorine. Calcd., 23.23; found, 23.84. [h] See also, D. Seymour and K. B. Wolfstirn, *J. Am. Chem. Soc.*, **70**, 1177 (1948).

TABLE VI

N-(SUBSTITUTED-BENZYL)ACRYLAMIDES



Substituent R	Yield G.	Yield %	M.P., °C.	Percentage Composition Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H	90	20	112–113	76.15	76.20	7.99	8.06	7.40	7.22
p-Cl	30	22	117–118	64.43	64.27	6.32	6.24	6.26[a]	6.11
m-CF_3	19	72	127–128	60.69	60.82	5.49	5.35	6.45[b]	5.45

[a] Chlorine. Calcd., 15.90; found, 15.47. [b] Fluorine. Calcd., 22.16; found, 22.66.

It was postulated that a strong *meta*- directing group in the *meta*- position to an α-methylstyrene should decrease the susceptibility of its parent alcohol to dehydration and should decrease the nucleophilicity of its derived α-methylstyrene. It was predicted that a trifluoromethyl group *meta* to the vinyl group in an α-methylstyrene should result in a carbonium ion reactive with acrylonitrile but less likely to react with its own α-methylstyrene. Trifluoromethylbenzene was brominated to give the *m*-bromobenzotrifluoride; this was converted by reaction of its Grignard reagent with acetone to *m*-trifluoromethyl-α,α-dimethylbenzyl alcohol. This was treated with acrylonitrile in acetic acid–sulfuric acid medium to give a 72% yield of the *N*-(*m*-trifluoromethyl-α,α-dimethylbenzyl)acrylamide (see Table VI).

The acrylamides successfully prepared were converted to their hexachlorocyclopentadiene Diels-Alder adducts as derivatives (see Table VII).

The acrylamides were emulsion polymerized and co-polymerized to give materials having softening points in homopolymers from 128–160°; copolymers of *N*-cumylacrylamide and styrene showed higher softening points (see TableVIII).

EXPERIMENTAL[18]

Preparation of N-(α,α-dimethylbenzyl)acrylamide (N-cumylacrylamide) from α-methylstyrene. Tetrahydrofuran as solvent. In a 3-l., three necked, round bottomed flask equipped with a stirrer, closed-circuit addition funnel, condenser with drying tube, and a thermometer was placed 1 l. of tetrahydrofuran. The flask was cooled in an ice bath and to it was added 196 g. (2 mol.) of concentrated sulfuric acid during 15 min. To the cooled mixture was added 116.6 g. (2.2 mol.) of acrylonitrile during 15 min. The temperature of the reaction mixture was raised to 25°, and 236 g. (2 mol.) of α-methylstyrene was added during 60 min. with stirring. The solution was homogeneous at this point and was allowed to stand for 48 hr. at 25°. The solution was then poured into a mixture of ice and water and neutralized with 50% sodium

(13) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *J. Am. Chem. Soc.*, **79**, 1897 (1957).

(14) Y. Okamoto and H. C. Brown, *J. Am. Chem. Soc.*, **79**, 1903 (1957).

(15) H. C. Brown, Y. Okamoto, and G. Ham, *J. Am. Chem. Soc.*, **79**, 1906 (1957).

(16) Y. Okamoto and H. C. Brown, *J. Am. Chem. Soc.*, **79**, 1909 (1957).

(17) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **79**, 1913 (1957).

(18) Melting points (capillary) are corrected. Elemental analyses by Dr. S. Shrader, The Dow Chemical Co., Midland, Mich.

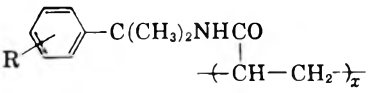
TABLE VII

HEXACHLOROCYCLOPENTADIENE ADDUCTS OF THE *N*-(SUBSTITUTED-BENZYL)ACRYLAMIDES

Substituents			Yield		M.P.,	Percentage Composition							
						Carbon		Hydrogen		Nitrogen		Chlorine	
R_1	R_2	R_3	G.	%	°C.	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3	CH_3	H	20	85	144–145	44.19	43.88	3.27	3.15	3.03	3.10	46.04	45.85
CH_3	CH_3	*m*-CF_3	5	35	156–157	40.80	40.15	2.46	2.48	2.62	2.58	40.20	39.80
CH_3	CH_3	*p*-Cl	8	31	139–140	41.20	42.09	2.63	2.78	2.83	2.90	50.10	49.66

TABLE VIII

POLYMERS FROM *N*-(SUBSTITUTED-α,α-DIMETHYLBENZYL)ACRYLAMIDES



Substituent R	Polymerization		Co-monomer, %	Conversion, %	Specific Viscosity	Softening Point, C°
	Method	Catalyst				
H	Emul.	CHP	None	85–90	0.155	138–147
m-CF_3	Emul.	CHP + DETA	None	60–70	0.049	120–140
p-Cl	Emul.	CHP	None	80–85	0.157	138–156
H[a]	Emul.	CHP	Styrene 90[b]	75–80	2.155	180
H	Emul.	CHP	Styrene 70[b]	75–80	1.575	160–197
H	Emul.	CHP	Styrene 40[b]	75–80	0.451	150–170

[a] Other copolymers were made from the acrylamide with acrylonitrile, styrene, acrylamide, *N*-*t*-butylacrylamide, and methylmethacrylate; these were not characterized. [b] Nitrogen analysis of the isolated copolymers indicated that in each example only about one half of the acrylamide entered the copolymer.

hydroxide solution. Three 100-ml. portions of chloroform were used to extract the neutral mixture. The chloroform extracts were combined, washed with deionized water, dried over anhydrous magnesium sulfate, and filtered into a round bottomed flask. The chloroform was evaporated under vacuum and *n*-heptane was added to the residue; the crystalline product (33 g., 8.7%) was separated from the mother liquor by filtration and dried, m.p. 110–111.5°.

When acetic acid was used instead of tetrahydrofuran as solvent, only dimeric products (from α-methylstyrene) were isolated.

Preparation of N-(α,α-dimethylbenzyl)acrylamide. Effect of formic acid as solvent and catalyst. In a 3-l., three-necked, round bottomed flask equipped with stirrer, reflux condenser, thermometer, and addition funnel was placed a mixture (see Table I) of acrylonitrile and formic acid with or without inert solvent. The contents of the flask were maintained at the indicated temperatures and 118 g. (1 mol.) of α-methylstyrene added. The mixture was stirred at the temperatures and for the times shown in Table I. The reaction mixture was poured into 1 l. of ice water and extracted with chloroform. The extracts were combined, dried over magnesium sulfate, filtered, and evaporated. The semisolid residue, in each case, was treated with 10 vol. of *n*-heptane and chilled. The separated solid was washed with heptane and dried to constant weight. The combined heptane washes and filtrate were evaporated and the residue was submitted to infrared analysis for determination of α-methylstyrene, liquid dimer, and indane content. The results of this series of experiments are in Table I.

Several very tentative conclusions may be reached on the basis of these experiments. A low concentration of formic acid in tetrahydrofuran (12, 14) gives a lower yield of *N*-substituted acrylamide at room temperature or at elevated temperatures. Under comparable conditions except for temperature (7, 8) the higher temperature favors amide formation. The order of mixing does not seem to make a great difference in the yield of amide (10, 22, 23). A ten-fold excess of acrylonitrile (10, 23) at higher reaction temperatures leads to higher yields of amide, but the conditions also give rise to polyacrylonitrile (infrared showed no amide in by-product polymer). A somewhat better yield is obtained when the volatile reactants are removed under vacuum before addition to water; this may be due to loss in the aqueous layer of amide under usual isolation conditions.

Preparation of N-cumylacrylamide from 2-phenyl-2-propanol and α-methylstyrene. Rate studies. In two identical runs the following procedure was used, one using 2-phenyl-2-propanol and the other α-methylstyrene. In a 3-l., three necked, round bottomed flask equipped with a stirrer, closed circuit addition funnel, water-cooled reflux condenser protected with a drying tube, and a thermometer was placed 1 l. of tetrahydrofuran. The flask was cooled in an ice bath and to it was added 196 g. (2 mol.) of concentrated sulfuric acid during 10 min. To the cooled mixture was added 116.6 g. (2.2 mol.) of acrylonitrile during 15 min., the temperature raised to 45°, and the mixture was stirred for 30 min. While maintaining the temperature at 45°, 272.4 g. (2 mol.) of 2-phenyl-2-propanol (or 236 g., 2 mol. of α-methylstyrene) was added during 30 min. A temperature of 45° and agitation were maintained for the remainder of the reaction. At time intervals of 1, 2, 3, 4, 20, 23, 28, 93, 99, 117 hr. from addition of the 2-phenyl-2-propanol, 50 ml. portions were removed from the reaction flask by means of a pipette. Each 50-ml. sample was stirred into a mixture of ice and water which was then neutralized with 50% sodium hydroxide solution. Three 75-ml. portions of chloroform were used to extract the neutral mixtures. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, and filtered into a round bottomed flask, and the

chloroform was evaporated under vacuum. The residue was treated with 75 ml. of *n*-heptane and the crystalline product separated by filtration. The crystalline product was dried in a desiccator and the melting point was taken. The heptane filtrate was transferred to a 100-ml. volumetric flask and additional *n*-heptane was added to bring the volume to 100 ml. A 10-ml. sample was taken from each volumetric flask and was sent for analysis. The results are summarized in Table II for 2-phenyl-2-propanol and in Table III for α-methylstyrene.

Preparation of 2-(m-trifluoromethylphenyl)-2-propanol. In a 3-l., three necked, round bottomed flask equipped with a stirrer, closed circuit addition funnel, thermometer, and a water cooled reflux condenser protected with a drying tube was placed 34.8 g. (1.43 g.-atom) of magnesium turnings which were then covered with anhydrous diethyl ether. The flask was cooled in an ice bath and to it was added 321 g. (1.43 mol.) of 3-bromobenzotrifluoride with stirring during 90 min. The solution was refluxed gently for 2 hr., at which time no magnesium metal was visibly evident. The flask was cooled in an ice bath and 83 g. (1.43 mol.) of anhydrous acetone was added during 30 min. The solution was refluxed for 90 min. and stirring was continued at room temperature overnight. To the solution was added 180 ml. of saturated ammonium chloride solution during 15 min. The solution was stirred for 30 min. and the ether layer decanted. Four additional 200 ml. extracts which were made of the reaction residue were combined and washed with deionized water until the etheral solution was neutral. The neutral solution was dried over anhydrous magnesium sulfate, and filtered, and the solvent evaporated. Fractional distillation gave a main fraction of 208 g. (71.5%) of product, b.p. 80–82°/1.5 mm., n_D^{20} 1.4603 (see Table IV).

Other carbinols were prepared in an analogous fashion and the results are summarized in Table IV.

Ring-substituted-α-methylstyrenes. Ring-substituted-α-methylstyrenes were prepared either inadvertently while attempting to distill the corresponding carbinols or by purposeful acetic anhydride dehydration of the carbinols. The results are summarized in Table V.

Preparation of N-(m-trifluoromethyl-α,α-dimethylbenzyl)-acrylamide. In a 3-l., three necked, round bottomed flask equipped with a stirrer, water-cooled reflux condenser protected with drying tube, addition funnel, and thermometer was placed 500 ml. of glacial acetic acid. To the flask, cooled in an ice bath were added 98 g. (1 mol.) of concentrated sulfuric acid and 58.3 g. (1.1 mol.) of acrylonitrile. The solution was warmed to 45° and 204 g. (1 mol.) of 2-(*m*-trifluoromethylphenyl)-2-propanol was added during 60 min. The temperature was raised to 70° for 5 hr. and the solution poured into an ice and water mixture. The mixture was neutralized with aqueous sodium hydroxide and the product precipitated. The solid was separated by filtration and recrystallized from a mixture of acetone, *n*-heptane, and benzene to give a total of 51.9 g. (20%) of product, m.p. 122–123°.

Other successful acrylamide preparations are summarized in Table VI. As derivatives of the acrylamides, their hexachlorocyclopentadiene adducts were prepared in a standard fashion.[19]

Polymerization. Emulsion polymerization of N-cumylacrylamide (N-α,α-dimethylbenzyl)acrylamide. In a 350-ml. citrate-of-magnesia bottle were placed 150 ml. of a 5% Ivory soap solution, 30 g. (0.159 mol.) of *N*-cumylacrylamide, 214 mg. of a 70% cumene hydroperoxide solution (0.5% wt. equiv. based on monomer), and 103 mg. (1 mol. equivalent based on cumene hydroperoxide) of diethylenetriamine. The bottle was flushed with nitrogen and sealed. The bottle was rotated in a constant temperature bath at 80° for 19 hr. and then at 95° for 24 hr. The bottle was removed from the bath, cooled, and the contents were poured into 800 ml. of methanol. The precipitated polymer was separated, washed with methanol, and dissolved in benzene. The filtered benzene solution was lyophilized to give 22 g. (74%) of product. The polymer had the following properties: softening point, 134°, m.p. 136–140°; specific viscosity (1% in toluene) 0.061; and a heat distortion (compression molded bar) of 92°.

Anal. Calcd. for the pure polymer $(C_{12}H_{15}NO)_x$: N, 7.40. Found N. 6.86.

Emulsion copolymerization of N-cumylacrylamide (N-α,α-dimethylbenzyl)acrylamide. The preceding emulsion technique was employed in effecting the copolymerization of 1 g. portions of *N*-cumylacrylamide with acrylonitrile (1 meq.), styrene (1 and 3 meq.), acrylamide (1 meq.), *N-t*-butylacrylamide (1 meq.), and methyl methacrylate (1 meq.) in a rotating bath at 70° for 24 hr. Cumene hydroperoxide (1% based on total monomer concentration) was used as catalyst in 35 ml. of a 5% (Ivory) soap solution. The results from these preliminary experiments were: acrylonitrile—no polymer; styrene (1 equiv.)—moderate amount of rubbery precipitate; styrene (3 equiv.)—large amount of rubbery precipitate; acrylamide—no polymer; *N-t*-butylacrylamide—gummy brown precipitate which could be drawn to a figure, methyl methacrylate—gummy white polymer.

Emulsion polymerization of N-(m-trifluoromethyl-α,α-dimethylbenzyl)acrylamide. In a 350-ml. citrate-of-magnesia bottle were placed 150 ml. of a 5% Ivory soap solution, 10 g. (0.039 mol.) of the acrylamide, and 0.05 g. (0.5% by wt.) of 70% cumene hydroperoxide. The bottle was flushed with nitrogen and sealed. The bottle was rotated in a constant temperature bath at 70° for 38 hr.; 1 drop of cumene hydroperoxide was added and the bottle returned to the 70° bath for 24 hr.; 2 drops of diethylenetriamine was added and the bottle returned to the 70° bath for 6 hr. and then at 95° for 16 hr. The precipitated polymer was allowed to settle and most of the methanol decanted. The remaining solution was centrifuged and the polymer dissolved in benzene. The filtered benzene solution was lyophilized to give 8.5 g. (85%) of product. The polymer had the following properties: m.p. 121–140°; specific viscosity (1% in toluene) 0.049.

Anal. Calcd. for the pure polymer $(C_{13}H_{14}F_3NO)_x$: N, 8.65%. Found N, 8.13% (see Table VIII).

Emulsion copolymerization of N-(m-trifluoromethyl-α,α-dimethylbenzyl)acrylamide with styrene. The preceding emulsion polymerization technique was used to copolymerize the acrylamide with styrene. Three polymers were made, having monomer ratios of the acrylamide to styrene of 1:9, 3:7, and 6:4, which will be referred to as Nos. 1, 3, and 6, respectively. Each bottle contained 150 ml. of a 5% Ivory soap solution and the total amount of washed styrene used (20 g.) contained 1 g. cumene hydroperoxide. The bottles were placed in a constant temperature bath at 70° for 28 hr. Numbers 1 and 3 were removed from the bath, cooled and poured into 800 ml. of methanol; 1 drop of cumene hydroperoxide was added to No. 6 and the bottle returned to the 70° bath for 24 hr.; 2 drops of diethylene triamine was added and the bottle returned to the 70° bath for 6 hr. and then at 95° for 16 hr. The bottle was removed from the bath, cooled, and the contents were poured into 1 l. of methanol. The three precipitated polymers were filtered, redissolved in toluene, filtered, and precipitated again in 800 ml. of methanol. The resulting polymers were dried under vacuum. Polymer 1 was shiny, white, and hard; m.p., approximately 180°, specific viscosity (1% in toluene) 2.11.

Anal. Calcd. for per cent nitrogen of the monomer ratio 1:9, 0.54%. Found: N, 0.27%.

Polymer 3 was hard, brittle, and white; softened at 160° became clear at 197°, specific viscosity (1% in toluene) 1.57.

(19) *Cf.* C. W. Roberts, *Chem. and Ind. (London)*, 110 (1958).

Anal. Calcd. for per cent nitrogen of the monomer ratio 3:7, 1.63%. Found: N, 1.11%.

Polymer 6 was a white powder; softened at 105°, had m.p. 120–125°, and a specific viscosity (1% in toluene) 0.45.

Anal. Calcd. for per cent nitrogen in the monomer ratio 6:4, 3.26%. Found: N, 1.56% (see Table VIII).

Acknowledgment. The authors gratefully acknowledge the able assistance with some of these preparations by Mr. D. H. Haigh and Mr. J. H. Penfold.

MIDLAND, MICH.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Orientation in the 10-Thiaxanthenone[1] Nucleus

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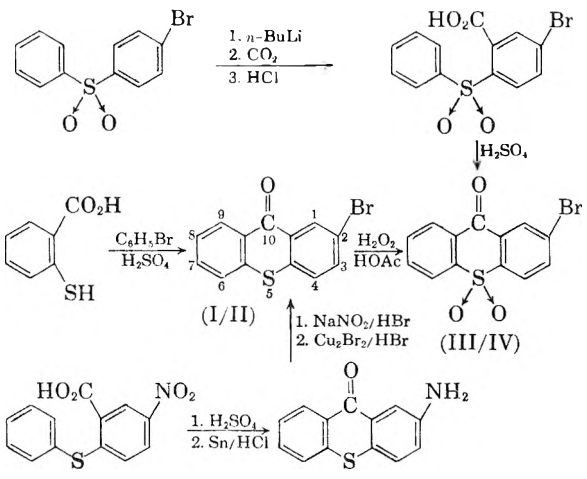
It has been found that cyclization by the procedure of Smiles of *o*-mercaptobenzoic acid with monosubstituted benzene derivatives in concentrated sulfuric acid leads to the formation of 10-thiaxanthenone compounds in which the substituent is in the 2-position. A mechanism incorporating a sulfenium ion accounts for these *o*-mercaptobenzoic acid cyclizations.

In the course of investigating the action of concentrated sulfuric acid on aromatic disulfides, Smiles[2,3] synthesized several substituted 10-thiaxanthenone derivatives. The position of the substituent has now been determined for some of these compounds.

Reaction of either 2,2′-dithiodibenzoic acid or *o*-mercaptobenzoic acid with bromobenzene in concentrated sulfuric acid gave a compound (I) with a melting point, 166–167°, which does not agree with that, 141°, reported for *x*-bromo-10-thiaxanthenone prepared initially by Smiles in an analogous manner.[3] The bromine atom was shown to be in the 2-position by the following sequence of reactions. A Sandmeyer reaction on 2-amino-10-thiaxanthenone[4] gave 2-bromo-10-thiaxanthenone (II) which showed no depression in melting point when admixed with the above *x*-bromo-10-thiaxanthenone (I). Additional evidence was furnished by infrared absorption measurements which indicated that the monosubstituent was related to 1,2,4-trisubstitution in a molecule. The position of the bromine atom was also established by another route. Metalation of 4-bromodiphenyl sulfone with *n*-butyllithium followed by carbonation gave 4-bromo-2-carboxydiphenyl sulfone.[5] Cyclization of this acid in concentrated sulfuric acid gave 2-bromo-10-thiaxanthenone-5,5-dioxide (III). This compound (III) was identical with the substance (IV) obtained by the oxidation of *x*-bromo-10-thiaxanthenone (I) with 30% hydrogen peroxide in glacial acetic acid.

Reaction of the strongly *ortho-para* directing anisole molecule with *o*-mercaptobenzoic acid gave



an 80% yield of *x*-methoxy-10-thiaxanthenone.[2,6] The methoxy group was later shown to be in the 2-position by the cyclization of 2′-carboxy-4-methoxydiphenyl sulfide.[7] Cyclization of phenol with *o*-mercaptobenzoic acid gave *x*-hydroxy-10-thiaxanthenone.[8] The position of the hydroxy group in *x*-hydroxy-10-thiaxanthenone was determined by methylation and the resulting methoxy derivative was shown by Smiles and co-workers to be identical with the 2-methoxy-10-thiaxanthenone compound.[7,8]

2-Chloro-10-thiaxanthenone was prepared in a 53.4% yield by the reaction of chlorobenzene with *o*-mercaptobenzoic acid in concentrated sulfuric acid. Diazotization of 2-amino-10-thiaxanthenone followed by treatment with copper (I) chloride in hydrochloric acid yielded 2-chloro-10-thiaxanthenone and this compound was identical with that obtained from the cyclization reaction. Oxidation of 2-chloro-10-thiaxanthenone with 30% hydrogen peroxide in glacial acetic acid gave 2-chloro-10-thia-

(1) The nomenclature and numbering are those recommended in the introduction to the 1952 Subject Index of "Chemical Abstracts."

(2) W. Prescott and S. Smiles, *J. Chem. Soc.*, 640 (1911).

(3) E. Marsden and S. Smiles, *J. Chem. Soc.*, 1353 (1911).

(4) F. Mayer, *Ber.*, 42, 3046 (1909).

(5) W. Truce and M. Amos, *J. Am. Chem. Soc.*, 73, 3013 (1951).

(6) S. Smiles and E. Davis, *J. Chem. Soc.*, 1290 (1910).

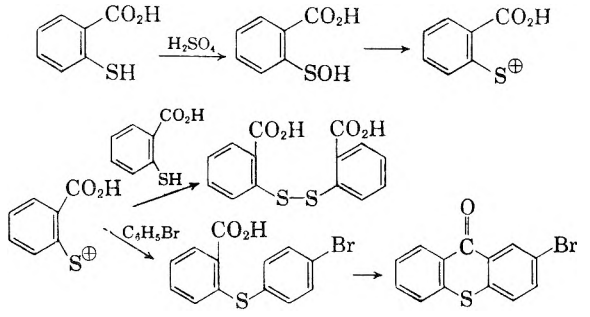
(7) K. Roberts and S. Smiles, *J. Chem. Soc.*, 863 (1929).

(8) W. Price and S. Smiles, *J. Chem. Soc.*, 3154 (1928).

xanthenone-5,5-dioxide, m.p. 226°; the literature[9] melting point is 222°.

When toluene was condensed with *o*-mercaptobenzoic acid a mixture was obtained which melted over a range of 98–110° even after repeated crystallizations. Oxidation of this mixture with 30% hydrogen peroxide in glacial acetic acid gave a 76% yield of 2-methyl-10-thiaxanthenone-5,5-dioxide[10] and a 12% yield of a second substance which might possibly be 3-methyl-10-thiaxanthenone-5,5-dioxide (V). This latter substance (V) showed 1,2,4-trisubstitution in the infrared.

The principal by-product of the *o*-mercaptobenzoic acid cyclizations is 2,2′-dithiodibenzoic acid. Stenhouse[11] has reported that disulfides could be formed by treatment of mercaptans with concentrated sulfuric acid. A possible mechanism for these *o*-mercaptobenzoic acid cyclizations in concentrated sulfuric acid is shown in the equations below. The mercapto group is oxidized[12] to the sulfenic acid[13] which immediately decomposes to the sulfenium ion.[14,15] An electrophilic attack by this sulfenium ion on bromobenzene would occur in the electron dense *para*- position. The *para* condensation is preferred over the *ortho* because of the more favorable steric conditions. The sulfenium ion could also react with *o*-mercaptobenzoic acid forming the principal by-product, 2,2′-dithiodibenzoic acid (see also ref. 11).



Christopher and Smiles[16] suggested a sulfinic acid route for these cyclizations in which a sulfoxide is formed as an intermediate and this sulfoxide was easily reduced at the expense of excess sulfinic acid to the sulfide.[17] Their conclusions were based on the ability of sulfinic acids to condense with certain aromatic compounds.[18]

EXPERIMENTAL[19]

2-Bromo-10-thiaxanthenone (I). Ten g. (0.065 mol.) of *o*-mercaptobenzoic acid was slowly added to 100 ml. of concentrated sulfuric acid and excess bromobenzene (14 ml., 0.134 mol.). The resulting tan suspension was stirred for 10 hr. then permitted to stand for an additional 10 hr. The odor of sulfur dioxide was evident during the reaction. The reaction mixture was heated on a steam bath for 1 hr., cooled, poured slowly over ice, filtered, and washed acid-free. The yellow solid was thoroughly triturated with 10% sodium hydroxide, filtered, and washed alkali-free to yield 11.5 g. (61%) of 2-bromo-10-thiaxanthenone, m.p. 161–163°. Acidification of the alkali extract gave 2.0 g. of 2,2′-dithiodibenzoic acid, m.p. 286–288°. Recrystallization of the 2-bromo-10-thiaxanthenone from a mixture of ethanol and chloroform gave a yellow solid, m.p. 166–167°. Marsden and Smiles[3] report a melting point of 141°.

Preparation of 2-bromo-10-thiaxanthenone from 2,2′-dithiodibenzoic acid, bromobenzene, and concentrated sulfuric acid gave lower yields than by the above procedure.

An infrared spectrum gave bands at 6.06μ and 12.4μ indicative of the carbonyl group and 1,2,4-trisubstitution, respectively.

2-Bromo-10-thiaxanthenone-5,5-dioxide (IV). Three g. (0.0103 mol.) of 2-bromo-10-thiaxanthenone was dissolved in 40 ml. of glacial acetic acid. To the solution was added 5 ml. of 30% hydrogen peroxide; the reaction mixture was heated to reflux and maintained, with stirring, for 4 hr. Greenish white needles separated upon cooling, which after filtration and drying weighed 2.9 g. (87.4%) and melted at 231–233°. After one crystallization from glacial acetic acid the white crystals melted at 233–234°.

Anal. Calcd. for $C_{13}H_7BrO_3S$: Br, 24.73; S, 9.92. Found: Br, 24.68, 24.82; S, 10.03, 10.11.

Infrared analysis gave a band at 8.65μ indicating the presence of the sulfone grouping in the molecule.

4-Bromo-2-carboxydiphenyl sulfone.[5] Metalation of *p*-bromodiphenyl sulfone with *n*-butyllithium, followed by carbonation and hydrolysis gave a 50% yield of 4-bromo-2-carboxydiphenyl sulfone, m.p. 153–154°, lit.[6] 153–154°.

Cyclization of 4-bromo-2-carboxydiphenyl sulfone. Using the procedure of Ullmann and Lehner,[9] 1.0 g. (0.00293 mol.) of 4-bromo-2-carboxydiphenyl sulfone was heated at 185–195° with 20 ml. of concentrated sulfuric acid. Pouring over ice gave 0.70 g. (74%) of a white solid (III), m.p. 232–234°. Admixture of III with IV showed no depression in melting point. The infrared spectra of III and IV were identical.

2-Amino-10-thiaxanthenone. 2-Nitro-10-thiaxanthenone[20] was reduced to 2-amino-10-thiaxanthenone in a 60.6% yield by the reported procedure of Mann and Turnbull,[21] m.p. 227°, lit. 227°.[4]

2-Bromo-10-thiaxanthenone (II) by diazotization of 2-amino-10-thiaxanthenone. To a stirred suspension of 3.0 g. (0.01315 mol.) of 2-amino-10-thiaxanthenone, 10 ml. of 48% hydrobromic acid and 10 ml. of water, cooled to 0°,

(9) F. Ullmann and A. Lehner, *Ber.*, **38**, 740 (1905).

(10) W. Truce and O. Norman, *J. Am. Chem. Soc.*, **75**, 6023 (1953).

(11) J. Stenhouse, *Ann.*, **149**, 247 (1869). See also, S. Archer and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 4296 (1952).

(12) The sulfurous acid produced decomposes to water and sulfur dioxide. The sharp odor of sulfur dioxide is noted during the reaction.

(13) R. Connor in H. Gilman, "Organic Chemistry," Vol. 1, John Wiley and Sons, Inc., New York, 1943, Chap. 10, p. 920, gives a discussion on the general characteristics of sulfenic acids.

(14) N. Kharasch, *J. Chem. Ed.* **33**, 585 (1956). This article contains an extensive and splendid bibliography on sulfenium ions. See also, A. J. Parker and N. Kharasch, *Chem. Revs.*, **59**, 583 (1959).

(15) R. E. Benesch and R. Benesch, *J. Am. Chem. Soc.*, **80**, 1666 (1958), and references contained therein.

(16) H. Christopher and S. Smiles, *J. Chem. Soc.*, 2046 (1911).

(17) Attempts in this laboratory to prepare 10-thiaxanthenone-5-oxide by the mild oxidation of 10-thiaxanthenone with 30% hydrogen peroxide in ethanol were unsuccessful. A possible explanation is given by A. Weizmann, *Trans. Faraday Soc.*, **36**, 978 (1940).

(18) S. Smiles and R. LeRossingnol, *J. Chem. Soc.*, 696 (1906).

(19) All melting points are uncorrected.

(20) E. Amstutz and C. Neumoyer, *J. Am. Chem. Soc.*, **69**, 1925 (1947).

(21) F. Mann and J. Turnbull, *J. Chem. Soc.*, 747 (1951).

was added a solution of 3.0 g. of sodium nitrite in 10 ml. water. The temperature of the mixture was maintained at 0–5° during the addition of the sodium nitrite solution. After a period of 10 min., 45 ml. of freshly prepared copper (I) bromide[22] solution in hydrobromic acid was added to the mixture. A vigorous reaction followed the addition of the catalyst, and the red diazotized mixture became brown. The mixture was subsequently heated on the steam-bath for 30 min. and allowed to cool. The supernatant liquid was decanted off, and the brown residue was treated with hydrobromic acid and washed with water.

The crude black material was dissolved in benzene and the solution was chromatographed on an alumina column using benzene as the eluent. From the eluate was obtained 2.0 g. (52.4%) of crude 2-bromo-10-thiaxanthenone melting at 163–167°. Crystallization from ethanol gave 1.0 g. (26.2%) of pure product melting at 166–167°. A mixture melting point of this material (II) with I showed no depression. Oxidation of 2-bromo-10-thiaxanthenone (II) with 30% hydrogen peroxide in glacial acetic acid gave 2-bromo-10-thiaxanthenone-5,5-dioxide which showed no depression in melting point when admixed with either III or IV.

2-Chloro-10-thiaxanthenone. Treatment of 10 g. (0.0648 mol.) of *o*-mercaptobenzoic acid with excess chlorobenzene and concentrated sulfuric acid in an analogous manner as that described for the preparation of 2-bromo-10-thiaxanthenone (I) gave 8.6 g. (53.4%) of yellow solid melting at 152–153°.

Anal. Calcd. for $C_{13}H_7ClOS$: C, 63.30; H, 2.86. Found: C, 63.35, 63.41; H, 3.08, 3.15.

The infrared spectrum showed absorption bands at 6.06μ, 12.4μ, and 13.4μ, characteristic of the carbonyl, 1,2,4-trisubstitution and 1,2-disubstitution, respectively.

A Sandmeyer reaction on 2-amino-10-thiaxanthenone gave a 46% yield of 2-chloro-10-thiaxanthenone, m.p. 150–151.5°, which was identical with the *x*-chloro-10-thiaxanthenone obtained by the cyclization of *o*-mercaptobenzoic acid with chlorobenzene. Oxidation of 2-chloro-10-thiaxanthenone with 30% hydrogen peroxide in glacial acetic acid gave an 85% yield of 2-chloro-10-thiaxanthenone-5,5-dioxide, m.p. 226°. Ullmann and Lehner[9] prepared 2-chloro-10-thiaxanthenone-5,5-dioxide by cyclization of 4′-chloro-2-carboxydiphenyl sulfone and reported a melting point of 222°.

x-Methyl-10-thiaxanthenone. Reaction of toluene with *o*-mercaptobenzoic acid in a manner described for 2-bromo-10-thiaxanthenone (I) gave 7.9 g. (53%) of yellow solid melting 98–110°. Several crystallizations did not improve the melting point. Smiles and Davis[6] reported a melting point of 96–97° to the product they isolated from the reaction of *o*-mercaptobenzoic acid and toluene. 2-Methyl-10-thiaxanthenone[23] has a melting point of 123°.

An infrared analysis of the isomeric mixture showed absorption bands at 6.06μ, 12.4μ, and 13.4μ, characteristic of the carbonyl, 1,2,4-trisubstitution and 1,2-disubstitution, respectively.

2-Methyl-10-thiaxanthenone-5,5-dioxide and 3-methyl-10-thiaxanthenone-5,5-dioxide. Three and seven-tenths g. (0.0164 mol.) of *x*-methyl-10-thiaxanthenone was dissolved in 25 ml. of glacial acetic acid. To the solution was added 5 ml. of 30% hydrogen peroxide and the reaction mixture heated to reflux and maintained, with stirring for 4 hr. Pouring over ice gave 4.0 g. (94.7%) of yellow crystals melting at 158–190°. Fractional crystallization from ethanol gave 3.2 g. (76%) of 2-methyl-10-thiaxanthenone-5,5-dioxide,[10] m.p. 199°, lit. 199°, and 0.5 g. (12%) of yellow powder (V), m.p. 158.5–160°. The latter substance (V) gave absorption bands at 6.06μ, 12.4μ, and 13.4μ in the infrared which are characteristic of the carbonyl, 1,2,4-trisubstitution and 1,2-disubstitution, respectively.

Anal. Calcd. for $C_{14}H_{10}O_3S$: S, 12.38. Found: S, 12.33, 12.46.

Compound V could possibly be 3-methyl-10-thiaxanthenone-5,5-dioxide since the infrared did give absorption indicative of 1,2,4-trisubstitution and no absorption for 1,2,3-trisubstitution.

Acknowledgment. Infrared spectra were obtained through the courtesy of the Institute for Atomic Research, Iowa State College.

AMES, IOWA

(22) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 2nd ed., 1951, p. 186.

(23) F. Mayer, *Ber.*, **43**, 584 (1910).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE R. J. REYNOLDS TOBACCO CO.]

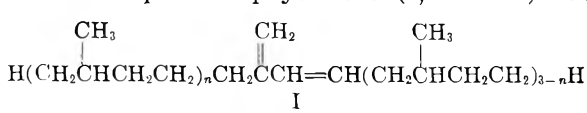
Composition of Cigarette Smoke. III. Phytadienes

ALAN RODGMAN

Received June 12, 1959

A series of isomeric conjugated phytadienes has been isolated from the cigarette smoke of a cased commercial blend of tobaccos. Evidence is presented to indicate that this series contains 3-methylene-7,11,15-trimethyl-1-hexadecene (neophytadiene), 3,7,11,15-tetramethyl-1,3-hexadecadiene, 2,6,10,14-tetramethyl-1,3-hexadecadiene, and a 1,2,4-trialkyl-1,3-butadiene and possibly as many as nine other conjugated phytadienes. Neophytadiene was the only phytadiene actually separated from the mixture. A similar series of phytadienes was observed in the cigarette smoke from flue-cured, burley, Turkish, and four other different commercial blends of tobacco.

The diterpene neophytadiene (I, $n = 3$) has



I

been identified as a component of flue-cured tobacco by Rowland,[1] as a component of aged burley and flue-cured tobaccos and as a major component of the total volatile oils of aged burley and flue-cured tobaccos by Gladding *et al.*,[2a,2b] as a component of

(1) R. L. Rowland, *J. Am. Chem. Soc.*, **79**, 5007 (1957).

(2) (a) R. N. Gladding, W. B. Wartman, and H. E. Wright, Paper presented at the 11th Annual Tobacco Chemists' Research Conference, New Haven, Conn., Oct. 10–11, 1957. (b) R. N. Gladding, W. B. Wartman, and H. E. Wright, *J. Org. Chem.*, **24**, 1359 (1959).

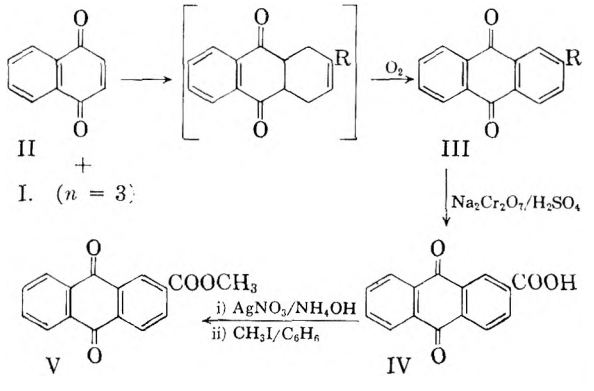
aged Japanese burley and flue-cured tobaccos by Onishi *et al.*,[3] and in the mainstream smoke of domestic cigarettes by Gladding *et al.*[2a,2b]

In a continuation of our study of the condensable portion of cigarette smoke from a cased commercial blend of tobaccos,[4,5] a hydrocarbon fraction was isolated by chromatographic separation of a base-free hexane soluble fraction of the cigarette smoke. Crystallization of this hydrocarbon fraction from acetone at $-27°$ gave a mixture of solid saturated hydrocarbons whose melting point and infrared absorption suggested a mixture of *n*-heptacosane, *n*-nonacosane, *n*-hentriacontane, and *n*-tritriacontane. A similar mixture has been described by other investigators.[6]

Chromatography of the material in the filtrate permitted separation of a liquid unsaturated hydrocarbon fraction. Infrared studies of this fraction showed absorption at 6.07, 6.27, 7.25, 7.31, 10.10, 10.20, 10.38, 11.0, 11.1, and 11.25μ. These absorptions[1] and the order of elution on chromatography strongly suggested the presence in the hydrocarbon fraction of a mixture of phytadienes among which would be neophytadiene (I, $n=3$).

Further chromatography of this material gave seven main fractions, the fifth of which was essentially neophytadiene. The four fractions preceding the neophytadiene fraction showed infrared and ultraviolet absorption characteristics of mixtures of tri- and dialkyl-substituted 1,3-butadienes. These five fractions were designated as *Phytadiene Fractions V, W, X, Y, and Z.*

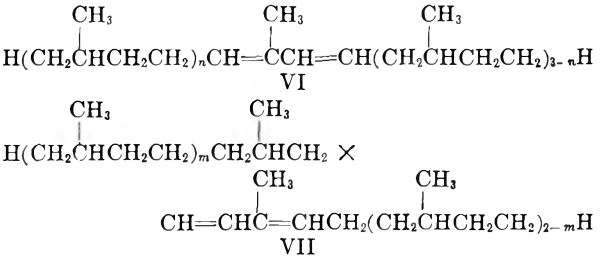
As the elucidation of the structure of neophytadiene (I, $n=3$) was facilitated by a study of the oxidation of 2-(4′,8′,12′-trimethyltridecyl)anthraquinone (III, R=4,8,12-trimethyltridecyl), the product obtained by air oxidation of the Diels-Alder adduct from I ($n=3$) and 1,4-naphthoquinone (II),[1] this reaction sequence was employed



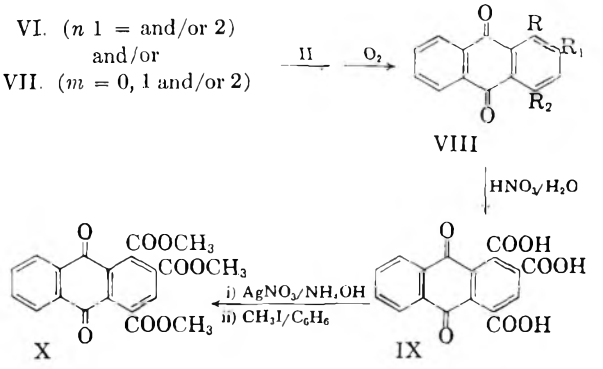
in our study of the above-mentioned five phytadiene fractions.

The Diels-Alder reaction of *Phytadiene Fraction V* with 1,4-naphthoquinone (II) followed by air oxidation of the adduct gave a low-melting solid derivative whose elemental analysis suggested that it was isomeric with 2-(4′,8′,12′-trimethyltridecyl)anthraquinone (III, R=4,8,12-trimethyltridecyl) obtained by similar treatment of neophytadiene (I, $n=3$).[1] Further oxidation of III (R=4,8,12-trimethyltridecyl) gave anthraquinone-2-carboxylic acid (IV),[1] whose identity was unequivocally established in our investigation by a mixture melting point study with an authentic sample, by infrared absorption analysis and by conversion to the known methyl ester.[7]

Further oxidation of the isomer of III (R=4,8,12-trimethyltridecyl) using nitric acid yielded an acid whose identity was established by a mixture melting point study with anthraquinone-1,2,4-tricarboxylic acid (IX) and by conversion to trimethyl anthraquinone-1,2,4-tricarboxylate (X). The products obtained from this reaction sequence indicate that *Phytadiene Fraction V* probably contains phytadiene VI ($n=1$ and/or 2) and/or VII ($m=0$, 1, and/or 2) and the structure of the isomer of III (R=4,8,12-trimethyltridecyl)



must be such as to give a product of the general formula VIII. The melting range observed (39–42°) for the material designated as VIII suggested that a mixture was obtained. It should be noted that structures I ($n=0$) and VI ($n=0$) represent the same phytadiene.



The Diels-Alder reaction of *Phytadiene Fraction W* with 1,4-naphthoquinone (II) followed by air oxidation of the adduct gave an oil. Nitric acid

(3) I. Onishi, M. Nagamawa, H. Tomita, and T. Fukuzumi, *Bull. Agr. Chem. Soc. Japan*, **22**, 57 (1958).

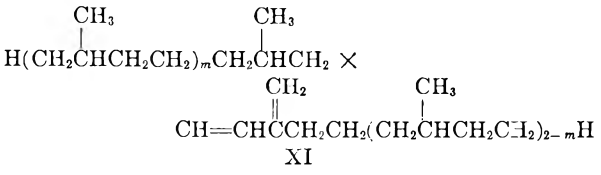
(4) A. Rodgman and L. C. Cook, *Tobacco Science*, **3**, 86 (1959).

(5) A. Rodgman, L. C. Cook, and P. H. Latimer, *Tobacco Science*, **3**, 125 (1959).

(6) A. I. Kosak, J. S. Swinehart, and D. Taber, *J. Natl. Cancer Inst.*, **17**, 375 (1956).

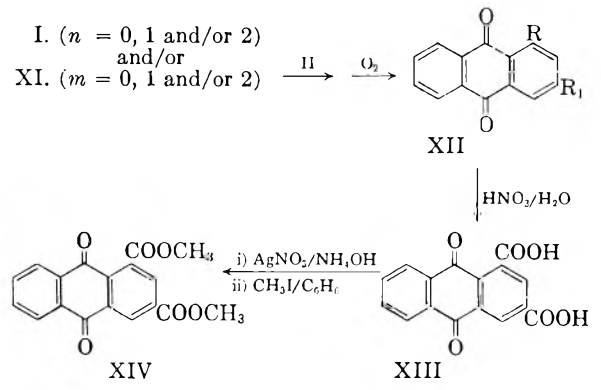
(7) P. Nawiasky and R. Robl (to I. G. Farbenind. A.-G.), Ger. Patent 609,401 (Feb. 25, 1935).

oxidation of this oil yielded a mixture of two acids which were separable by chromatography using silicic acid. One acid was anthraquinone-1,2,4-tricarboxylic acid (IX); the identity of the other acid was established by a mixture melting point study with anthraquinone-1,3-dicarboxylic acid (XIII) and by conversion to dimethyl anthraquinone-1,3-dicarboxylate (XIV). The products of this reaction sequence indicate that *Phytadiene Fraction W* contains the phytadiene I ($n=0$, 1,



XI

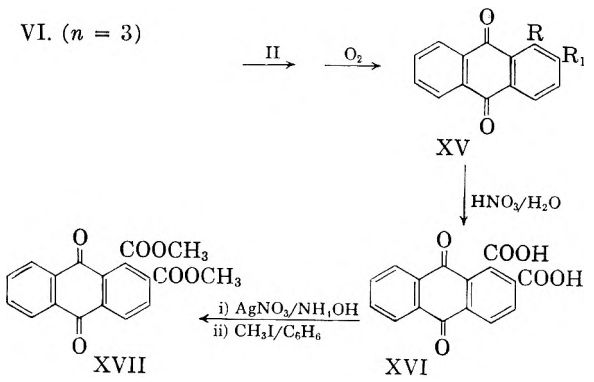
and/or 2) and/or XI ($m=0$, 1, and/or 2) as well as the phytadiene VI ($n=1$ and/or 2) and/or VII ($m=0$, 1, and/or 2). In addition to a substituted anthraquinone(s) represented by structure VIII, the oil arising from air oxidation of the Diels-Alder adduct must therefore contain a substituted anthraquinone(s) whose structure is represented by XII.



The Diels-Alder reaction of *Phytadiene Fraction X* with 1,4-naphthoquinone (II) followed by air oxidation of the adduct yielded an oil. Nitric acid oxidation gave a mixture of three anthraquinone carboxylic acids. Two of these acids were identified as anthraquinone-1,2,4-tricarboxylic acid (IX) and anthraquinone-1,3-dicarboxylic acid (XIII). The identity of the third acid was established by a mixture melting point study with anthraquinone-1,2-dicarboxylic acid (XVI) and by conversion to dimethyl anthraquinone-1,2-dicarboxylate (XVII).

The products of this reaction sequence indicate that *Phytadiene Fraction X* probably contains phytadiene VI ($n=3$) in addition to phytadiene VI ($n=1$ and/or 2) and/or VII ($m=0$, 1, and/or 2) and I ($n=0$, 1, and/or 2) and/or XI ($m=0$, 1, and/or 2).

The mixture of alkyl-substituted anthraquinones obtained by air oxidation of the Diels-Alder adduct



prepared from *Phytadiene Fraction X* probably contains the 1,2-dialkylanthraquinone (XV) which has to be identical with the 1-(3′, 7′,11′-trimethyldodecyl)-2-methylanthraquinone (XV, R=3,7,11-trimethyldodecyl, $R_1=CH_3$) described by Rowland.[1]

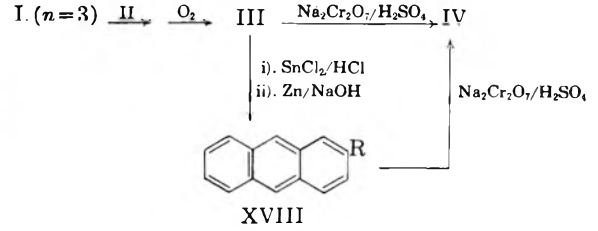
The Diels-Alder reaction of *Phytadiene Fraction Y* with 1,4-naphthoquinone (II) followed by air oxidation of the adduct also yielded an oil. Nitric acid oxidation of an aliquot yielded a mixture of at least three acids which were identified by mixture melting point and infrared absorption studies as anthraquinone-2-carboxylic acid (IV), anthraquinone-1,3-dicarboxylic acid (XIII), and anthraquinone-1,2-dicarboxylic acid (XVI). The 2-carboxylic acid (IV) probably arises from the Diels-Alder reaction between neophytadiene (I, $n=3$) and 1,4-naphthoquinone (II), air oxidation of the adduct and nitric acid oxidation of 2-(4′,8′,12′-trimethyltridecyl)anthraquinone (III, R=4,8,12-trimethyltridecyl).

Chromatography of the remaining air oxidized adduct using silicic acid gave several oily fractions, three of which eventually solidified. Elemental analyses of the three solids suggested that they were isomeric. One solid fraction, melting at 47–48°, was identified by mixture melting point and infrared absorption studies as 2-(4′,8′,12′-trimethyltridecyl)anthraquinone (III, R=4,8,12-trimethyltridecyl). Further oxidation yielded anthraquinone-2-carboxylic acid (IV) as described previously.[1] The second solid fraction, melting at 56–57°, was shown by mixture melting point and infrared absorption studies to be identical with the compound presumed by Rowland[1] to be 1-(3′,7′,11′-trimethyldodecyl)-2-methylanthraquinone (XV, R=3,7,11-trimethyldodecyl, $R_1=CH_3$) arising from 3,7,11,15-tetramethyl-1,3-hexadecadiene (VI, $n=3$). Further oxidation of this dialkyl-substituted anthraquinone yielded anthraquinone - 1,2 - dicarboxylic acid (XVI).

The third solid fraction, melting at 52–53°, is presumed to be 1-(2′,6′,10′-trimethyldodecyl)-3-anthraquinone (XII, R=2,6,10-trimethyldodecyl, $R_1=CH_3$) arising from 2,6,10,14-tetramethyl-1,3-hexadecadiene (I, $n=0$ or VI, $n=0$). Mixture melt-

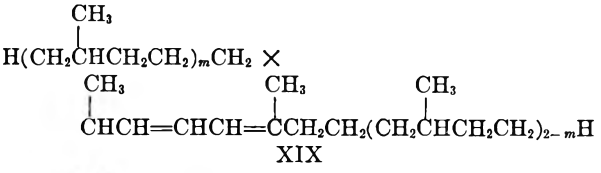
ing point studies of the three isomers indicated that they were different from one another.

Phytadiene Fraction Z was shown by infrared and ultraviolet absorption studies to be neophytadiene (I, $n=3$). Diels-Alder reaction of this fraction with 1,4-naphthoquinone (II) gave 2-(4′,8′,12′-trimethyltridecyl)anthraquinone (III, R=4,8,12-trimethyltridecyl). Reduction of this anthraquinone in two stages using stannous chloride-hydrochloric acid and zinc dust–sodium hydroxide[8] yielded 2-(4′,8′,12′-trimethyltridecyl)anthracene (XVIII, R=4,8,12-trimethyltridecyl) whose ultraviolet absorption was typical of a monoalkylsubstituted anthracene. XVIII (R=4,8,12-trimethyltridecyl) could also be converted to a hydrocarbon:trinitrofluorenone complex. Oxidation of either III (R=4,8,12-trimethyltridecyl) or XVIII (R=4,8,12-trimethyltridecyl) with dichromate in sulfuric acid gave anthraquinone-2-carboxylic acid (IV).

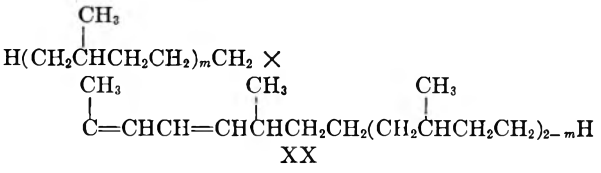


XVIII

No evidence has been obtained in our study to indicate that the six isomeric conjugated phytadienes represented by XIX and XX are present in the cigarette smoke investigated. It is felt that XIX and/or XX either would not react in the Diels-Alder reaction with 1,4-naphthoquinone or would react only slowly and incompletely. If so, these dienes would not be detected by the chemical methods used.

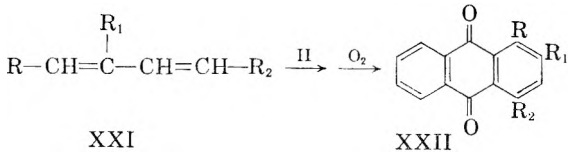


XIX

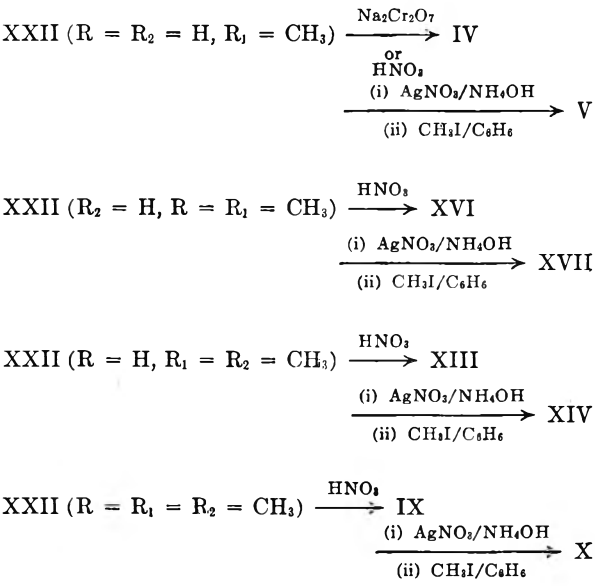


XX

As the identification of the isomeric phytadienes in cigarette smoke depended to a large extent on the identity of the carboxy-substituted anthraquinones and their methyl esters, a brief study of the methyl-substituted anthraquinones and their corresponding acids and methyl esters was undertaken.



XXI XXII



2-Methylanthraquinone (XXII, R=R$_2$=H, R$_1$=CH$_3$) has been prepared by intramolecular condensation of *o*-(4-methylbenzoyl)benzoic acid,[9,10] by condensation of 2-carbomethoxybenzoyl chloride and toluene,[11] and by air oxidation of the Diels-Alder adduct obtained from isoprene (XXI, R=R$_2$=H, R$_1$=CH$_3$) and 1,4-naphthoquinone (II).[12] The anthraquinone-2-carboxylic acid (IV)[13,14] and its methyl ester (V)[7] have been described previously. 1,2-Dimethylanthraquinone (XXII, R$_2$=H, R=R$_1$=CH$_3$) has been prepared by intramolecular condensation of *o*-(3,4-dimethylbenzoyl)benzoic acid[15,16] or *o*-(2,3-dimethylbenzoyl) benzoic acid[17] and by air oxidation of the Diels-Alder adduct from 1,2,6,6-tetramethyl-1,3-cyclohexadiene (*β*-pyronene) and 1,4-naphthoquinone.[18] The 1,2-dicarboxylic acid (XVI)[16,19] and its di-

(8) G. M. Badger and J. W. Cook, *J. Chem. Soc.*, 802 (1939).

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(10) L. Gresly, *Ann.*, **234**, 234 (1886).
(11) M. E. Smith, *J. Am. Chem. Soc.*, **43**, 1922 (1921).
(12) O. Diels, K. Alder, and G. Stein, *Ber.*, **62B**, 2337 (1929).
(13) M. A. Il'inskii, L. G. Gindin, and V. A. Kazakova, *Compt. Rend. Acad. Sci., U.R.S.S.*, **20**, 555 (1938).
(14) M. A. Il'inskii and V. A. Kazakova, *J. Gen. Chem., (U.S.S.R.)*, **11**, 16 (1941); *Chem. Abstr.*, **35**, 5487 (1941).
(15) E. D. Barnett and F. C. Morrison, *Ber.*, **64B**, 535 (1931).
(16) O. Fairbourne, *J. Chem. Soc.*, 1573 (1921).
(17) G. M. Badger, J. W. Cook, and F. Goulden, *J. Chem. Soc.*, 16 (1940).
(18) G. Dupont and R. Dulou, *Atti X° Congr. Internat. Chim.*, **3**, 129 (1939); *Chem. Abstr.*, **33**, 9312 (1939).
(19) R. Scholl and E. Schwinger, *Ber.*, **44**, 2992 (1911).

methyl ester (XVII)[20] have been described previously. 1,3-Dimethylanthraquinone (XXII, R = H, $R_1 = R_2 = CH_3$) has been prepared by intramolecular condensation of 2 - benzoyl - 4,6 - dimethylbenzoic acid,[21] by rearrangement and intramolecular condensation of *o*-(2,5-dimethylbenzoyl)benzoic acid,[22] by intramolecular condensation of *o*-(2,4-dimethylbenzoyl)-benzoic acid,[10,23] and by air oxidation of the Diels-Alder adduct obtained from 2-methyl-1,3-pentadiene (XXI, R = H, $R_1 = R_2 = CH_3$) and II.[12] The 1,3-dicarboxylic acid (XIII) has been described.[24] 1,2,4-Trimethylanthraquinone (XXII, $R = R_1 = R_2 = CH_3$) has been prepared by intramolecular condensation of *o*-(2,4,5-trimethylbenzoyl)benzoic acid,[22] and by oxidation of 1,2,4-trimethylanthracene obtained by condensation of *p*-xylene and 2,3,4,5-tetramethyl-2,5-hexanediol.[25] Nitric acid oxidation of either XXII ($R = R_1 = R_2 = CH_3$)[20,23] or 1-formyl-2,4-dimethylanthraquinone[26] yields the 1,2,4-tricarboxylic acid (IX). The trimethyl ester (X) of IX has been described.[27]

In the preparation of the necessary reference compounds, we elected to employ the Diels-Alder reaction between II and XXI, followed by air oxidation of the adduct,[12] oxidation of the methyl-substituted anthraquinone to the acid[10,14,23] and esterification to the methyl ester by the method described by Cook.[20,28]

1,2-Dimethyl-(XXII, $R_2 = H$, $R = R_1 = CH_3$) and 1,2,4-trimethylanthraquinone (XXII, $R = R_1 = R_2 = CH_3$) were prepared by air oxidation of the adduct obtained from II and 3-methyl-1,3-pentadiene (XXI, $R_2 = H$, $R = R_1 = CH_3$) and 3-methyl-2,4-hexadiene (XXI, $R = R_1 = R_2 = CH_3$), respectively. 2-Methyl-(XXII, $R = R_2 = H$, $R_1 = CH_3$) and 1,3-dimethylanthraquinone (XXII, R = H, $R_1 = R_2 = CH_3$) were prepared by air oxidation of the adduct obtained from II and isoprene (XXI, $R = R_2 = H$, $R_1 = CH_3$) and 2-methyl-1,3-pentadiene (XXI, R = H, $R_1 = R_2 = CH_3$), respectively, as described by Diels *et al.*[12]

It has been suggested that neophytadiene (I, n = 3) arises from the breakdown of phytol (*ex* chlorophyll) in the tobacco leaf.[1,2b] The isomeric conjugated phytadienes indicated in our study are presumed to result from the thermal isomerization of neophytadiene during the smoking process. When neophytadiene (I, $n = 3$) is heated at 180° for 2.5 hr., the changes observed in the infrared absorption indicate the formation of a mixture of isomers similar to the phytadienes described by Rowland.[1] The infrared absorption of the thermally isomerized neophytadiene is quite similar to that of the gross phytadiene fraction obtained from the cigarette smoke. A similar alteration in the infrared absorption may be observed when a benzene solution of neophytadiene containing a catalytic amount of *p*-toluene sulfonic acid is refluxed. Treatment of a hexane solution of neophytadiene with dilute hydrochloric acid in a procedure analogous to that employed in the isolation of the phytadiene fraction from cigarette smoke did not result in isomerization of the neophytadiene.

As the infrared absorption indicated that the mixture of isomeric phytadienes was present in the cigarette smoke fraction prior to reaction with 1,4-naphthoquinone in the Diels-Alder addition, it was felt that isomerization did not occur during this reaction. However, further confirmation of this point was desired. A solution of neophytadiene (I, $n = 3$) and 1,4-naphthoquinone (II) in ethanol was refluxed and aliquots were withdrawn after 4, 8, 16, and 32 hr. Air oxidation yielded only 2-(4′,8′,12′-trimethyltridecyl)anthraquinone (III, R = 4,8,12-trimethyltridecyl) determined by melting point, by infrared absorption and by conversion to anthraquinone-2-carboxylic acid (IV).

Discounting the optical isomers and the *cis*, *trans*, *cis-cis*, *trans-trans*, *cis-trans*, and *trans-cis* isomers, consideration of the isomerism of the conjugated phytadienes indicates that nineteen isomers are possible. These are described by structures I, VI, VII, XI, XIX, and XX. The reaction sequence employed in this study would not differentiate between the *cis* and *trans* isomers.

The evidence obtained in this study indicates that at least four of these isomers are present in cigarette smoke. These are (a) 3-methylene-7,11,15-trimethyl-1-hexadecene (neophytadiene) (I, $n = 3$), (b) 3,7,11,15-tetramethyl-1,3-hexadecadiene (VI, $n = 3$), (c) 2,6,10,14-tetramethyl-1,3-hexadecadiene (I, $n = 0$ or VI, $n = 0$), and (d) a 1,2,4-trialkyl-1,3-butadiene. The evidence herein presented could be presumed to indicate the presence in cigarette smoke of as many as thirteen of the isomeric conjugated phytadienes; namely, I ($n = 0,1,2,3$), VI ($n = 1,2,3$), VII ($m = 0,1,2$), and XI ($m = 0,1,2$). Again it should be noted that I ($n = 0$) and VI ($n = 0$) are identical. No evidence has been obtained to indicate the presence of the remaining six isomeric conjugated phytadienes, XIX ($m = 0,1,2$) and XX ($m = 0,1,2$).

No attempt was made to estimate the quantities in cigarette smoke of the phytadienes, I ($n = 3$), VI ($n = 3$), and I ($n = 0$), because of the uncertainty of the yields in the reaction sequence employed.

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EXPERIMENTAL[29]

Isolation of phytadienes. The smoking apparatus and smoking procedure have been described previously.[4,5] Two separate lots of cigarettes fabricated from the same commercial blend of tobaccos were smoked. Cigarettes A consisted of 20,000 cigarettes, Cigarettes B consisted of 32,000 cigarettes. After chemical fractionation, the so-called hexane soluble neutral acidic fraction[4,5] from Cigarettes A and the hexane soluble neutral fraction from Cigarettes B[4] were chromatographed in 15- to 16-g. aliquots using alumina. The material (3.0–3.5 g.) eluted by hexane (600 ml.) was combined to yield 9.0- to 10.0-g. samples and rechromatographed using alumina. Elution with hexane (275 ml.) gave 7.0 to 9.0 g. of a mixture of saturated and unsaturated hydrocarbons and an unsaturated alcohol. Combination of similar fractions from all the chromatograms gave 115 g. of this mixture. Two crystallizations from acetone at −27° gave 26.5 g. of normal saturated hydrocarbons, m.p. 62.5–64.5°. This mixture probably contains *n*-heptocosane, *n*-nonacosane, *n*-hentriacontane, and *n*-tritriacontane.[6]

The filtrate was concentrated at 40° using a water aspirator to yield 88 g. of a mixture of unsaturated hydrocarbons and alcohol(s) containing a trace of saturated hydrocarbons. Chromatography of this material on alumina using hexane as eluant yielded in order of elution: (a) 50.5 g. of a colorless free-flowing oil consisting of a mixture of unsaturated hydrocarbons, predominantly phytadienes; (b) 7.8 g. of a viscous unsaturated hydrocarbon mixture; (c) 8.2 g. of a viscous unsaturated hydrocarbon mixture; and (d) 11.35 g. of a viscous oil with infrared absorption indicative of an unsaturated alcohol.

Fractionation of phytadienes. The 50.5-g. sample described above was repeatedly chromatographed on alumina using pentane and hexane as eluants to give seven main fractions with the following weights: Fr. 1, 2.05 g.; Fr. 2, 6.85 g.; Fr. 3, 8.25 g.; Fr. 4, 6.70 g.; Fr. 5, 4.05 g.; Fr. 6, 10.60 g.; and Fr. 7, 7.22 g. In several instances, benzene and methanol were used to elute Fr. 6 and 7, respectively, as the major emphasis of this study is on Fr. 1 to 5.

On the basis of the similarity of their infrared absorption spectra to those of the phytadienes described by Rowland,[1] Fr. 1–5 were chosen for further study.

Fr. 1 was crystallized from acetone (10 ml.) at −27° to yield 0.23 g. of normal saturated hydrocarbons, m.p. 61–63°. The filtrate, designated as *Phytadiene Fraction V*, was concentrated to give a colorless, free-flowing oil with weak infrared absorption at 6.07, 11.0, and 11.28μ and moderately strong absorption at 10.38μ indicative of a *trans*-CH=CH grouping. Absorption was also present at 7.25 and 7.31μ. The ultraviolet absorption showed a maximum at 233 mμ, log ϵ 4.32.

Anal. Calcd. for $C_{20}H_{38}$: C, 86.25; H, 13.75. Found: C, 86.14; H, 13.56.

Fr. 2, designated as *Phytadiene Fraction W*, was a colorless oil with infrared absorption at 6.08, 6.25, 7.25, 7.31, 10.1, 10.38, 11.0, 11.1, and 11.23μ. The ultraviolet absorption showed a broad maximum from 228 to 232 mμ, log ϵ 4.25.

Fr. 3, designated as *Phytadiene Fraction X*, was a colorless oil with infrared absorption at 6.08, 6.25, 7.25, 7.31, 10.1, 10.35 (very weak), 11.1, and 11.22μ. The ultraviolet absorption showed a broad maximum from 225 to 228 mμ, log ϵ 4.28.

Fr. 4, designated as *Phytadiene Fraction Y*, was a colorless oil with infrared absorption at 6.07 (s), 6.25 (w), 7.25, 7.32, 10.1, and 11.2μ. The ultraviolet absorption showed a maximum at 225 to 228 mμ, log ϵ 4.30.

Fr. 5, designated as *Phytadiene Fraction Z*, was a colorless oil with infrared and ultraviolet spectra essentially the same as neophytadiene.[1,2b] Some infrared absorption was observed at 12.25μ. This was due to one of the main components of Fr. 6. Chromatography on alumina gave 3.76 g. of material with infrared absorption identical with that of neophytadiene.[1,2b]

Phytadiene Fraction V. Diels-Alder reaction with 1,4-naphthoquinone. A solution of 1.0 g. of *Phytadiene Fraction V* and 1.0 g. of 1,4-naphthoquinone in 35 ml. of ethanol was refluxed for 20 hr. A solution of 0.10 g. of potassium hydroxide in 10 ml. of ethanol was added and air was bubbled through the mixture for 6.0 hr. The mixture was concentrated under reduced pressure. Extraction with 35 ml. of hexane followed by chromatography using silicic acid gave (a) a diene mixture (0.75 g.), eluted by hexane, with infrared absorption essentially the same as the starting material; and (b) a pale yellow oil, the oxidized adduct (0.11 g.), eluted by 25:1 hexane:benzene. This oil subsequently solidified, m.p. 35–38°. Crystallization from methanol at −27° raised the melting point to 39–42° but did not reduce the melting range.

Anal. Calcd. for $C_{30}H_{40}O_2$: C, 83.28; H, 9.32. Found: C, 83.40; H, 9.30.

Anthraquinone-1,2,4-tricarboxylic acid (IX). A. *From the air oxidized adduct.* The air oxidized adduct (50 mg.), m.p. 39–42°, was oxidized with 3.0 ml. of 22% nitric acid at 250° for 3.5 hr. to yield 15 mg. of anthraquinone-1,2,4-tricarboxylic acid, m.p. softened at 195°, resolidified at 210°, melted at 316-318° (dec.).

Anal.[30] Calcd. for $C_{17}H_8O_8 \cdot H_2O$: C, 56.99; H, 2.81; neut. equiv., 119. Found: C, 56.02; H, 2.82; neut. equiv., 126, 127.[31a,31b]

A mixture melting point with an authentic sample of the 1,2,4-tricarboxylic acid gave melting characteristics identical with those of the authentic sample. The infrared absorption spectrum of this material was essentially the same as that of the authentic sample.

B. *From 1,2,4-trimethylanthraquinone.* 3-Methyl-2,4-hexadiene was prepared from 3-methyl-2-hexen-4-ol in 90% yield by the method of Abelmann.[32] A solution of 1,4-naphthoquinone (3.5 g., 0.022 mol.) and 3-methyl-2,4-hexadiene (6.0 g., 0.062 mol.) in 60 ml. of ethanol was refluxed for 12.0 hr. Addition of a solution of 1.1 g. of potassium hydroxide in 15 ml. of ethanol followed by air oxidation for 6.0 hr. yielded 2.7 g. (51%) of crude 1,2,4-trimethylanthraquinone, m.p. 157–158°. Crystallization from meth-

(29) All melting points were determined on a Fisher-Johns melting point apparatus. Elemental analyses were performed either by the Clark Microanalytical Laboratory, Urbana, Ill., or by the Huffman Microanalytical Laboratories, Wheatridge, Colo. Ultraviolet absorption spectra were determined using a Beckman DK2 Ratio Recording Spectrophotometer. Infrared absorption spectra were determined using a Perkin-Elmer Model 21 Spectrophotometer. The alumina employed was Aluminum Oxide Merck (Cat. No. 71707); the silicic acid was obtained from Mallinckrodt Chemical Works (Cat. No. 2844). Chromatograms involving material in excess of 1.0 g. employed approximately 45 mm. (diam.) × 200 mm. of adsorbent; those involving less than 1.0 g. employed approximately 24 mm. (diam.) × 100 mm. of adsorbent.

(30) Considerable difficulty was encountered in obtaining a satisfactory analytical sample of the 1,2,4-tricarboxylic acid prepared either from the air oxidized Diels-Alder adduct or from 1,2,4-trimethylanthraquinone. Diesbach *et al.* (ref. 26) reported the following analysis: Calcd. for $C_{17}H_8O_8$: C, 60.00; H, 2.37. Found: C, 60.25; H, 2.63.

(31) (a) R. H. Cundiff and P. C. Markunas, *Anal. Chem.*, **28**, 792 (1956). (b) This tribasic acid gave three inflections as expected on titration with tetrabutylammonium hydroxide in pyridine. (c) This dibasic acid gave two inflections as expected on titration with tetrabutylammonium hydroxide in pyridine. (d) This monobasic acid gave one inflection as expected on titration with tetrabutylammonium hydroxide in pyridine.

(32) P. Abelmann, *Ber.*, **43**, 1574 (1910).

anol raised the melting point to 161.5–162.0°. Melting points of 161°,[10] 162°,[22,23] and 155–158°[25] have been reported.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.59; H, 5.64. Found: C, 82.01; H, 5.58.

Chromatography on alumina of the material obtained in the mother liquor from the crystallization gave two fractions. In order of elution, these were (a) 0.11 g. of a pale yellow solid, m.p. 105–106°, and (b) 0.25 g. of a pale yellow crystalline solid, m.p. 161.5–162.0°. The low melting material gave an analysis compatible with $C_{17}H_{16}O_3$. No attempt was made to characterize this compound.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.69; H, 5.95. Found: C, 76.10; H, 6.01.

The second material was a further crop of 1,2,4-trimethylanthraquinone.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.59; H, 5.64. Found: C, 81.18; H, 5.53.

A suspension of 1,2,4-trimethylanthraquinone (0.4 g.) in 7.0 ml. of 22% nitric acid was heated at 255° for 6.0 hr. in a sealed tube to give 0.35 g. (64%) of the 1,2,4-tricarboxylic acid,[10,22] m.p. softened at 197°, resolidified at 212° and melted at 310–312° (dec.). Crystallization from 4:1 methanol:water raised the decomposition point to 317–318°. The 1,2,4-tricarboxylic acid has been prepared previously by the nitric acid oxidation of 1,2,4-trimethylanthraquinone[22,23] and of 1-formyl-2,4-dimethylanthraquinone.[26]

One oxidation of the 1,2,4-trimethyl derivative conducted at 210° gave a yellow crystalline product, m.p. 320–325°, whose analysis suggested a methylanthraquinone–dicarboxylic acid.

Anal. Calcd. for $C_{17}H_{10}O_6$: C, 65.81; H, 3.25; neut. equiv., 155. Found: C, 66.45; H, 3.28; neut. equiv., 150, 152.[31a,31c]

Trimethyl anthraquinone-1,2,4-tricarboxylate. The anthraquinone-1,2,4-tricarboxylic acid obtained from the air oxidized Diels-Alder adduct from *Phytadiene Fraction V* was converted to the trimethyl ester, m.p. 188–189°, employing the method of Cook.[28] Trimethyl anthraquinone-1,2,4-tricarboxylate (115 mg., 80%), m.p. 188–189°, was prepared from the 1,2,4-tricarboxylic acid obtained from 1,2,4-trimethylanthraquinone. Crystallization from methanol raised the melting point to 192–193°. A mixture melting point determination using the two samples described above gave no depression. The infrared absorption spectra of the two samples were identical. A melting point of 193° has been reported[27] for this ester.

Anal. Calcd. for $C_{20}H_{14}O_8$: C, 62.82; H, 3.69. Found: C, 62.46; H, 3.62.

Phytadiene Fraction W. Diels-Alder reaction with 1,4-naphthoquinone. A solution of *Phytadiene Fraction W* (3.0 g.) and 1,4-naphthoquinone (2.5 g.) in 75 ml. of ethanol was refluxed for 10 hr. The reaction mixture was treated with a solution of potassium hydroxide (0.15 g.) in ethanol (10 ml.) and air was bubbled through the mixture for 6.0 hr. The mixture was concentrated under reduced pressure. Extraction with 75 ml. of hexane followed by chromatography using silicic acid gave (a) a diene mixture (1.58 g.), eluted by hexane, and (b) the oxidized adduct (0.37 g.), eluted by 25:1 hexane:benzene. This material was a pale yellow oil with an infrared absorption spectrum typical of an anthraquinone.

Anthraquinone-1,3-dicarboxylic acid. A. *From the air oxidized adduct.* Oxidation with 20% nitric acid (sealed tube, 215°, 4.5 hr.) gave a mixture of acids, wt. 0.15 g. Chromatography of the acid mixture using silicic acid gave 0.09 g. of a pale yellow crystalline solid, m.p. 320–322°, eluted by ether. Crystallization from methanol at −27° raised the melting point to 325–326°.

Anal. Calcd. for $C_{16}H_8O_6$: C, 64.87; H, 2.72; neut. equiv., 148. Found: C, 65.23; H, 2.67; neut. equiv., 152, 154.[31a,31c]

A mixture melting point with an authentic sample of anthraquinone-1,3-dicarboxylic acid gave no depression. The infrared absorption spectrum of this material was identical with that of an authentic sample.

A second acid fraction (0.011 g.), m.p. softened at 196°, resolidified at 212°, melted at 310–314° (dec.), was obtained from the chromatogram. This material gave an infrared absorption spectrum identical with that of authentic anthraquinone-1,2,4-tricarboxylic acid.

B. *From 1,3-dimethylanthraquinone.* 2-Methyl-2,4-pentanediol (Carbide and Carbon Chemicals Co.) was dehydrated using sulfuric acid to yield 2-methyl-1,3-pentadiene, b.p. 78° (75%). A solution of 1,4-naphthoquinone (4.2 g., 0.027 mol.) and 2-methyl-1,3-pentadiene (12.3 g., 0.15 mol.) in 65 ml. of ethanol was refluxed for 6.0 hr. The 1,3-dimethylanthraquinone (4.9 g., 77%), m.p. 158–160°, was prepared and isolated as described previously.[12] Crystallization from ethanol raised the melting point to 161.5–162.0°. 1,3-Dimethylanthraquinone has been reported as melting at 162°.[12]

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12. Found: C, 81.40; H 5.01.

The 1,3-dimethylanthraquinone (0.5 g.) was heated at 180° for 6.0 hr. with 7.0 ml. of 20% nitric acid in a sealed tube[24] to yield 0.48 g. (76%) of the 1,3-dicarboxylic acid, m.p. 320–323°. Crystallization from methanol raised the melting point to 326–328°.

Dimethyl anthraquinone-1,3-dicarboxylate. Employing the method of Cook,[28] the dimethyl ester of anthraquinone-1,3-dicarboxylic acid from *Phytadiene Fraction W* was prepared, m.p. 188–189°. Crystallization from methanol did not alter the melting point.

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.66; H, 3.73. Found: C, 66.72; H, 3.63.

A mixture melting point with an authentic sample, m.p. 188.5–189.5°, prepared from the 1,3-tricarboxylic acid obtained by nitric acid oxidation of 1,3-dimethylanthraquinone gave no depression. The infrared absorption spectra of the two esters were identical.

Phytadiene Fraction X. Diels-Alder reaction with 1,4-naphthoquinone. A solution of *Phytadiene Fraction X* (3.0 g.) and 1,4-naphthoquinone (3.0 g.) in 75 ml. of ethanol was refluxed for 6.5 hr. The reaction mixture was treated with a solution of potassium hydroxide (0.15 g.) in ethanol (15 ml.) and air was bubbled through the mixture for 6.0 hr. The mixture was concentrated under reduced pressure and the residue was extracted with 75 ml. of hexane. Chromatography using silicic acid gave (a) a diene mixture (1.88 g.) and (b) the oxidized adduct (0.52 g.) which was a pale yellow oil. The infrared absorption spectrum of this oil indicated a substituted anthraquinone.

Anthraquinone-1,2-dicarboxylic acid. A. *From the air oxidized adduct.* Nitric acid oxidation (20% nitric acid solution, sealed tube, 210°, 6.0 hr.) was accomplished as before to give a mixture of acids (0.19 g.). Chromatography using silicic acid with hexane-ether solutions and ether as eluants gave 0.041 g. of anthraquinone-1,3-dicarboxylic acid, m.p. 321–323°, 0.060 g. of a second acid, m.p. 320–321°, and 0.011 g. of anthraquinone-1,2,4-tricarboxylic acid, m.p. softened at 192°, resolidified at 210°, melted at 315–317° (dec.). The acid, m.p. 320–321°, was shown by mixture melting point and infrared absorption studies to be anthraquinone-1,2-dicarboxylic acid.

Anal. Calcd. for $C_{16}H_8O_6$: C, 64.87; H, 2.72; neut. equiv., 148. Found: C, 64.02; H, 2.52; neut. equiv., 152.[31a,31c]

B. *From 1,2-dimethylanthraquinone.* 3-Methyl-1,3-pentadiene, b.p. 77–78°, was prepared from 3-methyl-3-penten-2-ol *via* 2-chloro-3-methyl-3-pentene by dehydrochlorination of the latter compound using the method of Abelmann.[32]

A solution of 1,4-naphthoquinone (3.5 g., 0.022 mol.) and 3-methyl-1,3-pentadiene (7.5 g., 0.09 mol.) in 60 ml. of ethanol was refluxed for 4.0 hr. A solution of 0.4 g. of potassium hydroxide in 15 ml. of ethanol was added. The reaction mixture was aerated for 16 hr. Filtration gave 3.63 g. (70%) of 1,2-dimethylanthraquinone, m.p. 147–148°. Crystallization from ethanol gave bright yellow needles,

wt. 2.8 g., m.p. 151.0–152.0°. A melting point of 154° has been reported for this compound.[17]

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12. Found: C, 81.76; H, 5.07.

Oxidation of the 1,2-dimethylanthraquinone using the method of Fieser and Martin[24] gave the 1,2-dicarboxylic acid monohydrate,[16] m.p. 266°, in 67% yield. Crystallization from methanol followed by prolonged drying at 80° *in vacuo* gave the diacid, m.p. 322–325°.

Dimethyl anthraquinone-1,2-dicarboxylate. Employing the method described by Cook,[28] the dimethyl ester of anthraquinone-1,2-dicarboxylic acid from *Phytadiene Fraction X* was prepared, m.p. 202–203°. Crystallization from methanol raised the melting point to 204.5–205.5°. A melting point of 208° has been reported.[20]

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.66; H, 3.73. Found: C, 66.18; H, 3.62.

Dimethyl anthraquinone-1,2-dicarboxylate, m.p. 203–204°, was prepared in 76% yield from the 1,2-dicarboxylic acid obtained from 1,2-dimethylanthraquinone. A mixture melting point of the two samples gave no depression. The infrared absorption spectra were identical.

Phytadiene Fraction Y. Diels-Alder reaction with 1,4-naphthoquinone. A solution of *Phytadiene Fraction Y* (3.0 g.) and 1,4-naphthoquinone (3.0 g.) in 75 ml. of ethanol was refluxed for 6.0 hr. A solution of potassium hydroxide (0.15 g.) in ethanol (15 ml.) was added and air was bubbled through the mixture for 6.0 hr. The mixture was concentrated under reduced pressure. The residue was extracted with hexane (30 ml.) and chromatographed using silicic acid to give (a) a diene mixture (1.45 g.) eluted by hexane and (b) the oxidized adduct (0.68 g.), eluted by carbon tetrachloride. Nitric acid oxidation of an aliquot (0.25 g.) of this material gave a mixture of acids (0.16 g.) which were separable by chromatography using silicic acid. Anthraquinone-2-carboxylic acid (0.045 g.), m.p. 291.5–293.0°, anthraquinone-1,3-dicarboxylic acid (0.038 g.), m.p. 321–323°, and anthraquinone-1,2-dicarboxylic acid (0.051 g.), m.p. 320–322°, were isolated from the mixture. These acids were identified by mixture melting point studies and by comparison of infrared absorption spectra with those of authentic samples.

Chromatography of the remaining oxidized adduct (0.43 g.) on silicic acid using hexane, hexane-carbon tetrachloride solutions, and carbon tetrachloride as eluants gave five fractions as follows:

Fr. A: oily solid, m.p. 48–51°, wt. 0.045 g.
Fr. B: yellow oil, wt. 0.016 g.
Fr. C: yellow solid, m.p. 54.5–56.5°, wt. 0.061 g.
Fr. D: yellow oil, wt. 0.021 g.
Fr. E: yellow solid, m.p. 46–48°, wt. 0.039 g.

Crystallization of Fr. A from methanol at −27° gave 0.028 g. of a pale yellow solid, m.p. 52–53°. This material was considered to be 1-(2′,6′,10′-trimethyldodecyl)-3-methylanthraquinone.

Anal. Calcd. for $C_{30}H_{40}O_2$: C, 83.28; H, 9.32. Found: C, 83.33; H, 9.09.

Crystallization of Fr. C from methanol at −27° gave 0.041 g. of a pale yellow solid, m.p. 56–57°. This material had an infrared absorption spectrum identical with that of the compound presumed by Rowland[1] to be 1-(3′,7′,11′-trimethyldodecyl)-2-methylanthraquinone.

Anal. Calcd. for $C_{30}H_{40}O_2$: C, 83.28; H, 9.32. Found: C, 83.38; H, 9.50.

After crystallization from methanol at −27°, Fr. E gave a pale yellow solid, m.p. 47.0–48.0°. The infrared absorption spectrum of this material was identical with that of 2-(4′,8′,12′-trimethyltridecyl)anthraquinone obtained from neophytadiene.[1]

Mixture melting point studies using approximately 1:1 mixtures of Fr. A plus Fr. C, Fr. A plus Fr. E, and Fr. C plus Fr. E gave an appreciable depression of the melting point in each instance.

Anthraquinone-carboxylic acids. Nitric acid oxidation (20% nitric acid solution, sealed tube, 210°, 3.5 hr.) of the material from Fr. A and from Fr. C gave anthraquinone-1,3- and 1,2-dicarboxylic acids, respectively. Chromic acid oxidation of the material from Fr. E gave anthraquinone-2-carboxylic acid. Mixture melting point determinations and infrared absorption studies were employed to establish the identity of these acids.

Phytadiene Fraction Z. Neophytadiene. The infrared absorption spectrum of *Phytadiene Fraction Z*, n_D^{27} 1.4600, was identical with that of neophytadiene reported by Rowland.[1] The ultraviolet absorption spectrum determined in cyclohexane at 25° showed a maximum at 225 mμ, log ε 4.37 with a weaker maximum at 278 mμ, log ε 2.78.

Anal. Calcd. for $C_{20}H_{38}$: C, 86.25; H, 13.75. Found: C, 86.16; H, 13.84.

Reduction of neophytadiene using palladium-charcoal catalyst gave phytane, n_D^{27} 1.4403.

Anal. Calcd. for $C_{20}H_{42}$: C, 85.03; H, 14.97. Found: C, 85.27; H, 14.73.

2-(4′,8′,12′-Trimethyltridecyl)anthraquinone. 2-(4′,8′,12′-Trimethyltridecyl)anthraquinone (0.21 g., 22%), m.p. 47–48°, was prepared from 0.6 g. of neophytadiene and 0.6 g. of 1,4-naphthoquinone in 15 ml. of ethanol as described by Rowland.[1] Crystallization from methanol at −27° raised the melting point to 48.5–49.0°.

Anal. Calcd. for $C_{30}H_{40}O_2$: C, 83.28; H, 9.32. Found: C, 83.21; H, 9.18.

2-(4′,8′,12′-Trimethyltridecyl)anthracene. A mixture of 2-(4′,8′,12′-trimethyltridecyl)anthraquinone (0.10 g., 0.23 mmol.), stannous chloride (0.22 g., 0.116 mmol.), acetic acid (3.0 ml.), and 37% hydrochloric acid (0.5 ml.) was refluxed for 2.0 hr., a procedure described by Badger and Cook.[8] The reaction mixture was cooled, diluted with water (30 ml.), and extracted with three 50-ml. portions of ether. Concentration of the extract gave 0.10 g. of a pale yellow oil.

This oil, suspended in 5 ml. of 2*N* sodium hydroxide, was treated with 0.30 g. of zinc dust and the suspension refluxed for 4.0 hr.[8] The initial red color of the reaction mixture faded to pale yellow within 30 min. Dilution of the reaction mixture with water (50 ml.) followed by acidification with 37% hydrochloric acid caused a pale yellow solid to separate. Filtration gave 0.10 g. of this material, m.p. 85–86°. Chromatography on alumina using 3% benzene-hexane solutions as eluant gave 0.09 g. of a highly fluorescent solid. Crystallization from 4:1 ethanol:water gave 0.08 g. of 2-(4′,8′,12′-trimethyltridecyl)anthracene, m.p. 92.0–93.0°.

Anal. Calcd. for $C_{30}H_{42}$: C, 89.48; H, 10.52. Found: C, 90.02; H, 9.98.

The ultraviolet absorption of this material at 25° (ethanol) showed typical anthracenoid maxima as follows: 246.5 mμ, log ε 5.35; 255 mμ, log ε 5.67; 322 mμ, log ε 3.59; 337 mμ, log ε 3.78; 356 mμ, log ε 3.90; 376 mμ, log ε 3.84.

This hydrocarbon gave a 1:1 *2,4,7-trinitrofluorenone:hydrocarbon complex* which crystallized from 4:1 methanol:benzene as deep violet needles, m.p. 104.5–105.5°.

Anal. Calcd. for $C_{30}H_{42}{\cdot}C_{13}H_5N_3O_7$: C, 71.94; H, 6.60. Found: C, 72.01; H, 6.52.

Anthraquinone-2-carboxylic acid. A. *From 2-(4′,8′,12′-trimethyltridecyl)anthraquinone.* As reported previously,[1] chromic acid oxidation of 2-(4′,8′,12′-trimethyltridecyl)anthraquinone gave anthraquinone-2-carboxylic acid, m.p. 295–296°. A melting point of 291–292° has been reported.[13,14]

Anal. Calcd. for $C_{15}H_8O_4$: C, 71.43; H. 3.19; neut. equiv., 252. Found: C, 71.67; H, 3.25; neut. equiv., 260.[31a,31d]

A mixture melting point with an authentic sample gave no depression. The infrared absorption spectrum was identical with that of an authentic sample.

B. *From 2-(4′,8′,12′-trimethyltridecyl)anthracene.* 2-(4′,8′,12′-Trimethyltridecyl)anthracene (0.030 g.) was dissolved in 2.0 ml. of glacial acetic acid. A solution of 0.25 g. of sodium dichromate in 0.5 ml. of concentrated sulfuric acid was added and the resulting solution was heated at 100° for

2.0 hr. Dilution with water, followed by ether extraction, yielded 0.014 g. of anthraquinone-2-carboxylic acid, m.p. 292–293°. A mixture melting point with an authentic sample gave no depression.

C. *From 2-methylanthraquinone.* 2-Methylanthraquinone, m.p. 178.5–179.0°, was prepared in 95% yield from isoprene and 1,4-naphthoquinone as described previously.[12]

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 81.07; H, 4.54. Found: C, 81.20; H, 4.52.

Oxidation of 2-methylanthraquinone by the method of Il'inskii and Kazakova[14] gave the 2-carboxylic acid, m.p. 290–292°, in 95% yield. Crystallization from 4:1 ethanol:water raised the melting point to 295–296°.

Methyl anthraquinone-2-carboxylate. Methyl anthraquinone-2-carboxylate, m.p. 169°, was prepared using the method of Cook[28] in 77% yield from anthraquinone-2-carboxylic acid obtained by oxidation of 2-(4′,8′,12′-trimethyltridecyl)anthraquinone. Crystallization from methanol raised the melting point to 171.0–171.5°. A melting point of 170° has been reported.[7]

Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.21; H, 3.78. Found: C, 72.08; H, 3.77.

A mixture melting point study of this material with an authentic sample of the ester prepared from the 2-carboxylic acid obtained by oxidation of 2-methyl-anthraquinone gave no depression. The infrared absorption spectra of the two ester samples were identical.

Isomerization of neophytadiene. A. *Thermal isomerization.* Neophytadiene (0.65 g.) was heated in an oil bath at 182° for 2.5 hr. Examination of the infrared spectrum indicated that the absorption at 6.27μ had lessened, the absorption at 11.1μ had shifted to 11.0μ, the ratio of the absorption at 11.1μ to that at 11.2μ had markedly altered and strong absorption at 10.38μ had appeared. These data are consistent with the migration of the conjugated system toward the center of the phytadiene molecule. The appearance of infrared absorption at 10.38μ is indicative of the formation of a *trans*-CH=CH grouping.

The ultraviolet absorption of the isomerized material showed a broad maximum at 230–233 mμ, log ϵ 4.22.

B. *Catalytic isomerization.* A solution of neophytadiene (0.65 g.) in 20 ml. of benzene containing 0.025 g. of *p*-toluenesulfonic acid was refluxed for 3.3 hr. The solution was cooled, extracted with 25 ml. of water, and concentrated under reduced pressure. The residue was chromatographed using alumina to give a diene mixture with strong infrared absorption at 10.38μ. The infrared absorption at 6.07 and 6.27μ had almost completely disappeared. The infrared absorption spectrum of this material was almost identical with that of the hydrocarbon obtained by *p*-toluenesulfonic acid–phthalic anhydride dehydration of phytol.[1]

C. *Dilute hydrochloric acid.* Neophytadiene (0.45 g.) was dissolved in 200 ml. of methanol, diluted with 300 ml. of 0.2*N* hydrochloric acid, and extracted with six 75-ml. portions of hexane. This procedure is essentially that employed in the isolation of the phytadiene fraction from cigarette smoke.[4,5] The hexane extract was washed with 100 ml. of 9:1 methanol:water, dried over sodium sulfate and concentrated to yield 0.43 g. of neophytadiene, identical with the starting material in respect to infrared and ultraviolet absorption. No evidence of infrared absorption at 10.38μ was obtained.

Study of Diels-Alder reaction between neophytadiene and 1,4-naphthoquinone. A solution of neophytadiene (1.0 g., 2.3 mmol.) and 1,4-naphthoquinone (0.55 g., 3.5 mmol.) in 25.0 ml. of ethanol was refluxed for 4.0 hr. The reaction mixture was chilled rapidly in ice water and 5.0 ml. were withdrawn using a pipette. The remaining reaction mixture was refluxed for an additional 4.0 hr., at which time the chilling and pipetting were repeated. This procedure was repeated at the end of 16.0 and 32.0 hr.

Each aliquot was treated with a solution of 0.05 g. of potassium hydroxide in 5.0 ml. of ethanol and air was bubbled through the mixture for 3.0 hr. The residue was extracted with 55 ml. of hexane and the hexane extract was chromatographed using silicic acid. In each instance, the air oxidized adduct was further oxidized to anthraquinone-2-carboxylic acid. Table I shows the results obtained. No other acid could be detected during examination of the oxidation products of the air oxidized adduct. The air oxidized adduct showed infrared absorption identical with that of 2-(4′,8′,12′-trimethyltridecyl)anthraquinone.

TABLE I

DIELS-ALDER REACTION BETWEEN NEOPHYTADIENE AND 1,4-NAPHTHOQUINONE

Aliquot No.	Reaction Time, Hr.	Air Oxidized Adduct		Anthraquinone-2-carboxylic Acid	
		Wt., mg.	M.p.	Wt., mg.	M.p.
1	4	55	41–44	25	292–293
2	8	71	40–43	32	292–293.5
3	16	106	45–46	47	295–296
4	32	149	43–45	75	294–296

Phytadienes in smoke from different tobacco types and blends. The smoke condensate from 3600 cigarettes of each of the following tobacco types was examined for phytadienes: (a) Turkish tobacco, (b) flue-cured tobacco, and (c) burley tobacco. The smoke condensate was collected and processed as described previously.[4,5] Infrared absorption studies indicated that the phytadiene mixture was present in the smoke from each tobacco type as evidenced by absorption at 6.07, 6.27, 7.25, 7.32, 10.1, 10.35, 11.0, 11.1, and 11.2μ. No attempt was made to show conclusively that the total series of phytadienes was present in each instance. However, neophytadiene was isolated from the smoke of cigarettes fabricated from Turkish, from flue-cured, and from burley tobacco.

Essentially the same phytadiene mixture was indicated by infrared absorption studies of four blends of cased commercial tobaccos different from the blend employed in our study.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

Methyl and Dimethylhydrazones

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The ultraviolet and infrared absorption characteristics and the tumor growth retardation properties of a series of methyl- and dimethyl-hydrazones have been studied. Characteristic absorption is observed at 232–234 mμ and 1604–1637 cm.$^{-1}$ for the methylamino or dimethylamino substituted carbon-nitrogen double bond. Several aromatic types show a weak but non-reproducible tumor growth retardation in Sarcoma 180 tests.

Previous tumor-growth retardation studies[1] with dimethylhydrazones suggested the desirability of further study of this structural type. Several additional dimethylhydrazones and a series of methylhydrazones have been prepared and characterized. The data describing these compounds and some related acyl derivatives are given in Tables I–IV.

TABLE I

DIMETHYLHYDRAZONES

Carbonyl Compound[a]	Yield, %	B.P. or[b] M.P., °C.	N_D[c]	*N* Analysis Calcd.	*N* Analysis Found	Ultraviolet Absorption[d]	
1-Butanal	54	134	1.4390/24	24.53	24.73	240/3.86	
2-Ethylbutanal	69	83/45	1.4442/24	19.70	19.91	241/3.86	
Citronellal	83	65/0.1	1.4695/24	14.27	14.35	242/3.72	
1-Allylcyclohexane-C	60	73/0.8	1.4883/26	14.42	14.41	239/3.82	
2-Ethyl-1-hexanal	87	62/0.5	1.4473/26	16.45	16.42	239/4.01	
2-Ethyl-1-hexenal	62	100/27	1.4482/23	16.65	16.65	241/3.86	
3-Ethoxypropanal	50	109/24	1.4470/24	19.43	19.48	242/3.87	
2-Phenyl-1-propanal	79	67/0.1	1.5308/24	15.90	16.10	245/4.03	269/3.43
4-Methyl-2-pentanone	55	68/42	1.4320/23	19.70	19.91		269/2.95
Cyclopentanone	48	86/61	1.4690/24	22.20	22.05		
3-Methylcyclohexanone	58	89/24	1.4673/26	18.16	18.43		272/2.85
3-Chloro B	83	132/3	1.6118/23	15.34	15.26	232/3.98	303/4.35
3,4,5-Trimethoxy B	88	m75W		11.75	11.57	227/4.27	303/4.38
9-Anthraldehyde	91	m85MW		11.24	11.01	219/4.33	255/4.96
Dehydroacetic acid	52	m84BP		13.33	13.19	233/4.16	310/4.15
Isatin	42	m124EW		22.20	22.20	260/3.81[e]	281/3.95
Indole-3-C	96	m102TP		22.44	22.45	273/4.18[f]	296/4.25

[a] C = carboxaldehyde; B = benzaldehyde. [b] M, melting point; recrystallized from W, water; M, methanol; B, benzene; P, petroleum ether; E, ethanol; T, toluene. [c] Reading/°C. [d] Absorption maximum mμ/log extinction coefficient. [e] Shoulder 228–255 mμ/log e 3.73. [f] Maximum at 234 mμ/log e 4.3.

The infrared absorption characteristics for this group of methyl and dimethylhydrazones provide further data for evaluation of the group assignments for such structural types previously discussed.[1] The absorption associated with the carbon-nitrogen double bond stretching vibration occurs in the saturated aliphatic types as a weak band in the 1604–12 cm.$^{-1}$ region for the aldehyde dimethylhydrazones; in the 1634–47 cm.$^{-1}$ region for the ketone dimethylhydrazones; in the 1625–1631 cm.$^{-1}$ region for the aldehyde methylhydrazones; and in the 1624–1652 cm.$^{-1}$ region for the ketone methylhydrazones. The relative positions of the bands for the aldehyde and ketone derivatives are in the reverse order to that observed for the carbonyl compounds themselves. The cyclopentanone methylhydrazone absorbs at 1652 cm.$^{-1}$ and the dimethylhydrazone at 1647 cm.$^{-1}$ the highest values observed. This represents a shift similar in magnitude and direction to that observed for the carbonyl group stretching absorption in cyclopentanone itself. The presence of either aliphatic or aromatic carbon-carbon double bonds complicates this assignment. The absorption bands in the 865 cm.$^{-1}$ and 1000 cm.$^{-1}$ regions, useful in previous correlations, do not appear with any regularity in the methylhydrazones. The absorption in the 1100–1140 cm.$^{-1}$ region does, however, appear in the methylhydrazones and, as noted previously, also in the dimethylhydrazones. Often with the methylhydrazones this is the only band in this region of the spectrum and is nearly always strong and well-defined. This can be tentatively assigned to a carbon-nitrogen stretching vibration in the methylhydrazone unit. It has been suggested before that aliphatic amines show absorption bands,

(1) R. H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, **22**, 204 (1957).

TABLE II

METHYLHYDRAZONES

Carbonyl Compound[a]	Yield, %	B.P. or[b] M.P., °C.	N_D[c]	N Analysis Calcd.	N Analysis Found	Ultraviolet Absorption[d]	
1-Hexanal	68	110/20	1.4544/24	21.86	22.10	235/3.62	
1-Heptanal	55	62/0.2	1.4555/26	19.70	19.71	233/3.72	
1-Octanal	33	112/20	1.4551/24	17.93	17.72	236/3.61	
1-Nonanal	50	72/0.3	1.4574/26	16.45	16.53	235/3.84	
1-Decanal	58	90/0.2	1.4593/23	15.20	15.01	233/3.76	
Citral	66	86/0.2	1.5210/27	15.54	15.50	270/3.95	
Cyclopentanone	70	87/26	1.4936/24	24.98	25.28	269/3.00	
Cyclohexanone	78	117/50	1.4998/24	22.20	22.44	234/3.72	
3-Methylcyclohexanone	49	99/20	1.4906/25	19.98	20.05	235/3.74	
Benzaldehyde	91	81/0.8	1.6140/24	20.88	20.98	217/4.23	283/4.34
3-Chloro B	34	92/0.3	1.6245/25	16.61	16.62	228/3.9	293/4.39
2-Methoxy B	50	130/0.6	1.6115/24	17.06	17.07	232/3.17	314/4.13
2-Ethoxy B	70	118/1.8	1.5918/25	15.72	15.91	225/3.98	312/4.08[g]
2-Hydroxy B	28	m46MW		18.65	18.80	220/4.07	308/4.05[h]
2-Hydroxy-5-nitro B	92	m148EW		21.55	21.51		289/4.14
2,4-Dihydroxy B	65	m148TP		16.86	17.09		306/4.22[i]
3-Nitro B	75	m67MW		23.45	23.36		295/4.29
9-Anthraldehyde	90	m100EW		11.97	11.76	218/4.37	255/5.04
Isatin	83	m179EW		23.98	24.01	239/3.9	335/4.19[j]
Pyridine-3-C	94	107/0.2[e]		31.09	31.09	229/3.55	293/4.07
6-Methylpyridine-2-C	80	95/1	1.6020/25	28.17	28.17		308/4.51
Thiophene-2-C	87	150/18	1.6489/24	19.98	20.22		306/4.44

[a,b,c,d] See footnotes a–d, Table I. [e] M.p. 35°. [f] Additional maximum: 281/3.95. [g] 280/4.04. [h] 281/4.13. [i] 289/4.24. [j] 252/3.07 and 278/4.19.

TABLE III

1,2-DIACYL DERIVATIVES OF METHYLHYDRAZINE

Acyl Group	Yield, %	M.P., °C.	Solvent[a]	N Analysis Calcd.	N Analysis Found
Cinnamoyl	76	170	MW	9.15	9.33
2-Furoyl	78	88	W	11.96	11.83
2-Methoxybenzoyl	69	134	TP	8.92	9.20
4-Methoxybenzoyl	80	90	MW	8.92	8.79
1-Napthoyl	78	185	TP	7.91	7.74
3-Nitrobenzoyl	76	164	EW	16.28	16.24
Phenoxyacetyl	83	138	MW	8.92	8.86

[a] See footnote b, Table I.

TABLE IV

1-METHYL-1-ACYLHYDRAZONES

Compound	Yield, %	M.P., °C.	Solvent[a]	N Analysis Calcd.	N Analysis Found
3-Chlorobenzaldehyde, 1-methyl-1-phenoxyacetylhydrazone	63	140	TP	9.25	9.22
3-Methoxybenzaldehyde, 1-methyl-1-phenoxyacetylhydrazone	93	109	EW	9.39	9.52
3-Nitrobenzaldehyde, 1-benzenesulfonyl-1-methylhydrazone	67	125	MW	13.16	12.94
Citronellal, 1-methyl-1-phenoxyacetylhydrazone	56	201	MW	13.59	13.52
Isatin, 1-methyl-1-phenoxyacetylhydrazone	35	137	E	8.85	8.92

[a] See footnote b, Table I.

although of low intensity, in the 1220–1020 cm.$^{-1}$ region assignable to this vibration. The variability is presumably eliminated in this series of structurally related derivatives. The absorption bands in the 860–920 cm.$^{-1}$ region show little regularity and it is not possible to state with certainty that a band in this region can be assigned to the aldehyde carbon-hydrogen[2] or the nitrogen-nitrogen stretching frequency.[3] Within the narrow range of 870–910 cm.$^{-1}$ there are a few aldehyde derivatives which show no absorption and a few ketone derivatives which do. The long chain aldehyde methylhydrazones show very weak, if any, absorption. Both the methyl- and dimethylhydrazones with-

(2) N. B. Colthup, *J. Opt. Soc. Amer.*, 40, 397 (1950).

(3) D. W. Scott, G. D. Oliver, M. E. Gross, W. N. Hubbard, and H. M. Huffman, *J. Am. Chem. Soc.*, 71, 2293 (1949).

out exception, show an absorption band at 1475±5 cm.$^{-1}$ attributable to the carbon-hydrogen deformation modes of the methyl groups. The strong methyl group absorption near 2850 cm.$^{-1}$ obscures the carbon-hydrogen stretching absorption, if any, often found in the aldehyde at 2720 cm.$^{-1}$

The ultraviolet absorption data for a series of the methyl and dimethylhydrazones is recorded in Table I and II. The statement is often found in discussions of the characteristic ultraviolet chromophores that the isolated, unconjugated carbon-nitrogen double bond has no absorption maximum in the ultraviolet range above 220 mμ. Our data show that the saturated aliphatic dimethylhydrazones have a characteristic absorption maximum of moderate intensity (log ε, 3.7–4.0) at 239–242 mμ. The saturated aliphatic aldehyde monomethylhydrazones have a similar maximum at 232–6 mμ (log ε, 3.6–3.8). Conjugated unsaturation shifts this to 270 mμ (log ε 3.95) in the citral derivative. Absorption in this series must be attributed to the bathochromic effect of the methyl or dimethyl amino group attached to the carbon-nitrogen double bond as the chromophore. The benzaldehyde derivatives absorb at 283 mμ (log ε, 4.34) and 217 mμ (log ε, 423). Substituted aromatic types show two or three maxima between 233 and 310 mμ. The principal maxima at 280–315 mμ (log ε, 4.05–4.39) is attributable to the hydrazone chromophore shifted approximately 60 mμ on conjugation with the aromatic ring. The reports that the eneamine from acetone and methylamine has an absorption maximum at 230 mμ,[4] suggest that other similar types may absorb in the ultraviolet range above 220 mμ. The corresponding oximes, in which the methylamino- or dimethylamino-group of the hydrazines is replaced by hydroxyl, absorb at significantly lower wave lengths with maxima at approximately 190 mμ for saturated aldehyde oximes and 229.5 mμ (log ε, 2.28) for α,β-unsaturated aldehyde oximes.[5]

Preliminary screening data[6] have shown the following tumor growth retardation effects for compounds described in this report: 2,3-dimethoxybenzaldehyde dimethylhydrazone ±(250), −(125); pyridine-3-carboxaldehyde methylhydrazone ?, ±(125), −(30); 2,4-dihydroxybenzaldehyde methylhydrazone ±, −(250), —, −(125); indole-3-carboxaldehyde dimethylhydrazone —, −(500), ±, −(250), −(125). The values in parentheses are the dose levels in mg./kg. in tests at different levels. The significance of the ± rating has been stated elsewhere.[6] These results do not establish either strong or consistent activity.

During the course of this study several diacyl derivatives of methylhydrazine were prepared. Physical properties and analytical data for these are given in Table III. These were obtained using the acyl chloride under reaction conditions which indicate a 1,2-diacyl structure. Apparently, the only previously known[7,8] derivatives of this type are the dibenzoyl and diacetyl compounds which have also been assigned the 1,2-diacyl structure. The structural assignment is based on the observation[7,8] that the monobenzoyl derivative of methylhydrazine gives a hydrazone derivative with benzaldehyde. This indicates that the first acylation occurs at the more basic methylated nitrogen to leave an amino group to form the hydrazone or react with the second acyl halide to give the 1,2-diacyl structure. The reaction of methylhydrazine with esters is known to give the 1-methyl-2-acyl structure.[9] Several acylated derivatives of the *N*-methyl-hydrazones are described in Table IV.

EXPERIMENTAL[10]

The aldehydes, ketones, and dimethyl- and methylhydrazines were commercial materials. The dimethylhydrazones were prepared as described previously.[1] Typical preparations for methylhydrazones and the acyl derivatives are given in detail. Data for all of the hydrazones are given in Table I and II. The methylhydrazones were acylated readily to give solid derivatives. Data for several of these are given in Table III and IV. The liquid hydrazones are colorless and remain so if stored under nitrogen. They become colored on exposure to air.

The methylhydrazone of benzaldehyde has previously been reported[11] as a solid, m.p. 179°, with analytical data which were not in good agreement with calculated values, and as a liquid N_D 1.6053/21.5°, with analysis only for a derivative.[12] The product we have obtained, from the reaction in methanol, is a liquid, N_D 1.6140/24°, and has physical, analytical, and spectroscopic properties in accord with the assigned structure. The reaction of methylhydrazine with 2,4-dichlorobenzaldehyde gave a variety of products. At least four different products were obtained depending on reaction time, solvent, and concentrations. The usual product, obtained in 23% yield, was a yellow, crystalline solid, m.p. 217–218° which gave a nitrogen analysis (8.37, 8.41%) in agreement with the theory (8.21%) for the 1-methyl-1-(3′-chloro-4′-formylphenyl)hydrazone of 2,4-dichlorobenzaldehyde. The methylhydrazone of β-ethoxypropanal was very unstable and darkened in a few hours even when placed under nitrogen. Two layers were present after several days. A sample was sealed under nitrogen immediately following distillation and gave a nitrogen analysis 0.66% below theory. It apparently was undergoing decomposition prior to the analysis. The methylhydrazone of veratraldehyde (m.p. 103–105°) decomposes to an oil

(4) F. A. Miller in H. Gilman, "Organic Chemistry—An Advanced Treatise," J. Wiley and Sons, New York, 1953, Vol. III, p. 166.

(5) L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, **1943**, 565.

(6) C. C. Stock, F. S. Philips, Alice E. Moore, Sonja M. Buckley, D. A. Clarke, R. K. Barclay, and K. Sugiura, Cancer Research Suppl. No. 1, p. 91 (1953); Suppl. No. 2, p. 179 (1955). The authors are indebted to Drs. C. C. Stock, Ralph K. Barclay, and D. A. Clarke, Sloan-Kettering Institute, for conducting these tests.

(7) A. Michaelis and E. Hadanck, *Ber.*, **41**, 3285 (1908).

(8) R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 2463 (1956).

(9) R. L. Hinman and D. Fulton, *J. Am. Chem. Soc.*, **80**, 1895 (1958).

(10) Analyses by Micro Tech Laboratories, Skokie, Illinois.

(11) C. Harries and T. Haga, *Ber.*, **31**, 62 (1898).

(12) D. Todd, *J. Am. Chem. Soc.*, **71**, 1353 (1949).

on standing a few hours. The methylhydrazone of indole-3-carboxaldehyde was obtained in large colorless crystals from ethanol, but turned pink after a few hours. Chromatography removed the color, but it returned rapidly. The methylhydrazone of 2-hydroxy-1-naphthaldehyde (m.p. 70–73° crude) decomposed upon attempted recrystallization and could not be obtained pure. Most of the pure aliphatic methyl and dimethylhydrazones were tested with acidic ethanolic 2,4-dinitrophenylhydrazine reagent and gave immediate precipitation of the corresponding 2,4-dinitrophenylhydrazone.

Pyridine-3-carboxaldehyde methylhydrazone. Nine grams (0.085 mole) of the aldehyde were cooled in a dry-ice acetone bath during the addition of 4.0 g. (0.087 mol.) of methylhydrazine. The reaction mixture was heated on a water bath for one hour and fractionated to give 8.4 g., 73.9%, of product, b.p. 107°/0.2 mm. The distillate solidified in the receiver.

Cyclohexanone methylhydrazone Nine and eight tenths grams (0.1 mol.) of cyclohexanone were cooled in a dry-ice acetone bath as 4.6 grams (0.1 mol.) of methylhydrazine were added dropwise. The mixture was heated to reflux for 0.5 hr., 25 ml. of water were added and the product extracted with 100 ml. of ether. The ether extracts were dried over magnesium sulfate, the ether removed, and the residue fractionated to give 9.8 g., 77.7%, of the product, b.p. 117°/50 mm. Unless ether-extracted from an aqueous solution, the product foams uncontrollably on distillation.

1-Methyl-2-phenoxyacetylhydrazine. A mixture of 6.8 g. (0.0377 mole) of ethyl phenoxyacetate and 3 g. (0.0653 mol.) of methylhydrazine was allowed to stand at room temperature 24 hr. The crystals which formed were collected and recrystallized twice from toluene–petroleum ether to give 5.1 g. 75.2%, of the product, m.p. 86–89°. This compound is recovered unchanged after attempted reaction with 3-nitrobenzaldehyde or 5-nitrosalicylaldehyde establishing the 1,2-structure.

Anal. Calcd. for $C_9H_{12}O_2N_2$: N, 15.55. Found: N, 15.57.

1-Methyl-1,2-di(1-naphthoyl)-hydrazine. A solution of 4 g. (0.021 mol.) of 1-naphthoyl chloride in 50 ml. of benzene was cooled to approximately 10° prior to the dropwise addition of 1 g. (0.217 mol.) of methylhydrazine. The solvent was then removed and the residue recrystallized from toluene-petroleum ether to give 2.9 g., 78%, of the product, m.p. 185°.

Isatin, 1-methyl-1-phenoxyacetylhydrazone. To 1.75 g. (0.01 mol.) of isatin methylhydrazone in 25 ml. of benzene was added dropwise 1.7 g. of phenoxyacetyl chloride. This mixture was heated at 60° on a water bath for 15 min. and evaporated to dryness. After being washed with 10% sodium bicarbonate and water, the red residue was recrystallized from methanol-water to give 1.74 g., 56.3%, of the product, m.p. 201–202°.

N-Phenoxyacetyl citronellal methylhydrazone. To 3.0 g. (0.0165 mol.) of citronellal methylhydrazone dissolved in 15 ml. of toluene was added 3.0 g. (0.0176 mol.) of phenoxyacetyl chloride. Evaporation of the solvent and recrystallization of the residue from ethanol gave 1.8 g., 34.6%, of the product, m.p. 137–139°.

The infrared absorption data were obtained using chloroform or carbon tetrachloride solutions or potassium bromide pellets and a Baird double beam recording spectrophotometer. The ultraviolet absorption data were obtained using a Beckman DK-2 recording ultraviolet spectrophotometer using methanol (Baker, purified) as solvent.

Acknowledgment. The authors wish to acknowledge partial support of this research through grant C-2457 from the National Cancer Institute of the National Institutes of Health and to the Research Corporation and the Brown-Forman Company for grants for the purchase of the infrared spectrophotometer.

LOUISVILLE, KY.

[CONTRIBUTION FROM THE LABORATORIES OF LEPETIT S.P.A.]

5,5-Disubstituted Dihydro-1,3-oxazine-2,4-diones. Research on Compounds Active on Central Nervous System. XII[1a]

EMILIO TESTA, LUIGI FONTANELLA, GIANFRANCO CRISTIANI, AND GIANGUALBERTO GALLO[1b]

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A number of 5,5-dialkyl-, alkyl- aryl-, alkyl-cycloalkyl-, and polymethylene-, dihydro-1,3-oxazine-2,4-diones (I)[1c] have been synthesized by treating the suitable α,α-disubstituted β-hydroxypropionic acids (V) with sodium cyanate and hydrochloric acid to give α,α-disubstituted β-carbamyloxypropionic acids (VI); the latter are cyclized to I by treatment with thionyl chloride and pyridine. From compounds I the corresponding 3-methyl derivatives (XI) have been obtained as well as some dihydro-1,3-oxazine-2,4-dithiones (XII) which by oxydation with hydrogen peroxide yield the original oxazine-2,4-diones (I). Some examples of the ring opening of compounds I by alkaline hydrolysis and by reduction with $LiAlH_4$ present evidence for the assigned structure I. The 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones and some derivatives thereof show promising activity on central nervous system (CNS).

As a part of our studies on CNS-acting substances we have synthesized a number of 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones (I) which represent a class of compounds[1d] of potentially great pharmacological interest. Actually, oxazinediones I are structurally related to some heterocyclic rings, whose basic features are common to a number of clinically useful hypnotic, narcotic, sedative, and anticonvulsant agents; namely barbiturates, glutarimides, and oxazolidinediones. Furthermore,

(1) (a) E. Testa, L. Fontanella, and G. F. Cristiani, *Ann.*, 626, 114 (1959).

(1) (b) Physical chemical department of Lepetit S.p.A.

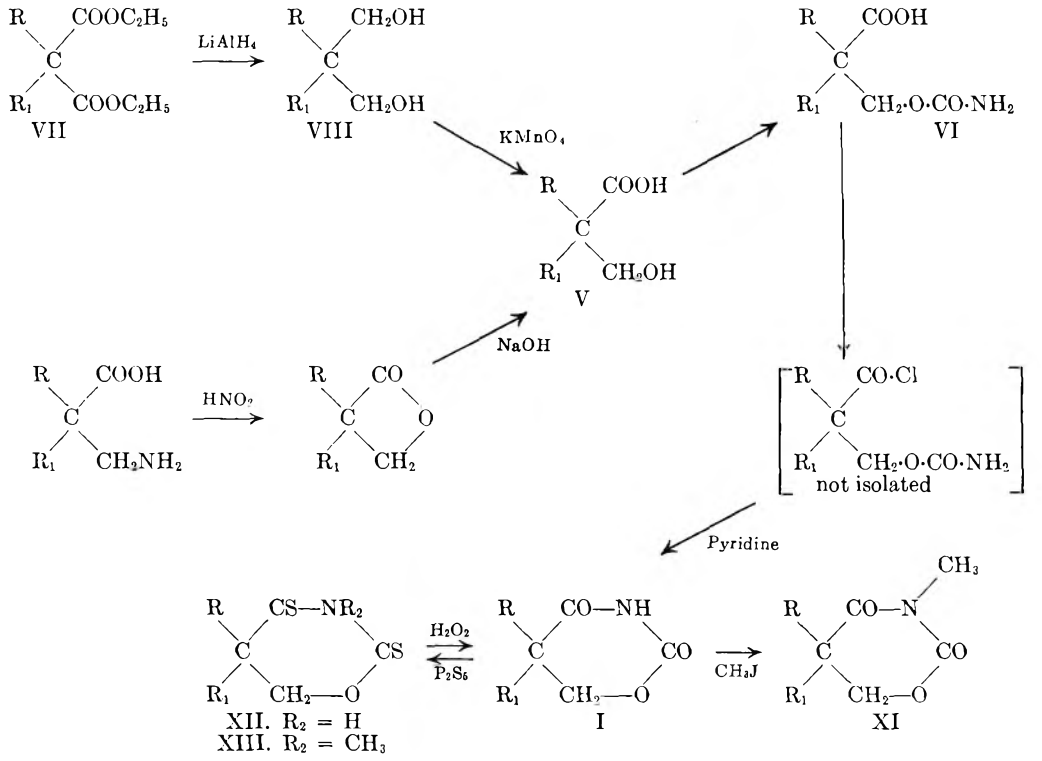
(1) (c) It is to note that the described new heterocyclic compounds may also be named tetrahydro-1,3-oxazine-2,4-diones.

(1) (d) Recently R. S. Safir and R. J. Lopresti briefly described various 5,6-substituted dihydro-1,3-oxazine-2,4-diones (U. S. Patent 2,797,217) with possible sedative action on CNS.

oxazinediones I are cyclic carbamates and may be related to meprobamate and its derivatives.

A member of this series, 5-ethyl-5-phenyldihydro-1,3-oxazine-2,4-dione has been described by R. Fusco and one of us[2] and has also been prepared in its optically active forms. In a preliminary pharmacological screening the expected sedative action of Ii has been confirmed[3] and the promising results obtained prompted us to carry on further work on this subject.

Oxazinediones I have been synthesized according to the following scheme:



Most of the key intermediate α,α-disubstituted hydroxypropionic acids (V) have been already described by us[2,4] and by others.[5-10] We have prepared V by two different ways. The compounds V lacking an aryl substituent in the α-position have been obtained by reduction with lithium aluminum hydride of α,α-disubstituted diethyl malonate (VII) followed by partial oxidation with alkaline $KMnO_4$ of the resulting 2,2-disubstituted 1,3-propanediols (VIII) (Method A). This procedure which was first described by J. B. Ludwig[7] for the preparation of the α,α-diethyl derivative, has been now slightly modified and found to be of general value for the synthesis of α,α-dialkyl-β-hydroxypropionic acids. When compounds VIII bear in the α- position a phenyl substituent the above method produces the desired V only in trace amounts together with large quantities of starting products VIII and of substances obtained by further oxidative degradation of the molecule. Therefore we obtained the α-alkyl tropic acids by diazotizing the suitable α,α-disubstituted-β-aminopropionic acid (IX) and hydrolyzing the resulting α,α-disubstituted β-lactone (X) according to a general method previously described by us[4] (Method B).

Because of difficulties occurring in the preparation of some of the amino acids IX through an acid hydrolysis of their ethyl esters[4,11] (Method C-1), we have found it more convenient in some instances to perform the hydrolysis on the α,α-disubstituted 2-azetidinones (Method C-2) obtained by cyclizing the ethyl esters of aminoacids.[12,13] This two-stage hydrolysis affords smoothly and in high yields some compounds IX. From the α,α-disubstituted β-hydroxypropionic acids (V) by reaction with finely powdered sodium cyanate and hydrogen chloride in dry chloroform medium the corre-

(2) R. Fusco and E. Testa, *Farmaco Ed. sci.*, **12**, 823 (1957).

(3) G. Maffii, Personal communication.

(4) E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Ann.*, **619**, 47 (1958).

(5) J. L. Green and H. J. Hagenmeyer, *J. Am. Chem. Soc.*, **77**, 3016 (1955).

(6) V. Neustädter, *Ann.*, **351**, 304 (1907).

(7) B. J. Ludwig, *J. Am. Chem. Soc.*, **72**, 5329 (1950).

(8) A. Vecchi and G. Melone, *J. Org. Chem.*, **24**, 109 (1959).

(9) H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 3001 (1950).

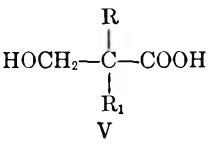
(10) F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, **74**, 1730 (1952).

(11) E. Testa, L. Fontanella, and F. Fava, *Farmaco Ed sci.*, **13**, 152 (1958).

(12) E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Ann.*, **614**, 158 (1958).

(13) E. Testa and L. Fontanella, *Ann.*, **625**, 95 (1959).

TABLE I



V

Compound	R	R_1	Procedure	Yield, % Theory	M.P.	Formula
Va[5]	CH_3—	CH_3—	A	67	125–127	$C_5H_{10}O_3$
Vb[6]	CH_3—	C_2H_5—	A	73	B.p. 110°/1 mm.	$C_6H_{12}O_3$
Vc	CH_3	n-C_3H_7—	A	66	49–51 B.p. 107°/0.5 mm.	$C_7H_{14}O_3$[a]
Vd[7]	C_2H_5—	C_2H_5—	A	55	60–62	$C_7H_{14}O_3$
Ve	n-C_3H_7—	n-C_3H_7—	A	51	93–95 B.p. 100–115°/0.6 mm.	$C_9H_{18}O_3$[b]
Vf	n-C_4H_9—	n-C_4H_9—	A	30	B.p. 150–155°/0.8 mm.	$C_{11}H_{22}O_3$[c]
Vg	—CH_2—CH_2—CH_2—CH_2—		A	82	94–95 (from benzene)	$C_7H_{12}O_3$[d]
Vh[8]	C_6H_5—	CH_3—	B(C-1)	52	86–87	$C_{10}H_{12}O_3$
Vi[2,4]	C_6H_5—	C_2H_5—	B(C-1)	74	96–98	$C_{11}H_{14}O_3$
Vl[4]	C_6H_5	n-C_3H_7—	B(C-1)	68.7	104–107	$C_{12}H_{16}O_3$
Vm[4]	C_6H_5—	iso-C_3H_7—	B(C-2)	50	138–140	$C_{12}H_{16}O_3$[e]
Vn[4]	C_6H_5—	n-C_4H_9—	B(C-2)	57	91–92	$C_{13}H_{18}O_3$[f]
Vo[4,10]	C_6H_5—	C_6H_5·CH_2—	B(C-2)	44	191–193	$C_{16}H_{16}O_3$
Vp[10]	C_6H_5—	C_6H_{11}—[g]	B(C-2)	43.5	146–148	$C_{15}H_{20}O_3$
Vq[4,9]	C_6H_5—	C_6H_5—	B(C-1)	12	161–163	$C_{15}H_{14}O_3$

[a] *Anal.* Calcd.: C, 57.51; H, 9.65. Found: C, 57.59; H, 9.88. [b] *Anal.* Calcd.: C, 62.03; H, 10.41. Found: C, 61.91; H, 10.18. [c] *Anal.* Calcd.: C, 65.28; H, 10.81. Found: C, 65.15; H, 10.75. [d] *Anal.* Calcd.: C, 58.31; H, 8.39. Found: C, 58.11; H, 8.64. [e] The intermediate β-amino-α-phenyl-α-iso-propyl-propionic acid previously described[4] as crude product has now been purified. M.p. 275–277°C. (from water). *Anal.* Calcd. for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.44. [f] *Anal.* Calcd.: C, 70.23; H, 8.16. Found: C, 70.15; H, 8.15. [g] Cyclohexyl.

sponding carbamates (VI) have been obtained.[2] VI are white stable crystalline compounds, partially soluble in $CHCl_3$ and ether, and may be recrystallized from water. Surprisingly, the reaction does not occur when potassium cyanate is substituted for sodium cyanate. The α,α-disubstituted-β-carbamyloxypropionic acids (VI) have been treated with thionyl chloride to give the corresponding acid chlorides, which were not isolated but cyclized to the desired dihydro-oxazinediones by means of anhydrous pyridine. In some cases the ring closure of compounds VI has been accomplished in one stage by directly adding thionyl chloride to the carbamate in anhydrous pyridine.

The 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones (I) are stable compounds which may be distilled in vacuo whithout decomposition. Except the 5-phenyl-5-*n*-butyl-derivative, which is a liquid, they are white crystalline substances.

Oxazinediones I have been transformed into the corresponding *N*-methyl-derivatives (XI) by the method of Davies *et al.*[14] successfully applied previously by one of us[15] to the *N*-alkylation of some five-membered heterocyclic compounds. The 3,5,5-trisubstituted dihydro-1,3-oxazine-2,4-diones (XI) are colorless oils and may be distilled *in vacuo* without decomposition; many of the products crystallize on standing.

Some of the 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones and the 3-methyl-5-phenyl-5-ethyl-dihydro-1,3-oxazine-2,4-dione (XIII) have been converted into the corresponding dihydro-1,3-oxazine-2,4-dithiones (XII and XIII) by reaction with phosphorus pentasulfide. Compounds XII and XIII on treatment with alkaline hydrogen peroxide yield the original oxazinediones. Attempts to introduce only one sulfur atom in the molecule of compounds I or XI were unsuccessful.

We have performed some degradative studies on 5-phenyl-5-ethyl-dihydro-1,3-oxazine-2,4-dione (Ia) to reach the evidence that no rearrangement occurred during the cyclization process and the structure assigned to compounds I is correct. In fact, by alkaline hydrolysis of the above derivative α-ethyltropic acid has been obtained[2]; by $LiAlH_4$ reduction of the same product 2-methylamino-2-phenyl-1-butanol (XIV) has been isolated.

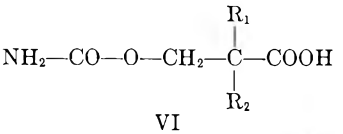
Compound XIV has also been synthesized from ethyl β-amino-α-ethyl-α-phenylpropionate[16] (XV) by reaction with ethyl chloroformate followed by reduction with $LiAlH_4$ of ethyl β-carbethoxyamino-α-ethyl-α-phenylpropionate (XIV). Compound XIV obtained by synthesis is identical with the $LiAlH_4$ reduction product of 5-phenyl-5-ethyl-dihydro-1,3-oxazine-2,4-dione.

(14) J. S. H. Davies and W. H. Hook, *J. Chem. Soc.*, 30 (1950).

(15) E. Testa and R. Ettorre, *Arch. Pharm.*, **290**, 532 (1957).

(16) E. Testa, L. Fontanella, and G. F. Cristiani, *Farmaco Ed. sci.*, **13**, 437 (1958).

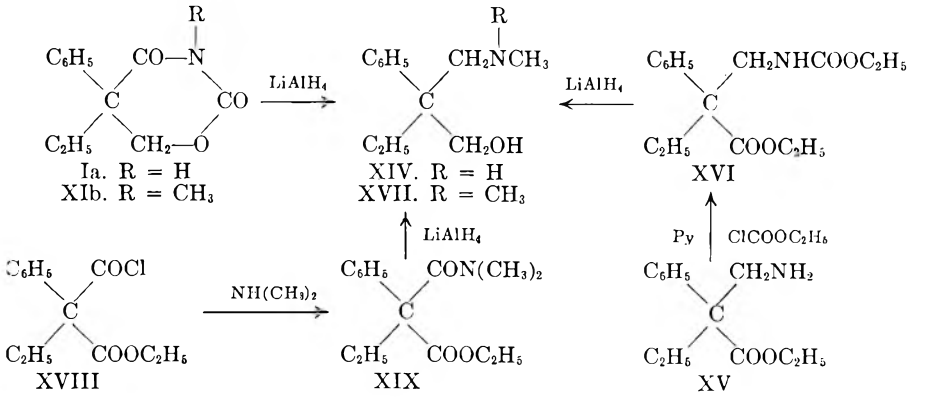
TABLE II



VI

Compound	R_1	R_2	Yield	M.P.	Formula (M.W.)	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIa	CH_3—	CH_3—	27.5	173–174	$C_6H_{11}NO_4$ (161.15)	44.71	6.88	8.69	44.85	7.10	8.65
VIb	CH_3—	C_2H_5—	62	139–140	$C_7H_{13}NO_4$ (175.18)	47.99	7.48	7.99	48.01	7.52	8.08
VIc	CH_3—	n-C_3H_7—	37	138–140	$C_8H_{15}NO_4$ (189.21)	50.78	7.99	7.40	50.85	8.10	7.68
VId	C_2H_5—	C_2H_5—	49.5	128–129	$C_8H_{15}NO_4$ (189.21)	50.78	7.99	7.40	50.88	7.88	7.45
VIe	n-C_3H_7—	n-C_3H_7—	83	184–185	$C_{10}H_{19}NO_4$ (217.26)	55.28	8.81	6.45	55.48	9.01	6.47
VIf	n-C_4H_9—	n-C_4H_9—	69.2	169–171	$C_{12}H_{23}NO_4$ (245.31)	58.75	9.45	5.71	58.63	9.41	5.34
VIg	—CH_2—CH_2—	CH_2—CH_2—	27	186–187	$C_8H_{13}NO_4$ (187.18)	51.32	7.00	7.48	51.71	6.99	7.32
VIh	C_6H_5—	CH_3—	70	136–137	$C_{11}H_{13}NO_4$ (223.22)	59.18	5.87	6.27	59.15	6.12	6.30
VIi	C_6H_5—	C_6H_5—	85.8	169–170	$C_{12}H_{15}NO_4$ (237.25)	60.74	6.37	5.90	60.55	6.29	5.94
VIl	C_6H_5—	n-C_3H_7	79.5	157–159	$C_{13}H_{17}NO_4$ (251.27)	62.13	6.82	5.57	62.15	6.81	5.79
VIm	C_6H_5	iso-C_3H_7—	91	146–148	$C_{13}H_{17}NO_4$ (251.27)	62.13	6.82	5.57	61.98	6.77	5.53
VIn	C_6H_5	n-C_4H_9—	91	167–168	$C_{14}H_{19}NO_4$ (265.3)	63.37	7.22	5.28	63.28	7.25	5.58
VIo	C_6H_5	C_6H_5·CH_2—	96	178–180	$C_{17}H_{17}NO_4$ (299.31)	68.21	5.72	4.68	68.25	5.75	4.66
VIp	C_6H_5—	C_6H_{11}—[a]	85	175–180	$C_{16}H_{21}NO_4$ (291.34)	65.95	7.26	4.81	65.75	7.23	4.75
VIq	C_6H_5—	C_6H_5—	97	193–195	$C_{16}H_{15}NO_4$ (285.19)	67.38	5.30	4.91	67.31	5.47	4.90

[a] Cyclohexyl.

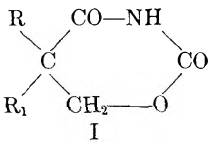


Therefore Ia behaves toward $LiAlH_4$ reduction like a carbamate[17]; in analogous manner its *N*-methyl derivative (XIb) yields by reduction with $LiAlH_4$ 2-dimethylaminomethyl-2-phenyl-1-butanol (XVII). The structure of XVII was also confirmed by synthesis[18] from α-carbethoxy-α-phenylbutyryl chloride (XVIII),[2] first converted to XIX, which was then reduced to XVII with $LiAlH_4$. To provide further evidence of the structure assigned to the series of compounds V, VI, I, and XI and to better

(17) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publ. Inc., New York, 1956, p. 636.

(18) We are indebted to Dr. A. Vecchi for the communication of the method of synthesis and for providing us with a sample of compound XVII.

TABLE III



I

Compound	R_1	R_2	Procedure	Yield, % Theory	M.P.	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	CH_3—	CH_3—	A	45.7	124–127[a]	$C_6H_9NO_3$ (143.14)	50.34	6.33	9.78	50.24	6.20	9.89
Ib	CH_3—	C_2H_5—	B	42.7	83–85[a]	$C_7H_{11}NO_3$ (157.16)	53.49	7.05	8.91	53.38	7.02	8.88
Ic	CH_3—	n-C_3H_7—	A	41	60–62 (from CH_3—COO-C_2H_5 and petroleum ether)	$C_8H_{13}NO_3$ (171.19)	56.12	7.65	8.18	56.30	7.49	8.13
Id	C_2H_5—	C_2H_5—	A	56.2	97–98[b]	$C_8H_{13}NO_3$ (171.19)	56.12	7.65	8.18	56.08	7.58	8.85
Ie	n-C_3H_7—	n-C_3H_7—	A	71.6	95–97[a]	$C_{10}H_{17}NO_3$ (199.24)	60.27	8.60	7.03	60.41	8.62	6.91
If	n-C_4H_9—	n-C_4H_9—	B	81	92–95[a]	$C_{12}H_{21}NO_3$ (227.29)	59.24	9.31	6.16	59.12	9.25	6.14
Ig	—CH_2—CH_2—	CH_2—CH_2—	A	35.7	105 (from benzene-petroleum-ether)	$C_8H_{11}NO_3$ (169.17)	56.79	6.55	8.28	56.81	6.75	8.27
Ih	C_6H_5—	CH_3—	A	78	134–135[c]	$C_{11}H_{11}NO_3$ (205.20)	64.38	5.40	6.83	64.31	5.25	6.83
Ii	C_6H_5—	C_2H_5—	A	69.3	130–132[c]	$C_{12}H_{13}NO_3$ (219.23)	65.74	5.97	6.38	65.95	5.92	6.44
Il	C_6H_5—	n-C_3H_7—	B	65	118–120[c]	$C_{13}H_{15}NO_3$ (233.26)	66.93	6.48	6.03	66.75	6.58	6.03
Im	C_6H_5—	iso-C_3H_7—	B	66	174–175[c]	$C_{13}H_{15}NO_3$ (233.26)	66.93	6.48	6.03	66.91	6.55	6.15
In	C_6H_5—	n-C_4H_9	B	80.5	B.p. 175–180/0.2 mm.	$C_{14}H_{17}NO_3$ (247.28)	67.99	6.92	5.66	67.81	5.75	5.70
Io	C_6H_5—	C_6H_5·CH_2—	B	53.2	141–145[c]	$C_{17}H_{15}NO_3$ (281.30)	72.58	5.37	4.98	72.29	5.35	5.02
Ip	C_6H_5—	C_6H_{11}—[d]	B	50.5	164–165[c]	$C_{16}H_{19}NO_3$ (273.32)	70.30	7.01	5.12	70.18	7.08	5.11
Iq	C_6H_5—	C_6H_5—	A	91	220–221[e]	$C_{16}H_{13}NO_3$ (267.27)	71.89	4.90	5.24	72.01	4.97	5.09

[a] From ligroin. [b] From ethyl ether. [c] From abs. ethanol. [d] Cyclohexyl. [e] From ethyl acetate.

characterize the new described products, their infrared spectra between 4000 and 650 cm.$^{-1}$ have been measured. The infrared spectra have been carried out using a Perkin Elmer Model 12 C single-beam spectrophotometer fitted with a NaCl prism. The substances were examined as such when liquid and in a Nujol mull when solid. For each basic structure the most typical bands have been selected and assigned as arising from the vibration of chemical bonds of the structures.[20] The upper and lower limits of the frequencies of the members of the four series and the types of the vibrations from which the bands take origin are given in Table VI.

A preliminary pharmacological screening have shown that oxazinediones I and their *N*-methyl-derivatives XI possess the foreseen sedative action; furthermore some member of this series show an interesting exciting activity on CNS. The results of the pharmacological investigation on the described 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones and derivatives will be published elsewhere by G. Maffii *et al.*

EXPERIMENTAL

α,α-DISUBSTITUTED β-HYDROXYPROPIONIC ACIDS (V)

(A) *α,α-Dialkyl and α,α-tetramethylene derivatives* (Va–g). 2,2-Dimethyl-1,3-propandiol.[21] In a 3-l. flask fitted with a mechanical stirrer, a thermometer, a reflux condenser, and a dropping funnel, 42.5 g. of lithium aluminum hydride and 400 ml. of anhydrous ether were placed. Into the stirred suspension, 150 g. of diethyl α,α-dimethylmalonate[22] were slowly dropped. After the addition was over, the mixture

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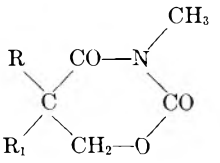
(20) L. K. Bellamy, *The Infra-red Spectra of Complex Molecules*, Methuen and Co., London (1958).

(21) R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **70**, 946 (1948).

(22) L. C. Thorne, *J. Chem. Soc.*, **39**, 543 (1881).

TABLE IV

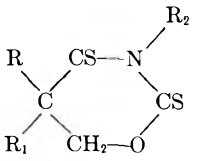


XI

Compound	R	R_1	Yield, % Theory	B.P./Mm. (a–g) M.P. (h–q)	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIa	CH_3—	CH_3—	71.5	75–80/0.4[a]	$C_7H_{11}NO_3$ (157.16)	53.49	7.05	8.91	53.31	7.25	9.22
XIb	CH_3—	C_2H_5—	82.5	125–130/1[a]	$C_8H_{13}NO_3$ (171.19)	56.12	7.65	8.18	55.98	7.41	8.25
XIc	CH_3—	n-C_3H_7—	53.5	106–107/0.6	$C_9H_{15}NO_3$ (185.22)	58.36	8.16	7.56	58.42	8.29	7.60
XId	C_2H_5—	C_2H_5—	33.1	90–95/0.4[a]	$C_9H_{15}NO_3$ (185.22)	58.36	8.16	7.56	58.28	8.15	7.76
XIe	n-C_3H_7—	n-C_3H_7—	68.5	85–90/0.4[a]	$C_{11}H_{19}NO_3$ (213.27)	61.94	8.98	6.57	62.08	9.15	6.65
XIf	n-C_4H_9—	n-C_4H_9—	71.5	115–125/0.6[a]	$C_{13}H_{23}NO_3$ (241.32)	64.70	9.61	5.80	64.71	9.58	5.90
XIg	—CH_2—CH_2—CH_2—CH_2—		70.5	140–145/0.5 M.p. 43–44°	$C_9H_{13}NO_3$ (183.20)	59.00	7.15	7.65	58.90	7.25	7.65
XIh	C_6H_5—	CH_3—	68	90–92[b]	$C_{12}H_{13}NO_3$ (219.23)	65.74	5.97	6.39	65.58	5.91	6.37
XIi	C_6H_5—	C_2H_5—	47	73–76	$C_{13}H_{15}NO_3$ (233.26)	66.93	6.48	6.00	66.87	6.45	6.07
XIl	C_6H_5—	n-C_3H_7—	73.5	65–66[b]	$C_{14}H_{17}NO_3$ (247.28)	67.99	6.93	5.66	67.85	6.85	5.62
XIm	C_6H_5—	iso-C_3H_7—	94	94–96[b]	$C_{14}H_{17}NO_3$ (247.28)	67.99	6.93	5.66	68.05	6.80	5.51
XIn	C_6H_5—	n-C_4H_9—	79.5	82–84[b]	$C_{15}H_{19}NO_3$ (261.31)	68.94	7.24	5.36	68.75	7.08	5.07
XIo	C_6H_5—	C_6H_5-CH_2—	84	102–105[b]	$C_{18}H_{17}NO_3$ (295.32)	73.20	5.80	4.74	73.18	5.75	4.59
XIp	C_6H_5—	C_6H_{11}[c]	74.3	133–135[b]	$C_{17}H_{21}NO_3$ (286.34)	71.30	7.39	4.89	71.25	7.43	4.72
XIq	C_6H_5—	C_6H_5—	70.5	123–124[b]	$C_{17}H_{16}NO_3$ (281.38)	72.56	5.37	4.98	72.51	5.35	4.92

[a] Kügelrohr technique of Ronco and Cows.[19] [b] From ligroin. [c] Cyclohexyl.

TABLE V



Compound	R	R_1	R_2	Reaction Time, Min.	Yield, % Theory	Formula	M.P.	Analysis Calcd. N	Calcd. S	Found N	Found S
XIIc	CH_3—	n-C_3H_7—	H	75	60.5	$C_8H_{13}NOS_2$ (203.31)	51–55[a]	6.89	31.54	6.85	31.25
XIId	C_2H_5—	C_2H_5—	H	75	57	$C_8H_{13}NOS_2$ (203.34)	80–82[a]	6.89	31.54	6.76	31.30
XIIe	n-C_3H_7—	n-C_3H_7—	H	75	51.5	$C_{10}H_{17}NOS_2$ (231.31)	74–76[a]	6.05	27.71	6.36	27.50
XIIh	C_6H_5—	CH_3—	H	45	24.5	$C_{11}H_{11}NOS_2$ (237.33)	136–138[b]	5.93	27.02	5.87	26.87
XIIIi	C_6H_5—	C_2H_5—	CH_3	360	64	$C_{13}H_{15}NOS_2$ (265.38)	83–84[c]	5.28	24.16	5.32	24.55

[a] From ligroin. [b] From benzene. [c] From methanol.

TABLE VI

Structure	Frequency Range, Cm.$^{-1}$	Vibration
V	3470–3300	Alcoholic OH stretching
	2740–2520	Acid OH stretching
	1710–1690	C=O stretching
	1268–1200	Acid C—O stretching
	1055–1022	Alcoholic C—O stretching
VI	3470–3400	Asymmetric NH stretching
	3370–3280	Symmetric NH stretching
	2770–2550	Acid OH stretching
	1735–1700	C=O stretching
	1610–1585	NH_2 deformation (Amide II)
	1270–1220	Acid C—O stretching
	1100–1054	Alcoholic C—O stretching
I	3230–3090	NH stretching
	1765–1740	(2) C=O stretching
	1735–1700	(4) C=O stretching
	1248–1210	(2-1) C—O stretching
	1090–1042	(6-1) C—O stretching
XI	1760–1740	(2) C=O stretching
	1700–1690	(4) C=O stretching
	1305–1278	(2-1) C—O stretching
	1102–1060	(6-1) C—O stretching

was refluxed 3 hr., cooled to 0°, and cautiously treated with 220 ml. of water, 110 ml. of 10% hydrochloric acid and eventually with 110 ml. of concentrated hydrochloric acid. The mixture was extracted with ethyl ether and the mother liquor concentrated in vacuo to a volume of about 200 ml. The residue was first extracted once with the ether previously used, then twice with fresh ethyl ether. The combined extracts were dried over Na_2SO_4 and evaporated to a small volume: 46 g. of diol were obtained, which were slurried in benzene, filtered, dried, and employed for the following steps without further purification. M.p. 125–127°.

α,α-Dimethyl-*β*-hydroxypropionic acid[5] (Va). To a stirred suspension of 46 g. of crude 2,2-dimethyl-1,3-propanediol in 11.5 g. of sodium hydroxide and 560 ml. of water, 114 g. of potassium permanganate in 1870 ml. of water were slowly added at room temperature. After completion of the addition (about 2 hr.), the mixture was warmed on water bath until the pink color of the solution faded, then it was cooled, filtered, and washed with water. The filtrate was acidified with hydrochloric acid to *p*H 4.0–5.0 and evaporated to dryness *in vacuo*. The residue was treated with ethyl ether, dried, and concentrated; an oil was obtained, which crystallized on rubbing. The crude product (43 g.) was dissolved in 100 ml. of hot benzene, filtered and the filtrate treated with petroleum ether. After standing some hours in the refrigerator, 35 g. (67%) of crystals were obtained. The m.p. (123–125°) remained unchanged after a further recrystallization from ligroin.

Anal. Calcd. for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.89; H, 8.56.

α,α-Disubstituted β-hydroxypropionic acids (Vb–g) were prepared exactly as described for Va; their properties and yields are reported in Table I.

(B) *α-Substituted α-phenyl-β-hydroxypropionic acids* (*α-substituted tropic acids*) (Vh–q). *α*-Substituted *β*-amino-*α*-phenyl-*β*-hydroxypropionic acids:

C-1. *By hydrolysis of the ethyl esters.* The ethyl esters were hydrolyzed with concentrated hydrochloric acid according to the procedure described in previous papers.[4,11]

C-2. *By cyclization to 3-substituted 3-phenyl-2-azetidinones followed by acid hydrolysis.* Example for *β*-amino-*α*-benzyl-*α*-phenylpropionic acid (Vo).

Sixty g. of 3-benzyl-3-phenyl-2-azetidinone (obtained in 84.8% yield from ethyl *β*-amino-*α*-benzyl-*α*-phenylpropionate, as formerly described by us[13]) were refluxed for 4 hr. with 1200 ml. of concentrated hydrochloric acid, then allowed to stand overnight. The precipitate was collected by filtration: 74.5 g. (100% of the theoretical amount) were obtained consisting of the hydrochloride of *β*-amino-*α*-benzyl-*α*-phenylpropionic acid melting at 263–265° (dec.).

Anal. Calcd. for $C_{16}H_{17}NO_2.HCl$: Cl, 12.15. Found: Cl, 12.38.

The above hydrochloride (70 g.) was suspended in 200 ml. of water, treated with the molar equivalent of 50% sodium hydroxide solution and stirred 2 hr. The mixture was filtered, washed with cold water, and dried on water bath: yield 58 g., m.p. 278–280°.

Cyclization of α-substituted β-amino-α-phenylpropionic acid (IX) *to α,α-disubstituted β-lactones* (X) *followed by alkaline hydrolysis to α-substituted β-hydroxy-α-phenylpropionic acids* (Vh–q). This process was carried out exactly as formerly described by us and co-workers[4]; the properties and yields of the acids Vh–q are reported in Table I.

The previously unreported intermediate *α-cyclohexyl-α-phenyl-β-propiolactone* (Xp) was synthesized from *β*-amino-*α*-cyclohexyl-*α*-phenylpropionic acid[11] exactly as formerly described.[4] M.p. 97–98° (from light petroleum).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.06; H, 8.05.

α,α-DISUBSTITUTED *β*-CARBAMYLOXYPROPIONIC ACIDS (VIa–q)

α,α-Dimethyl-β-carbamyloxypropionic acid (VIa). A solution of 24 g. of *α,α*-dimethyl-*β*-hydroxypropionic acid (Va) in 400 ml. anhydrous chloroform was cooled to 0° and treated with 18 g. of finely powdered sodium cyanate. A stream of hydrogen chloride was bubbled into the mixture

while stirring at 0° to +5°; after 2 hr. 9 g. of sodium cyanate were added and hydrogen chloride was bubbled into the mixture for an additional 2 hr. under stirring at 0° to +5°. The gas stream was then discontinued, the mixture allowed to stand 30 min. at 0°, and filtered. The collected precipitate was dried on water bath, suspended in 350 ml. of water, and extracted with about 750 ml. of ether. The ether extract was evaporated *in vacuo* and the residue recrystallized from water: yield 9 g. of crystals melting at 173–174°. By evaporating to dryness the chloroform mother liquors, treating the residue with 25 ml. of ether, filtering, and evaporating, 4 g. of starting compound (Va) were obtained.

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 45.01; H, 7.15; N, 8.86.

The α,α-disubstituted β-carbamyloxypropionic acids VIb–q, prepared as described for VIa, are collected in Table II.

It is to note that in most cases (VIb,d,e,h,m–p) the compound VI will go into the chloroform solution and may be isolated after evaporation of the solvent through a crystallization from water.

5,5-DISUBSTITUTED DIHYDRO-1,3-OXAZINE-2,4-DIONES (Ia–q)

Method (A). *5,5-Dimethyldihydro-1,3-oxazine-2,4-dione* (Ia). Eight g. of β-carbamyloxy-α,α-dimethylpropionic acid (VIa) and 18 ml. of thionyl chloride were refluxed for 1 hr. The excess of thionyl chloride was then removed in vacuo, the residue treated with benzene and evaporated to dryness; this last procedure was repeated three times. To the oil obtained, 10 ml. of pyridine were added while cooling in an ice salt bath to avoid the temperature's rising above 35–40°. The mixture was allowed to stand at room temperature for 1 hr., poured into 25 g. ice and made acidic to Congo red with hydrochloric acid. The resinous precipitate was extracted with six 50-ml. portions of ether; the ether extract was washed with water, dried over Na_2SO_4, and concentrated to a final volume of 50 ml. After one night at 0° the precipitate was collected by suction: yield 2.8 g., m.p. 125–127°. By evaporating to dryness the mother liquor and crystallizing the residue from ligroin an additional crop of 0.3 g. was obtained.

Anal. Calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.33; N, 9.78. Found: C, 50.24; H, 6.20; N, 9.99.

By the same method compound Ic–e,g–i,q, were prepared; their properties and yields are reported in Table III.

Method (B).[22a] *5-Ethyl-5-methyldihydro-1,3-oxazine-2,4-dione* (Ib). To 11.7 g. of α-ethyl-α-methyl-β-carbamyloxypropionic acid (VIb) in 55.8 ml. of thionyl chloride 5.7 ml. of anhydrous pyridine were added in about 10 min. while stirring and avoiding the temperature's exceeding 25°. The crystalline VIb slowly dissolved and the solution became clear and yellow. After completion of the addition the mixture was refluxed 1 hr., then evaporated to dryness *in vacuo*. The residue was treated twice with benzene and the solvent removed *in vacuo* each time. The residue was slurried in water, extracted with ethyl ether, the ether extract washed with water, sodium carbonate, and finally water, and dried over Na_2SO_4. By concentrating to a small volume 6.1 g. of Ib crystallized on standing. The product was recrystallized from ligroin: yield 4.5 g.; m.p. 83–85°.

Anal. Calcd. for $C_7H_{11}NO_3$: N, 8.91. Found: N, 8.88.

Compounds Ib,f,l–p were prepared by the same method; their properties and yields are reported in Table III.

5,5-DISUBSTITUTED 3-METHYLDIHYDRO-1,3-OXAZINE-2,4-DIONES (XIa–q)

3-Methyl-5-ethyl-5-phenyldihydro-1,3-oxazine-2,4-diones (XIi). A mixture of 5 g. of Ii, 2.55 g. of anhydrous potassium carbonate, 5 g. of methyl iodide in 50 ml. of anhydrous acetone was refluxed 10 hr., then cooled, and filtered. The filtrate was evaporated to dryness *in vacuo* and the oily residue was crystallized from 150 ml. of light petroleum. After one night in the refrigerator the precipitate was collected and dried. Yield 2.5 g., m.p. 73–76°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 6.00. Found: N, 6.07.

The other compounds (XI) were prepared with the same method; in most cases they were oily and were purified by distillation with the technique of Ronco *et al.*[19] The properties and yields of XIa–q are recorded in Table IV.

5,5-DISUBSTITUTED DIHYDRO-1,3-OXAZINE-2,4-DITHIONES (XIIc–e,h, AND XIIIi)

5-Methyl-5-n-propyldihydro-1,3-oxazine-2,4-dithiones (XIIc). Five g. of 5-methyl-5-*n*-propyldihydro-1,3-oxazine-2,4-dione (Ic) were thoroughly mixed with 10 g. of powdered phosphorus pentasulfide and the mixture was heated on an oil bath at 165–170° for 75 min. After cooling the reaction mixture was slurried with ether, filtered, and the operation repeated until the ether was colorless. The collected ether filtrates were treated with charcoal, filtered, and the solvent was removed *in vacuo*. The oily residue was crystallized from ligroin (30 ml.): yield 3.6 g., m.p. 51–55°.

Anal. Calcd. for $C_8H_{13}NOS_2$: N, 6.89; S, 31.54. Found: N, 6.85; S, 31.25.

By this method compound XIId, e, and h and compound XIIIi were prepared; their properties and yields are reported in Table V.

OXIDATION OF 5,5-DISUBSTITUTED DIHYDRO-1,3-OXAZINE-2,4-DITHIONES (XII AND XIII) TO THE CORRESPONDING 1,4-DIONES (I AND XI)

5-Methyl-5-n-propyldihydro-1,3-oxazine-2,4-dithiones (XIIc). To a suspension of 600 mg. of 5-methyl-5-*n*-propyldihydro-1,3-oxazine-2,4-dithione (XIIc) in 15 ml. of water, enough 10% sodium hydroxide solution was added to obtain a clear solution, then 30 ml. of 30% hydrogen peroxide were added while cooling in an ice water bath. The mixture was heated on a water bath until discolorated, then cooled, acidified with 10% hydrochloric acid, and extracted with ethyl ether. The ether extract was dried and evaporated *in vacuo:* 350 mg. of a crystalline compound melting at 59–60° were obtained. The mixed melting point with an authentic sample of Ic was not depressed. The infrared spectra of samples of Ic obtained both by cyclization of VIc and by oxidation of the corresponding dithio compound XIIc were identical.

ALKALINE HYDROLYSIS OF 5-ETHYL-5-PHENYLDIHYDRO-1,3-OXAZINE-2,4-DIONE (Ii)

A mixture of 800 mg. of Ii, 10 ml. of ethanol, and 10 ml. of 50% potassium hydroxide were refluxed for 0.5 hr., the solvent was removed *in vacuo* and the residue extracted with ethyl ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl ether. The latter ether extract was evaporated to dryness and the oily residue was crystallized from benzene-light petroleum. The crystalline product melting at 93–94° was identical (mixed melting point, infrared spectra) with an authentic sample of α-ethyl-α-phenyl-β-hydroxypropionic acid (α-ethyltropic acid)[2] (Vi).

2-METHYLAMINOMETHYL-2-PHENYL-1-BUTANOL (XIV) BY REDUCTION OF 5-ETHYL-5-PHENYLDIHYDRO-1,3-OXAZINE-2,4-DIONES (Ii) WITH $LiAlH_4$

In a 1-l. flask fitted with a dropping funnel, a thermometer, and a reflux condenser, 4 g. of $LiAlH_4$ in 100 ml. of anhydrous ethyl ether were placed. To the suspension 7.5 g. of Xi in 300 ml. of anhydrous ethyl ether were slowly added while cooling. When the addition was over (about 1 hr.), the mix-

(22a) We are indebted to Dr. A. Passera for the development of this procedure.

ture was refluxed for 4 hr., then allowed to stand overnight. A 10% ammonium chloride solution (100 ml.) was cautiously added, then the mixture was filtered. The solid residue was slurried with ethyl ether and filtered. The collected ether filtrates were washed with water and concentrated to a final volume of 250 ml. and extracted with two 50-ml. portions of 10% hydrochloric acid. The acidic extract was made alkaline with a saturated solution of sodium carbonate and extracted with ethyl ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue distilled *in vacuo*. The fraction boiling at 102° with a pressure of 0.4 mm. was collected and crystallized on standing: yield 3.1 g., m.p. 41–42°.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.56; H, 9.91; N, 7.25. Found: C, 74.61; H, 9.95; N, 7.20.

The infrared spectrum was identical with an authentic sample of XIV prepared by another way as described below. The mixed melting points of samples of XIV obtained by the two different methods were not depressed.

2-METHYLAMINOMETHYL-2-PHENYL-1-BUTANOL (XIV) FROM ETHYL β-AMINO-α-ETHYL-α-PHENYLPROPIONATE (XV)

β-Carbethoxyamino-α-ethyl-α-phenylpropionic acid (XVI). In a flask fitted with a mechanical stirrer, a thermometer, and a dropping funnel, 20 g. of ethyl β-amino-α-ethyl-α-phenylpropionate[16] (XV) and 100 ml. of anhydrous pyridine were placed. The mixture was cooled to 0°, then 20 g. of ethyl chloroformate were slowly added while stirring. When the addition was complete, the mixture was further stirred at 0° for 1 hr. then cautiously poured into 350 ml. of ice water, acidified with 10% sulfuric acid and extracted with ethyl ether. The ether extract was washed with water until neutral, dried over sodium sulfate, filtered, and concentrated to dryness. The residue was distilled *in vacuo* collecting the fraction boiling at 150° with a pressure of 0.4 mm. Yield 23.1 g.

Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90; N, 4.77. Found: C, 65.76; H, 7.87; N, 5.00.

2-Methylaminomethyl-2-phenyl-1-butanol (XIV) To a suspension of 15 g. of $LiAlH_4$ in 150 ml. of anhydrous ethyl ether 10 g. of XVI in 100 ml. of anhydrous ethyl ether were slowly added at low temperature. The mixture was refluxed 3 hr., allowed to stand overnight, then cautiously treated with 100 ml. of 10% ammonium chloride. The mixture was filtered, treated with ethyl ether and the ether layer extracted with two 30 ml. portions of 10% hydrochloric acid. The ether layer was discarded; the acid extract was made alkaline with a saturated solution of sodium carbonate, then extracted three times with ether. The combined ether extracts were washed with water, dried over sodium sulfate, concentrated, and the residue was distilled with the technique of Ronco *et al.*[19] Yield 2.77 g. of XIV, b.p. 90° (air bath) with a pressure of 0.2 mm. The distilled product solidified on standing, m.p. 41–42.5°.

2-DIMETHYLAMINOMETHYL-2-PHENYL-1-BUTANOL (XVII) BY REDUCTION OF 3-METHYL-5-ETHYL-5-PHENYLDIHYDRO-1,3-OXAZINE-2,4-DIONE (XII)

Twenty g. of XIi were reduced with 10 g. of $LiAlH_4$ by the same method described above for the reduction of Ii: 12.55 g. of XVII were obtained, b.p. 95–96° with a pressure of 0.4 mm.; XVII solidified on standing, m.p. 68.5–69°.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.30; H, 10.00; N, 6.74.

The infrared spectrum was identical with an authentic sample of the product prepared by another way described hereunder.[18] The mixed melting point of samples of XVII obtained by the two different methods was not depressed.

2-DIMETHYLAMINOMETHYL-2-PHENYL-1-BUTANOL (XVII) FROM α-CARBETOXY-α-PHENYL BUTYRYL CHLORIDE (XVIII)[18]

N,N-Dimethyl-α-carbetoxy-α-phenylbutyramide (XIX). A 17.5% benzene solution of dimethylamine (100 ml.) was added to 30 g. of α-carbetoxy-α-phenylbutyryl chloride (XVIII).[2] After 15 min. the solution was treated with water, acidified with hydrochloric acid, and extracted with ethyl ether. The ether extract was evaporated to dryness and the residue crystallized from ligroin. Yield 28 g., m.p. 52–55°.

2-Dimethylaminomethyl-2-phenyl-1-butanol (XVII). Into a suspension of 17.4 g. of $LiAlH_4$ in 150 ml. of anhydrous ethyl ether a solution of 15 g. of XIX in 90 ml. of anhydrous ethyl ether was gradually dropped without exceeding 25–27°. The mixture was refluxed 1.5 hr. and poured cautiously after cooling into 2 volumes of cold water. The mixture was extracted with ethyl ether and the organic layer evaporated to dryness *in vacuo*. The residual oil was distilled *in vacuo* collecting the fraction boiling at 95–96° with 0.4 mm. Yield 9 g. of XVII. The product crystallized on standing, m.p. 68–69°.

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MILAN, ITALY

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF AYERST, MCKENNA & HARRISON LTD.]

New Analeptics: 1-(Diphenylmethyl)-2-methyl-2-thiopseudourea Analogs

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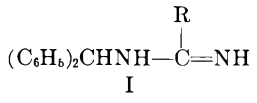
1-(Diphenylmethyl)pseudoureas, guanidines, and amidines have been prepared as potential analeptics. Analogs of 1-(diphenylmethyl)-2-methyl-2-thiopseudourea where the diphenylmethyl moiety has been replaced by other groupings are also reported. Certain of these compounds possess appreciably analeptic activity.

In a previous paper[1] some 1-(diphenylmethyl)-2-alkyl-2-thiopseudoureas were described and reported to possess analeptic activity. The first member of the series proved to be the most potent with respect to increasing the spontaneous activity of the rat. Since this compound is structurally quite unlike any of the known analeptic drugs, it was of interest to prepare certain of its analogs for pharma-

(1) S. O. Winthrop, S. Sybulski, G. Gavin, and G. A. Grant, *J. Am. Chem. Soc.*, **79**, 3496 (1957).

cological screening. The related cyclized 1-(diphenylmethyl)-2-thiopseudoureas were found to be central nervous system depressants.[2] The present paper deals for the most part with the synthesis of analogs represented by formula I where the methylthio grouping (R) of the pseudothiourea has been replaced with alkoxy, alkylamino, and alkyl groups, yielding pseudoureas, guanidines, and amidines, respectively.



I

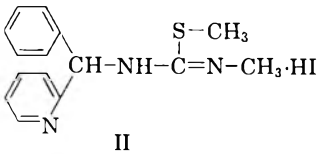
11-Diphenylmethylamine and cyanogen bromide gave (diphenylmethyl)cyanamide, which was then converted to a pseudourea with the appropriate alcohol and one equivalent of hydrogen chloride. In methanol the formation of the pseudourea was considered complete after 24 hr.[3] Progressively longer reaction times were required, however, for the higher alcohols. A modification of this procedure was found to give the desired pseudoureas more readily. (Diphenylmethyl)cyanamide and an excess of hydrogen chloride yielded a product which was assumed to be 1-chloro-*N*-(diphenylmethyl)-formamidine hydrochloride. This latter compound, when heated under reflux for 30 min. in the appropriate alcohol and allowed to stand at room temperature overnight, gave the pseudourea.

A direct displacement of the methylthio grouping by alkoxy was also considered as a possible method of synthesis. A reaction of this type was recently reported[4] wherein 2-(methylthio)-2-imidazoline on treatment with sodium alkoxides gave the desired 2-alkoxy-2-imidazolines. 1-(Diphenylmethyl)-2-methyl-2-thiopseudourea and sodium ethoxide were heated under reflux in ethanol. However, no pseudourea could be identified from the reaction mixture, the major product being (diphenylmethyl)-cyanamide.

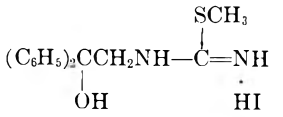
The pseudourea salts were stable, high melting, crystalline solids. They were generally considerably more water-soluble than the corresponding thiopseudoureas. The free bases were easily prepared, found to be stable, and could be used for the preparation of other salts.

The amidines and guanidines were prepared by standard procedures described in the chemical literature. 1,1-Diphenylmethylamine and an ester of an imidic acid, hydrochloride gave the former compounds, while an alkylamine hydrochloride and (diphenylmethyl)cyanamide produced the latter.

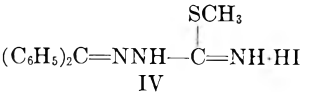
Analogs were also prepared wherein the diphenylmethyl moiety is replaced by other closely related groupings. The replacement of a benzene ring with a pyridine ring has on occasion resulted in enhancement of pharmacological activity. 2-(α-Aminobenzyl)pyridine was prepared by the zinc in acetic acid reduction of phenyl-2-pyridyl ketone, oxime. The fusion of the ammonium salt of thiocyanic acid with 2-(α-aminobenzyl)pyridine, dihydrochloride, proved to be unsatisfactory. The free base with the methyl ester of isothiocyanic acid readily gave 1-(α-2-pyridylbenzyl)-3-methyl-2-thiourea, which was converted with iodomethane to the thiopseudourea (II).



II



III



IV

1-(2,2-Diphenyl-2-hydroxyethyl)-2-thiourea, prepared by fusion of the appropriate amine hydrochloride with the ammonium salt of thiocyanic acid, on treatment with iodomethane gave the thiopseudourea (III). The thiosemicarbazone of benzophenone on methylation gave benzophenone 3-methyl-3-thioisosemicarbazone hydriodide (IV).

Pharmacological activity. The compounds were screened for their effect on the spontaneous activity of the rat by the method of Chappel and coworkers.[5] The pseudoureas (Table I) were found to have appreciable central stimulant activity but were more toxic than the corresponding thiopseudoureas. The amidines and guanidines were convulsants at high doses while the pyridine analog (II) retained the activity of the parent compound. The other compounds were devoid of significant pharmacological activity. The stimulant activity and acute toxicity for some of these compounds are compared with *dl*-amphetamine sulfate in Table II. Detailed results will be reported elsewhere.

EXPERIMENTAL[7]

(*Diphenylmethyl)cyanamide.* Cyanogen bromide (40 g., 0.38 mol.) dissolved in 250 ml. of ethyl acetate was added dropwise with stirring and cooling to 1,1-diphenylmethylamine (117 g., 0.75 mol.) in 750 ml. of ethyl acetate. When the addition was complete and the exothermic reaction had subsided, the reaction mixture was heated at reflux for an additional hour. The 1,1-diphenylmethylamine, hydro-

(2) S. O. Winthrop and G. Gavin, *Can. J. Chem.*, **36**, 879 (1958).

(3) R. H. McKee, *Am. Chem. J.*, **42**, 1 (1909).

(4) C. K. Cain, J. Kleis, and G. I. Poos, *J. Org. Chem.*, **22**, 1283 (1957).

(5) C. I. Chappel, G. A. Grant, S. Archibald, and R. Paquette, *J. Am. Pharm. Assn.*, **46**, 497 (1957).

(6) Handbook of Toxicology, Vol. 1, William S. Spector, W. B. Saunders Co., Philadelphia, Pa. (1956).

(7) All melting points are uncorrected.

TABLE I

PSEUDOUREAS, GUANIDINES, AND AMIDINES $(C_6H_5)_2CHNH-\underset{\displaystyle R}{\overset{\displaystyle |}{C}}=NH.HCl$

R	Yield, %	M.P.[h]	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
OCH_3[a,b,d]	67	124–125	$C_{15}H_{17}ClN_2O$					10.12	9.95	12.81	13.02
OCH_2CH_3[c,e]	78	130–131	$C_{16}H_{19}ClN_2O$					9.63	9.50	12.20	12.33
$OCH_2CH_2CH_3$[f]	55	125–126	$C_{17}H_{21}ClN_2O$					9.18	9.13	11.63	11.91
$OCH(CH_3)_2$[e]	79	136–138	$C_{17}H_{21}ClN_2O$					9.18	9.02	11.63	12.03
$NHCH_3$[e]	54	233–234	$C_{15}H_{18}ClN_3$	65.32	65.67	6.59	6.74			12.85	12.32
$NHCH_2CH_3$[e]	50	198–200	$C_{16}H_{20}ClN_3$	66.31	66.67	6.96	7.05	14.50	14.41	12.23	12.58
CH_3[g]	92	286–288	$C_{15}H_{17}ClN_2$	69.10	69.53	6.56	6.53	10.74	10.64	13.60	13.25
CH_2CH_3[g]	53	230–232	$C_{16}H_{19}ClN_2$					10.20	10.16	12.91	12.96

[a] Free base melted at 105–107°; Calcd. for $C_{15}H_{16}N_2O$: C, 74.85; H, 6.71; N, 11.64. Found: C, 75.04; H, 6.61; N, 11.86. [b] Other salts are described in the experimental. [c] Free base melted at 83–84°; calcd. for $C_{16}H_{18}N_2O$: N, 11.01. Found: N, 11.04. [d] Recrystallized from methanol ether. [e] Recrystallized from ethanol ether. [f] Recrystallized from acetone ether. [g] Recrystallized from ethanol. [h] The pseudoureas invariably melted with decomposition.

TABLE II

1-Diphenylmethyl Compounds	DIA_{50} S.C.,[a] Mg./Kg.	$L.D._{50}$ I.P.,[b] Mg./Kg.
2-Methylpseudourea, hydrochloride	13	50
2-Ethylpseudourea, hydrochloride	5	50
2-Methyl-2-thiopseudourea, hydriodide[c]	2.5	92
2-Ethyl-2-thiopseudourea, hydroiodide[c]	12	80
dl-Amphetamine, sulfate	2[d]	12[e]

[a]Subcutaneous dose increasing spontaneous activity of the rat by 50%. [b]Intraperitoneal dose in the mouse causing death in 50% of the animals. [c]See Reference 1. [d]Intraperitoneally. [e]Values as high as 100 mg./kg., have been reported in the literature.[6]

bromide, was filtered off and the filtrate evaporated *in vacuo*, leaving a solid residue. The crude product was purified by dissolving it in a solution of 500 ml. of ethanol and 2500 ml. of 0.5% aqueous sodium hydroxide, boiling the solution for a few minutes, filtering and finally neutralizing with acetic acid to precipitate the product, a white solid, 35 gm., 44%, m.p. 119–121°. One recrystallization from benzene-hexane raised the melting point to 121–122°.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.72; H, 5.82; N, 13.46. Found: C, 80.35; H, 5.78; N, 13.15.

1-Chloro-N-(diphenylmethyl)formamidine hydrochloride. (Diphenylmethyl)cyanamide (20.8 g., 0.1 mol.) was dissolved in 600 ml. of ether and hydrogen chloride gas was introduced in excess. The precipitated hydrochloride was filtered off to yield 26 g., 92%, m.p. 178–180° dec. One recrystallization from acetonitrile raised the melting point to 180–181° dec.

Anal. Calcd. for $C_{14}H_{14}Cl_2N_2$: N, 9.97; Cl, 25.25. Found: N, 10.23; Cl, 25.35.

1-(Diphenylmethyl)-2-methylpseudourea hydrochloride. 1-Chloro-*N*-(diphenylmethyl)formamidine hydrochloride (10 g.) was heated under reflux for 30 min. in 100 ml. of methanol and then allowed to stand at room temperature for 16 hr. The methanol was removed *in vacuo* and the oil residue was crystallized from acetone ether to yield 6.7 g., 69%, m.p. 124–125° dec. One recrystallization from methanol ether did not change the melting point (see Table I).

The hydrochloride (2.8 g., 0.01 mol.) was dissolved in 50 ml. of methanol containing 0.59 g. (0.011 mol.) of sodium methoxide. Enough ether was then added to completely precipitate the sodium chloride, which was removed by filtration. The filtrate was evaporated *in vacuo* to yield 2.0 g., 83% of the free base, 1-(diphenylmethyl)-2-methylpseudourea, m.p. 101–104°. Two recrystallizations from hexane raised the melting point to 105–107° (see Table I).

(Diphenylmethyl)-2-methylpseudourea salts. The following salts were prepared by the addition of the appropriate acid to an ether solution of (diphenylmethyl)-2-methylpseudourea: hydrobromide, m.p. 122–123° dec. Calcd. for $C_{15}H_{17}BrN_2O$: N, 8.72; Br, 24.88. Found: N, 8.69; Br, 25.46. Hydriodide, m.p. 117–118° dec. Calcd. for $C_{15}H_{17}IN_2O$: N, 7.62; I, 34.50. Found: N, 7.48; I, 34.42. Maleate, m.p. 157–158° dec. Calcd. for $C_{19}H_{29}N_2O_5$: N, 7.94. Found: N, 7.61.

1-(Diphenylmethyl)-2-propylpseudourea hydrochloride. (Diphenylmethyl)cyanamide (3.6 g., 0.017 mol.) was dissolved in 50 ml. of 1-propanol containing 0.63 g. (0.017 mol.) of hydrogen chloride. The reaction mixture was allowed to stand at room temperature for 1 week. It was then evaporated *in vacuo* and the oil residue was triturated with ether to yield 4.1 g., 79% of product, m.p. 115–119° dec. Two recrystallizations from acetone ether raised the melting point to 125–126° dec. (see Table I).

Reaction of sodium ethoxide with 1-(diphenylmethyl)-2-methyl-2-thiopseudourea, hydrochloride. 1-(Diphenylmethyl)-2-methyl-2-thiopseudourea hydrochloride,[1] (14.6 g., 0.05 mol.) was suspended in 250 ml. of absolute ethanol containing 2.3 g. (0.1 mol.) sodium. The solution was heated under reflux for 16 hr. and the sodium chloride filtered off. The ethanol was removed *in vacuo*, leaving a solid residue which was triturated with water and neutralized with acetic acid to yield 6 g. of (diphenylmethyl)cyanamide, 58%, m.p. 110–118°. One recrystallization from benzene-hexane gave 3.6 g., m.p. 116–118°, whose infrared spectrum was identical with that of (diphenylmethyl)cyanamide.

1-(Diphenylmethyl)-3-methylguanidine hydrochloride. (Diphenylmethyl)cyanamide (8.4 g., 0.04 mol.) and methylamine, hydrochloride (2.8 g., 0.04 mol.) were dissolved in 200 ml. amyl alcohol and heated under reflux for 4 hr. The amyl alcohol was removed *in vacuo* and the oily residue triturated with ether to yield 6.0 g., 54% of product, m.p. 208–211°. Two recrystallizations from ethanol-ether gave an analytically pure material with m.p. 233–234° (see Table I).

N-(Diphenylmethyl)acetamidine hydrochloride. 1,1-Diphenylmethylamine (20.2 g., 0.11 mol.) in 25 ml. of absolute ethanol was added dropwise with stirring to (12.4 g., 0.1 mol.) ethyl ester of acetimidic acid, hydrochloride[8] in 100 ml. of absolute ethanol. Stirring was continued for 3 hr. at room temperature. Enough ether was then added to completely precipitate the product, 24 g., 84%, m.p. 270–280° dec. Three recrystallizations from ethanol gave

(8) H. Gilman, *Org. Syntheses*, **Coll. Vol. I**, 5 (1943).

analytically pure material, m.p. 287–288° dec. (see Table I).

2-(α-Aminobenzyl)pyridine, dihydrochloride.[9] Phenyl-2-pyridyl ketone, oxime, 120 g., (0.06 mol.) was dissolved in 800 ml. of glacial acetic acid containing 30 ml. of water. The solution was brought to reflux and 210 g. (3 mol.) of zinc dust was added portionwise at a rate sufficient to maintain reflux. The addition was complete in 1 hr. and heating was continued for an additional hour. The reaction mixture was then filtered and the filtrate was made strongly alkaline, causing the product to separate. It was taken up in ether, dried over sodium sulfate and the ether was removed *in vacuo*. The oily residue was distilled to yield 69 g., 62%, of a pale yellow liquid, b.p. 159–165° at 3 mm., n_D^{20} 1.5961. On standing 1 day at room temperature it turned dark brown and emitted a strong odor of ammonia.

Anal. Calcd. for $C_{12}H_{12}N_2$: N, 15.22. Found: N, 14.38.

Because of its instability it was converted to a dihydrochloride salt, which was crystallized from ethanol ether, m.p. 242–244° dec.

Anal. Calcd. for $C_{12}H_{14}Cl_2N_2$: C, 56.10; H, 5.46; Cl, 27.55. Found: C, 56.46; H, 6.56; Cl, 27.44.

1-(α-2-Pyridylbenzyl)-3-methyl-2-thiourea. 2-(α-Aminobenzyl)pyridine, 5 g. (0.027 mol.); methyl ester of isothiocyanic acid, 2 g., (0.027 mol.), and 50 ml. of absolute ethanol were heated under reflux for 2 hr. Cooling and addition of ether caused 6 g., 86%, of product, m.p. 165–166° to precipitate. One recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{14}H_{15}N_3S$: C, 65.37; H, 5.87; N, 16.30. Found: C, 65.43; H, 5.66; N, 16.24.

1-(α-2-Pyridylbenzyl)-2,3-dimethyl-2-thiopseudourea, hydriodide. 1-(α-2-Pyridylbenzyl)-3-methyl-2-thiourea was converted into its hydriodide by treatment with hydriodic acid in an acetone solution. The hydriodide, 4.1 g., (0.011 mol.), iodimethane, 2.1 g. (0.015 mol.), and 50 ml. of ethanol were heated under reflux for 3 hr. On cooling and addition of ether, 2.7 g., 61%, of product, m.p. 178–180° dec., precipitated. Two recrystallizations from ethanol raised the melting point to 182–183°.

Anal. Calcd. for $C_{15}H_{18}IN_3S$: N, 10.52; S, 8.02. Found: N, 10.30; S, 7.80.

1-(2,2-Diphenyl-2-hydroxyethyl)-2-thiourea. The fusion was carried out in the usual manner in refluxing xylene.[1] α-(Aminoethyl)benzhydrol, hydrochloride,[10] 7.5 g. (0.03 mol.) and the ammonium salt of thiocyanic acid, 2.4 g. (0.03 mol.), gave 3.2 g., 42% of product, m.p. 185–187° dec. One recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_{15}H_{16}N_2OS$: C, 66.14; H, 5.92; N, 10.03; S, 11.77. Found: C, 65.72; H, 5.96; N, 10.63; S, 11.90.

1-(2,2-Diphenyl-2-hydroxyethyl)-2-methyl-2-thiopseudourea, hydriodide. The methylation was carried out in the usual manner with iodomethane.[1] 1-(2,2-Diphenyl-2-hydroxyethyl)-2-thiourea, 2.1 g. (0.008 mol.), gave 2.2 g., 69%, of the product, m.p. 150–151° dec. One recrystallization from isopropanol did not change the melting point.

Anal. Calcd. for $C_{16}H_{19}IN_2OS$: N, 6.77; S, 7.74; I, 30.63. Found: N, 6.68; S, 7.60; I, 30.97.

Benzophenone, 3-methyl-3-thioisosemicarbazone, hydriodide. The methylation procedure was identical to that used for the methylation of thioureas with iodomethane.[1] Benzophenone, thiosemicarbazone,[11] 2.6 g. (0.01 mol.), gave 3.7 g., 93%, of product, m.p. 192–194° dec. One recrystallization from isopropanol did not raise the melting point.

Anal. Calcd. for $C_{15}H_{16}IN_3S$: N, 10.58; S, 8.07; I, 31.94. Found: N, 10.59; S, 8.09; I, 31.96.

Acknowledgments. The authors wish to thank Dr. C. I. Chappel of our Laboratories for the pharmacological data, Mr. W. J. Turnbull for the analyses and Dr. Gilles Papineau-Couture and Mrs. J. Jachner for numerous infrared absorption spectra.

MONTREAL, CANADA

(9) 3-(α-Aminobenzyl)pyridine was prepared by La Forge in a similar manner, *J. Am. Chem. Soc.*, **50**, 2487 (1928).

(10) K. Thomas and F. Bettziecke, *Z. Physiol. Chem.*, **140**, 246 (1924).

(11) P. Chabrier and E. Cattelain, *Bull. soc. chim. France*, 48 (1950).

[CONTRIBUTION FROM THE SILICONES DIVISION, UNION CARBIDE CORPORATION]

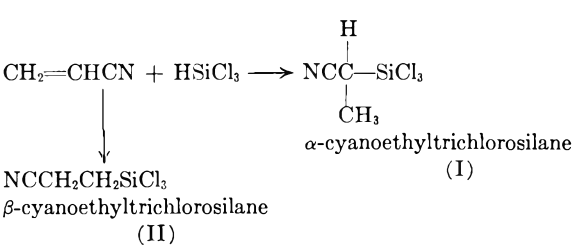
Preparation and Properties of β-Cyanoethyltrichlorosilane[1]

R. A. PIKE, J. E. McMAHON,[2] V. B. JEX,[2a] W. T. BLACK,[2b] AND D. L. BAILEY

Received June 19, 1959

Directive catalysts, organic derivatives of Group V A elements, are described for the addition of trichlorosilane to acrylonitrile, which produce only β-cyanoethyltrichlorosilane. The effect of the cyano group on the rate of hydrolysis of the chlorosilane and heat stability of the corresponding silicone polymer are discussed and the utilization of β-cyanoethyltrichlorosilane as a starting material for the preparation of β-carbethoxyethyl silanes and β-carboxyethyl silicones is illustrated.

Trichlorosilane can add to acrylonitrile with formation of two possible isomeric adducts:



(1) Presented at the 134th meeting of the American Chemical Society, Division of Organic Chemistry, at Chicago, Ill., Sept. 10, 1958.

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Under the conditions normally used for the addition of SiH compounds to olefins (*i.e.*, peroxide or platinum catalyzed), the reaction of trichlorosilane with acrylonitrile gives predominantly the α-isomer (I),[3,4] as well as polyacrylonitrile and other addition products. The α-isomer is hydrolytically unstable and of little synthetic value compared to the β-isomer (II).[5]

This paper reports the results of an investigation of new directive catalysts for the addition of trichlorosilane to acrylonitrile and some of the properties of the resulting β-cyanoethyltrichlorosilane (II).

It was discovered that tertiary phosphines, under conditions studied, appear to be the most effective catalysts for the addition with exclusive formation of the β-isomer (II). In general, organic compounds derived from Group V A elements were found to have some catalytic activity in the reaction. The relative effectiveness of representative catalysts is shown in Table I.

TABLE I

CATALYSTS FOR ADDITION OF $HSiCl_3$ TO ACRYLONITRILE[a]

Catalyst	Product (Wt. % Conversion)	Remarks[6]
None	42	α- adduct
$(n\text{-}C_4H_9)_3P$	55	β- adduct
$(C_6H_5)_2PCl$	47	β- adduct
$C_6H_5PCl_2$	39	β- adduct
$(C_6H_5)_3P$	56	β-isomer, no α
$(C_6H_5)_3N$	29.8	Mixture of α and β
Et_3N	30.7	β- adduct
$(C_6H_5)_3As$	25.8	Mainly α, some β
$(C_6H_5)_3Bi$	10.5	Mixture of α and β
$(C_6H_5)_3Sb$	Trace	Mixture of α and β

[a] 1:1 mole ratio reactants; 200°; 2 hr.; 2 wt. % catalyst, in 50-ml. stainless steel pressure vessel.

In addition to tertiary phosphines, tertiary amines, as previously reported,[3] are effective directive catalysts; the aliphatic amines gave only β-isomer, while the aryl amines gave a mixture of isomers. The tertiary arsines, bismuthines, and stibines are less effective and also gave mixtures. Variations in time, temperature, and catalyst concentration, on the addition reaction using triphenyl phosphine catalyst (Table II) showed that catalyst concentration and time of reaction over a small range has little effect on yield of product, whereas temperature affects the yield to a marked degree. This effect is partially due to the increase in polymer formation at the higher temperatures. This can be controlled to some extent by the addition of a polymerization inhibitor such as hydroquinone to the system.

TABLE II

EFFECT OF TEMPERATURE, TIME, AND CATALYST CONCENTRATION ON $HSiCl_3$:CH_2=CHCN REACTION USING $(C_6H_5)_3P$ CATALYST[a]

(Wt. %) Catalyst Concentration	Temp.	Time (Hr.)	% Conversion Product
2	200	2	56
2	150	2	65
1	150	2	67
0.5	150	2	59
1	100	0.5	71
1	100	2	70
1	75	2	13

[a] 1:1 mole ratio of reactants; 300 ml. stainless steel pressure vessel.

The other catalysts listed in Table I would undoubtedly exhibit the same temperature dependence as shown by triphenylphosphine, and several of them might be equally effective catalysts under optimum conditions.

To demonstrate the influence of the cyano group on the properties of chlorosilanes, measurements of the rate of hydrolysis of II were made and compared to the corresponding nonorganofunctional chlorosilanes. The relative rates of hydrolysis of the first chlorine as determined in dimethyl "Cellosolve"–water mixtures for several chlorosilanes[7] and β-cyanoethyl trichlorosilane, Table III, show the cyano group markedly increases the rate of hydrolysis, the relative increase being greater at higher temperatures.

TABLE III

RELATIVE RATES OF HYDROLYSIS OF FIRST CHLORINE IN ORGANOCHLOROSILANES IN DIMETHYL "CELLOSOLVE"[7]

$RSiCl_3$	At −51°	At −20°	At 0°
$C_2H_5SiCl_3$	1.0	1.0	1.0
CH_3SiCl_3	2.2	0.59	0.30
$C_6H_5SiCl_3$	4.1	2.0	1.4
$NCCH_2CH_2SiCl_3$	62.0	116.0	153.0

This increase may be due to the effect of the cyano group on the electropositive character of the silicon atom. By inductive effect (−I effect) the Si atom would become more positive and thus subject, to

(3) S. Nozakura and S. Konotsure, *Bull. Chem. Soc., Japan*, **29**, 326 (1956).

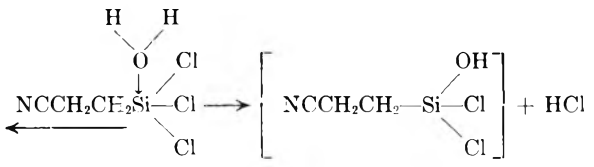
(4) L. Goodman, R. M. Silverstein, and A. Benitez, *J. Am. Chem. Soc.*, **79**, 3073 (1957).

(5) S. Nozakura and S. Konotsure, *Bull. Chem. Soc. Japan*, **29**, 322 (1956).

(6) Positive identification of α- and β- adducts of acrylonitrile and chlorosilane can be made on the basis of characteristic infrared absorption bands at 6.86μ (CH deformation) and 11.5μ in the spectrum of the α- adduct, and at 6.97μ (CH deformation) and 11.0μ in the spectrum of the β- adduct. Also the spectrum of the α- adducts shows a characteristic peak at 3.48μ which can be ascribed to the tertiary C—H stretching; this band does not appear in the β- adduct spectrum.

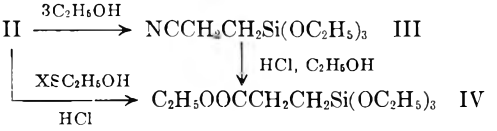
(7) L. H. Shaffer and E. M. Flanigen, *J. Phys. Chem.*, **61**, 1591, 1595 (1957).

a greater extent than in alkyl silanes, to nucleophilic attack by water.[8]

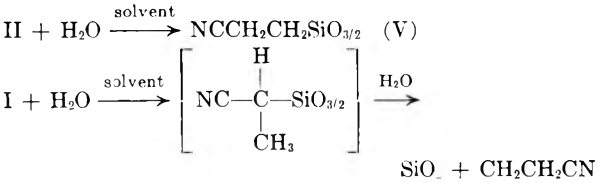


The β-cyanoethyl group attached to silicon undergoes the normal reactions of an aliphatic cyano compound. The silicon portion of the molecule may or may not enter into the reaction, depending upon the conditions employed. The synthesis of other silane monomers clearly demonstrates this versatility.

β-Cyanoethyltriethoxy silane[3] (III), a water-white, high boiling liquid, was obtained by addition of a stoichiometric amount of ethanol to the chlorosilane (II). The cyano group was converted to the ethyl ester by further reaction with ethanol, using an acid catalyst to give β-carbethoxyethyltriethoxy silane (IV). The ester (IV) can be prepared in one step by reaction of β-cyanoethyltrichlorosilane with excess alcohol, the hydrogen chloride liberated during the esterification being used as the acid catalyst.



Since the importance of an organofunctional silane depends to a great extent upon the ease of preparation and stability of the silicone polymer which can be derived from it, the polymers corresponding to the silanes described above were prepared and their properties investigated. β-cyanoethyl silicone,[5] $NCCH_2CH_2SiO_{3/2}$ (V) was prepared by hydrolysis of β-cyanothyltrichlorosilane (II), using an ether-water system,[9] showing that under usual hydrolysis conditions no silicon-carbon bond cleavage occurs. However, hydrolysis of α-cyanoethyltrichlorosilane (I) using a similar procedure gave silica and propoinitrile.[5] Nearly pure α-cyanoethyl silicone can be obtained, however, if the hydrolysis is carried out at 0°.



β-Cyanoethyl silicone (V) was found to have surprising thermal stability when heated in air at 250° for 100 hr. As shown in Table IV, the β-cyanoethyl group has nearly the same thermal stability, measured as percent retention of carbon, as methyl silicone, and markedly superior stability compared to ethyl or α-cyanoethyl silicones. The stability may be partially due to coordination of the cyano group with the silicon atom, either inter- or intramolecularly, involving expansion of the silicon valence shell.[10] No experimental data to support this postulate has been obtained to date.

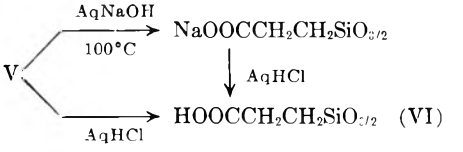
TABLE IV

COMPARISON OF SILICONE OXIDATIVE STABILITY IN AIR AT 250°

Siloxane	% Original C. Remaining after 100 Hr.
Diphenyl	98.4
Methyl	96.7
β-cyanoethyl	88.3
Dimethyl	81.5
α-cyanoethyl	12.6[a]
Ethyl	6.7

[a] After 25 hr. at 250°.

As was the case with the chlorosilane monomers, the cyano group in the silicone polymer can also undergo reaction. This was illustrated by synthesis of the corresponding carboxyalkyl silicones. The carboxy acid was prepared from β-cyanoethyl silicone (V) using either alkaline or acidic conditions. Using alkali the salt of the acid was obtained, which was easily neutralized to form the acid, β-carboxyethyl silicone (VI).



The acid (VI) is a white solid, soluble in hot water, sparingly soluble in cold water. The warm, concentrated solutions of the acid, when cooled, formed gel similar to that obtained with silicic acid in water. The compound is also soluble in methanol and dimethyl formamide, but insoluble in carbon tetrachloride, diethyl ether, and acetone. The acid can also be prepared from β-carbethoxyethyltriethoxy silane (IV) by saponification with aqueous base followed by neutralization of the resulting sodium carboxylate.

EXPERIMENTAL

β-Cyanoethyltrichlorosilane (II). All runs were made with equimolar mixtures of acrylonitrile and trichlorosilane mixed with the specified catalyst, and heated in a 300-cc. stainless

(8) A similar mechanism has been postulated for the effect of trifluoromethyl group attached to silicon through a CH_2 chain. O. W. Steward and O. R. Pierce, Abstract of Papers, Organic Division of the American Chemical Society, Chicago, Ill., Sept. 10, 1958, 50P.

(9) E. G. Rochow, *Chemistry of the Silicones*, J. Wiley and Sons, Inc., New York, N. Y., 2nd ed., p. 53.

(10) N. Sidgwick, *The Electronic Theory of Valency*, Oxford University Press, London, 1927, pp. 159 and 160.

steel pressure vessel placed in a rocking furnace for the specified temperature and time. At the end of the reaction the vessel was cooled, discharged, and the product filtered, using a fritted-glass filter. The filtrate was concentrated and distilled under reduced pressure through a glass-helix packed column to give β-cyanoethyltrichlorosilane (II), b.p. 57° (1 mm.), m.p. 36°. Hydrolyzable chlorine: theory, 56.4%; found, 56.0%. Literature value[3] b.p. 109° (30 mm.), m.p. 34.6–35.1°.

The α-isomer (I) was similarly prepared using no catalyst and had the following properties: b.p. 37° (1.0 mm.), n_D^{25} 1.4513. Hydrolyzable chlorine: theory 56.4%; found 55.5%. Literature value,[5] b.p. 96–8° (41.5 mm.).

β-Cyanoethyltriethoxysilane (III). In a 500-ml., three necked flask fitted with a reflux condenser, dropping funnel, gas inlet tube, and stirrer, was charged 36.35 g. (0.1 mol.) of β-cyanoethyltrichlorosilane and 75 ml. of diethyl ether. Ethanol (26.7 g., 0.58 mol.) was added slowly with stirring over a 0.5-hr. period. The stirring was continued for 3 hr. after the addition was complete with the system under a slow argon purge. The last traces of hydrogen chloride were neutralized by bubbling gaseous ammonia through the reaction mixture. The mixture was then filtered under reduced pressure through a Büchner funnel and the filtrate fractionally distilled through a 26-cm. column packed with 10 × 12 mesh alumina. There was obtained 24.21 g. (58%) n_D^{25} 1.4153, D_4^{25}, 0.970, b.p. 102° (3.8 mm.) of β-cyanoethyltriethoxysilane.

Anal. Calcd. for $C_9H_{19}NO_3Si$: C, 49.74; H, 8.81; OC_2H_5, 62.21. Found: C, 49.5; H, 8.7; OC_2H_5, 62.4.

Previous work[3] reports b.p. 111.5–112.5° (10 mm.), D_4^{24} 0.9699, n_D^{25}, 1.4103.

β-Carbethoxyethyltriethoxysilane (IV). A 500-ml., three necked flask, fitted with a dropping funnel, thermometer, magnetic stirrer, and a reflux condenser, was charged with 168.6 g. (0.89 mol.) of β-cyanoethyltrichlorosilane. Over the course of 2 hr., with stirring, was added 164.2 g. (3.58 mol.) of ethanol. Hydrogen chloride was evolved and nitrogen was used to purge the residual hydrogen chloride from the reaction mixture. Additional ethanol (115 ml., 197 mol.) was then added, and the solution heated at reflux for 16 hr. The solution was then concentrated under reduced pressure and the residue taken up in diethyl ether and filtered to separate the ammonium chloride. The filtrate was concentrated and the residue distilled under reduced pressure through a glass-helix packed column to give 150 g. (63.5%), b.p. 124–125° (10 mm.), n_D^{25} 1.4125, of β-carbethoxyethyltriethoxysilane.

Anal. Calcd. for $C_{11}H_{24}O_5Si$: C, 50.0; H, 9.15; Si, 10.6. Found: C, 50.3; H, 9.8; Si, 10.4.

β-Cyanoethylsilicone (V). In a 500-cc. beaker was charged 400 cc. of cracked ice and 100 ml. of diethyl ether. β-cyanoethyltrichlorosilane (15.46 g.) dissolved in 100 ml. of diethyl ether was added with stirring to the ice-solvent mixture. The hydrolysis was extremely rapid. The ether was allowed to evaporate from the aqueous acid layer, and the resulting oil layer separated and washed with distilled water until the water washings were neutral. The viscous oil was further concentrated under reduced pressure and the residue dried at 80° for 2 hr. to give 6.38 g. (99.7%) of a white, amorphous powder.

Anal. Calcd. for $C_3H_4NO_{1.5}Si$: Si, 26.44; N, 13.2. Found: Si, 25.8; N, 12.4.

β-Carboxyethylsilicone (VI) *from β-cyanoethyltrichlorosilane* (II). In a 2000-ml. beaker was charged 255 g. of β-cyanoethyltrichlorosilane dissolved in 800 ml. of isopropyl ether. To the ether solution was added, with constant stirring, 600 g. of crushed ice. Hydrogen chloride was evolved and a white precipitate formed, which was crude $NCCH_2CH_2SiO_{3/2}$. Sodium hydroxide solution (32.5%, 400 ml.) was then added and the mixture stirred until the solid dissolved in the aqueous layer. The aqueous layer was separated by means of a separatory funnel and neutralized by addition of concentrated hydrochloride acid at 10–20°. A heavy white precipitate formed which was filtered on a Büchner filter, washed with four 250-ml. portions of distilled water and dried under vacuum to give 147.3 g. (86.5%) of β-carboxyethylsilicone. Equivalent weight by titration of an aqueous solution with base: Theory: 125; Found: 127.4.

Anal. Calcd. for $C_3H_5SiO_7$: C, 28.8; Si, 22.4. Found: C, 28.3; Si, 21.3.

β-Carboxyethylsilicone (VI) *from β-carbethoxyethyltriethoxysilane* (IV). β-carbethoxyethyltriethoxysilane (88.9 g.) and 200 ml. of water were mixed in a 1-l., round bottomed flask, equipped with a reflux condenser and thermometer. The mixture was refluxed for 1 hr., but no noticeable reaction occurred. A small amount (30 ml.) of 3*N* hydrochloric acid was added, and the refluxing continued for 2 hr. The solution became cloudy during this period. The solution was then concentrated under reduced pressure to give a solid residue. The solid was ground to a white powder and dried at 100° for 6 hr. in a vacuum oven to remove traces of water. The yield of β-carboxyethylsilicone was 39.6 g. (93.8%).

Anal. Calcd. for $C_3H_5SiO_{7/2}$: C, 28.8; Si, 22.4. Found: C, 28.3; Si, 21.4. Equivalent weight by titration, 127.4; theory, 125.

α-Cyanoethylsilicone (I). By the procedure described above for β-cyanoethylsilicone, 19.6 g. of α-cyanoethyltrichlorosilane b.p. 55° (4 mm.) was hydrolyzed to give an amorphous solid. The chemical analysis showed that some cleavage of the carbon-silicon bond had occurred during hydrolysis.

Anal. Calcd. for $C_3H_4NO_{1.5}Si$: C, 33.95; H, 3.80; N, 13.2; Si, 26.44. Found: C, 28.8; H, 3.6; N, 8.6; Si, 27.8. After heating the sample in air at 250° for 25 hr. the analysis was: C, 3.0; H, 1.1; N, 1.3; Si, 40.8. Theory, Si for SiO_2, 46.6%.

Heat stability tests. These tests were run by heating a weighed sample of the material in a 150-ml. beaker in a forced draft oven at 250°. Samples were analyzed after every 24-hr. heating cycle. The values listed in Table IV are final results obtained on carbon analysis after 100 hr.

Acknowledgment. The authors wish to thank Dr. E. R. Shull and Mr. D. M. Ruttenbur of the Molecular Spectroscopy Group, Linde Company, Division of Union Carbide Corp. Tonawanda, N. Y., for the interpretation of the infrared data.

TONAWANDA, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PHARMACEUTICAL CHEMISTRY, MEDICAL COLLEGE OF VIRGINIA]

α-Aminoalkanesulfonic Acids[1,2]

L. NEELAKANTAN AND WALTER H. HARTUNG

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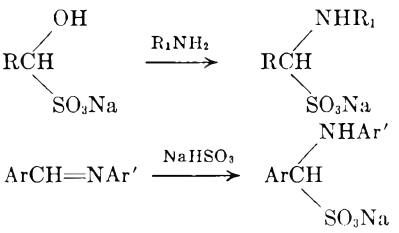
Various α-aminoalkanesulfonic acids and some of their derivatives were prepared to facilitate a study of their biological properties. This offered an opportunity to make a more thorough study of their chemical properties and reactions. Practical syntheses are described. The behavior of the amino sulfonic acids towards oxidizing agents and toward phenylhydrazine and semicarbazide are analogous to those of aldehyde. They form sulfonanilides. Their reaction with cyanide and with active methylene compounds is considered essentially an alkylation; the alkylation may proceed with elimination of the sulfonic acid group or with replacement of the amino group.

α-Amino sulfonic acids, analogs of amino acids in which the carboxyl group is replaced by a sulfonic acid group, have received limited study from the biological scientist, *e.g.*, for anticancer activity[3,4] and for antiviral properties.[5,6] Therefore, the present study was undertaken to make available a series to permit systematic study of their antitumor activity and any possible antagonism to the natural amino acids. In the Tables are listed some of the compounds prepared. *In vivo* studies are under way in the laboratories of Irvin and Wilson,[7] who are reporting their results elsewhere.

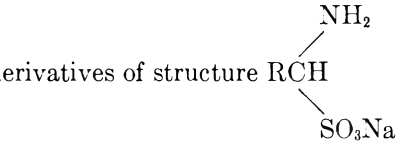
α-Aminoalkanesulfonic acids have been known for more than fifty years[8,9]; but many of their interesting properties have not been previously described.

The synthesis may proceed in either of two ways, indicated as follows:



Reaction a is generally applicable and may be employed with aliphatic or aromatic aldehydes, and the amine may be aliphatic or aromatic or even ammonia; equimolar amounts of aldehyde and bisulfite are stirred together in water, forming the aldehyde-bisulfite *in situ*, followed by an equimolar amount of amine; the reaction proceeds at room temperature but may be facilitated by warming. Reaction b has thus far been employed only with aromatic reagents, affording excellent yields for the most part.

The salts are stable in aqueous solution even up to about 70°. They decompose in boiling water, and they are unstable in the presence of alkali. They are stable to acid, as was noted by Backer.[10]



in hydrochloric acid *p*H = 2 afford good yields of the corresponding sulfonic acid.

The α-aminoalkanesulfonates show many reactions characteristic for aldehydes. They reduce Tollen's and Fehling's solutions; they decolorize solutions of permanganate, of dichromate, and of iodine–potassium iodide. (The aldehyde-bisulfite complex does not reduce iodine.[11]) They react readily with phenylhydrazine or semicarbazide to give good yields of the phenylhydrazone or semicarbazone, respectively, of the aldehyde employed in preparing the sulfonic acid. The speed with which these derivatives precipitate suggests their formation directly from the sulfonate.

The infrared spectra show characteristic bands for the —SO_3Na and —NHR groups and no presence of bisulfite or sulfite. Further studies are in progress.

An aqueous solution of sodium α-aminophenylmethanesulfonate, XI, stirred at room temperature with an equivalent of aniline slowly forms crystals of the less soluble α-anilinophenylmethanesulfonate (XII), showing that an amine exchange can occur under these conditions. This type of reaction requires further study before we can say how widely it may be applied.

An arylaminoalkanesulfonate in boiling water undergoes rearrangement which suggests the reaction

(1) Number 20 in Amino Acids series. For No. 19 see D. A. Coviello and W. H. Hartung, *J. Org. Chem.*, 1611.

(2) Supported by Public Health Service Grant **Cy-3024,** National Institutes of Health. For this support the authors are grateful.

(3) H. McIlwain, *J. Chem. Soc.*, 75 (1941).

(4) D. M. Greenberg and M. P. Schulman, *Science*, **106,** 271 (1947).

(5) W. W. Ackerman, *Proc. Soc. Exptl. Biol. Med.*, **80,** 362 (1952).

(6) R. L. Thompson, *J. Immunol.*, **55,** 345 (1947).

(7) J. L. Irvin and J. Wilson, University of North Carolina, S. E. Regional Meeting, Am. Chem. Soc., Richmond, Nov. 5, 1959.

(8) E. Knoevenagel, *Ber.*, **37,** 4087 (1904).

(9) H. Bucherer and A. Schwalbe, *Ber.*, **39,** 2810 (1906).

(10) H. J. Backer and H. Mulder, *Rec. trav. chim.*, **53,** 1120 (1934).

(11) Ripper, *Monatsh.*, **21,** 1079 (1900) through C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, New York, 1944, p. 127.

TABLE I

$$R{-}CH(NHR'){-}SO_3Na$$

α-AMINOALKANE SULFONATES

No.	—R	—R′	Softening Point	Crystals from	Yield, %	Nitrogen Calcd.	Nitrogen Found	Remarks
I	H-	H-	—	Water	60	—	—	a
II	H-	CH_3	—	Water	60	—	—	a
III	H-	Et-	—	Water	70	—	—	a
IV	H-	C_6H_5-	—	Water-alcohol	90	—	—	a
V	n-C_3H_7-	H-	—	Water	70	—	—	c
VI	n-C_3H_7-	C_6H_5-	108–110	Alcohol	85	5.59	5.7	
VII	i-C_3H_7-	H-	—	Water	65	—	—	c
VIII	i-C_3H_7-	C_6H_5-	110–112	Alcohol	80	5.59	5.8	
IX	i-C_4H_9	H-	—	Water	70	—	—	c
X	i-C_4H_9	C_6H_5-	118–120	Alcohol	80	5.28	5.15	
XI	C_6H_5-	H-	—	Water	75	—	—	c
XII	C_6H_5-	C_6H_5-	115–117	Alcohol	90	4.91	4.8	
XIII	C_6H_5-	p-$CH_3C_6H_4$-	138–140	Alcohol	95	4.68	4.72	
XIV	C_6H_5-	p-ClC_6H_4-	178–180	Alcohol	95	4.6	4.32	b
XV	C_6H_5-	p-C_6H_4COONa	—	Water	70	4.0	3.8	
XVI	C_6H_5-	p-$C_6H_4SO_3Na$	—	Water	65	—	—	a
XVII	C_6H_5-	C_5H_{11}-	—	Water	70	—	—	a
XVIII	p-ClC_6H_4-	H-	—	Water	90	5.76	5.5	
XIX	p-ClC_6H_4-	C_6H_5-	145–147	Alcohol	95	4.37	4.31	
XX	$C_6H_5CH_2$-	H-	—	Water	80	—	—	
XXI	$C_6H_5CH_2CH_2$-	H-	—	Water	85	5.95	5.82	
XXII	$C_6H_5CH_2CH_2$-	C_6H_5-	95–96	Alcohol	90	4.5	4.32	

[a] Properties of these compounds agree with those reported by Knoevenagel.[8] [b] $C_{13}H_{11}NO_3ClNa$ requires, N, 4.6; S, 8.96; Found, N, 4.32; S, 9.06.[17] [c] The compounds were converted to the corresponding aminonitriles; their melting points agreed well with the reported values. The free acids from the salts compared well with those reported by McIlwain.[3]

TABLE II

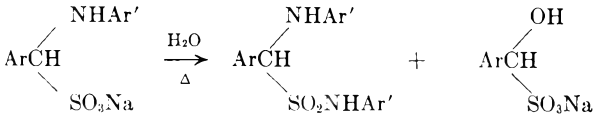
$$R{-}CH(NHAr){-}SO_2NHAr$$

ARYLAMIDES OF α-ARYLAMINOALKANE SULFONIC ACIDS

No.	R—	Ar—	M.P. (Dec.)	Crystals from	Yield, %	N, % Calcd.	N, % Found	Remarks
XXIII	n-C_3H_7-	C_6H_5-	123–124	Alcohol	80	9.2	9.34	
XXIV	i-C_3H_7-	C_6H_5-	120–121	Water	75	—	—	d
XXV	n-C_4H_9-	C_6H_5-	125–126	Water	75	8.76	8.79	
XXVI	i-C_4H_9	C_6H_5-	128–129	Water	80	—	—	dd
XXVII	C_6H_5-	C_6H_5-	125–126	Alcohol	85	—	—	e
XXVIII	C_6H_5-	p-$CH_3C_6H_4$-	117–118	Alcohol	90	—	—	f
XXIX	C_6H_5-	p-ClC_6H_4-	133–134	Alcohol	95	6.87	6.62	
XXX	C_6H_5-	p-C_6H_4COONa	—	Water	80	5.96	5.80	
XXXI	p-ClC_6H_4-	C_6H_5-	125–126	Alcohol	80	—	—	g
XXXII	p-ClC_6H_4-	p-$CH_3C_5H_4$-	124–125	Alcohol	85	7.00	6.81	
XXXIII	$C_6H_5CH_2CH_2$	C_6H_5-	118–120	Alcohol	90	7.65	7.41	
XXXIV	C_6H_5-	p-$NO_2C_6H_4$	132–133	Alcohol	75	6.55	6.44	

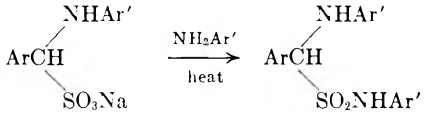
[d] Reported m.p. 126–127° (dec.), Eibner.[12] [dd] Reported m.p. 128° (dec.).

[e] $C_{19}H_{18}N_2O_2S.{}^1/_2H_2O$:	C, %	H, %	N, %	S, %
Requires	65.51	5.47	8.07	9.22
Found[17]	65.38	5.40	7.95	9.11
[f] $C_{21}H_{22}N_2O_2S.{}^1/_2H_2O$:				
Requires	67.14	6.173	7.463	
Found[17]	66.38	6.258	7.18	
[g] $C_{19}H_{19}N_2O_2SCl$:				
Requires	58.4	4.87	7.19	
Found[17]	58.34	4.9	7.37	

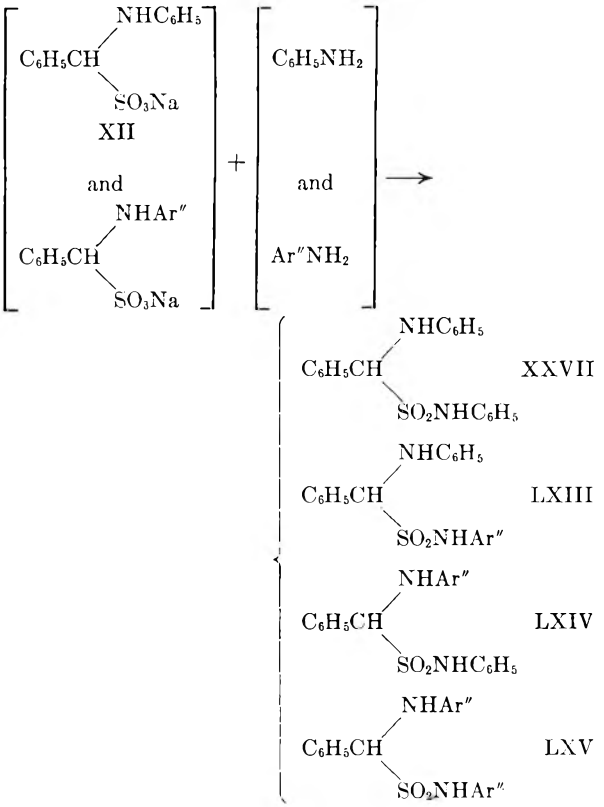


We have isolated both the amide and the aldehyde-bisulfite product. Sulfonamides of this type are known from the work of Eibner,[12] who prepared them by treating an aromatic aldehyde with an aromatic amine and sulfurous acid, or allowed the Schiff base to react in ether with sulfur dioxide. We were able to prepare such compounds in better yields by treating the desired aromatic aldehyde with two equivalents of sodium bisulfite followed by two equivalents of the aromatic amine, dissolving or suspending all in water, stirring and boiling for a few minutes; on cooling, the product crystallized in excellent yields. The compounds obtained in this manner are shown in Table II.

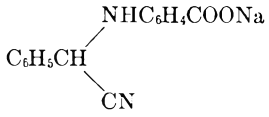
The compounds of Table II may also be obtained according to the reaction



However, when α-anilinophenylmethanesulfonate (XII) is heated with *p*-toluidine the product is not exclusively sulfotoluidide but rather a mixture. An identical mixture results when α-*p*-toluidinophenylmethanesulfonate (XIII) is heated with aniline. The products are quite as if one carried out the reaction simultaneously with four reagents as follows:



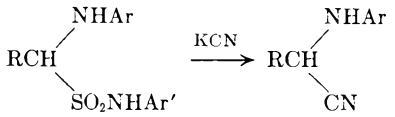
The separation of the mixture into its components by fractional crystallization or chromatography has not succeeded. However, by allowing XII to react with sodium *p*-aminobenzoate ($Ar''NH_2$=p-$NH_2C_6H_4COONa$) a mixture was obtained where separation was more successful. The water insoluble product was identified as XXVII. The water-soluble portion was treated with potassium cyanide, as described below, replacing the sulfonamido group with the cyano group; an insoluble substance, identified as α-anilinophenylaceonitrile (IXL), was isolated, which had its origin in an intermediate of type LXIII. A soluble nitrile was also formed:



which may have its origin from types LXIV or LXV, but more probably from both, although this has not yet been unequivocally established.

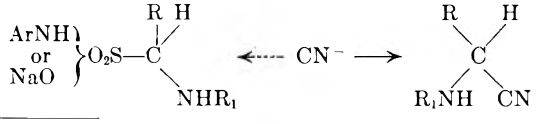
Further studies of these reactions are necessary before their machanism is understood. Since an amine-exchange is also possible, it cannot now be said that there is a reversion to aldehyde, amine, and bisulfite. The formation of sulfonanilides from sodium sulfonates in aqueous solution was unexpected.

The reaction of α-aminoalkanesulfonates with alkali cyanide to form nitriles has long been known.[13,14] We used it for the preparation of many α-amino nitriles, intermediate in the synthesis of amino acids not described here. Presumably this reaction also comes into play in the synthesis of α-hydroxylamino nitriles.[15] We find that the sulfonamide group is likewise susceptible to replacement by cyanide, giving identical nitriles, as listed in Table III.



The products may be obtained by stirring the reagents in water at room temperature, but their formation may be facilitated by employing alcohol solvent and heating for a short time.

If these reactions are considered as a base replacement and if formulated correctly to proceed as:



(12) A. von Eibner, *Ann.*, **316** 89 (1901).
(13) E. Knoevenagel, *Ber.*, **37**, 4073 (1904).
(14) W. V. Miller and J. Plöchl, *Ber.*, **25**, 2032 (1892).
(15) L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **23**, 964 (1958).

TABLE III

R—CH—CN
|
NHAr

α-ARYLAMINONITRILES

No.	R—	Ar—	Crystals from	Yield, %	Melting Point Observed	Melting Point Reported	Remarks
XXXV	n-C_3H_7-	C_6H_5-	Pet. ether	75	50–51	51	[h]
XXXVI	i-C_3H_7-	C_6H_5-	Ether–pet. ether	70	54–55	54	[h]
XXXVII	n-C_4H_9-	C_6H_5-	Benzene–pet. ether	70	63–64	65	[h]
XXXVIII	i-C_4H_9-	C_6H_5-	Ether–pet. ether	68	67–68	67	[h]
IXL	C_6H_5-	C_6H_5-	Alcohol	90	85–86	85	[i]
XL	C_6H_5-	p-$CH_3C_6H_4$-	Alcohol	90	109–110	109–110	[i]
XLI	C_6H_5-	p-ClC_6H_4-	Alcohol	85	121–122	—	[j]
XLII	p-ClC_6H_4-	C_6H_5-	Alcohol	75	112–113	112	[k]
XLIII	p-ClC_6H_4-	p-$CH_3C_6H_4$-	Alcohol	70	81–82	80	[k]
XLIV	C_6H_5-	p-$C_6H_4CO_2H$	Alcohol	75	163–164	—	[l]
XLV	C_6H_5-	p-$NO_2C_6H_4$-	Alcohol	80	128–129	129	[m]
XLVI	$C_6H_4CH_2CH_2$	C_6H_5-	Ether	55	88–90	—	[n]

[h] W. V. Miller, *et al.*,[14] (1892). [i] E. Knoevenagel.[8] [j] $C_{14}H_{11}N_2Cl$ requires N, 11.6. Found N, 11.45. [k] Walther, *et al.*, *J. pr. chem.* (2) **65**, 269. [l] $C_{15}H_{12}N_2O_2$ requires N, 11.1. Found N, 11.34. [m] H. Rohde, *et al.*, *Ber.*, **25**, 2054 (1892). [n] $C_{16}H_{15}N_2$ requires N, 11.9. Found N, 11.75.

TABLE IV

COOEt
R—CH—CH
| \
NHAr COOEt

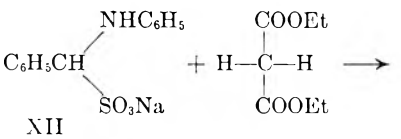
β-ARYL-β-ARYLAMINO-METHYL MALONIC ESTERS

No.	R—	Ar—	Crystals from	Yield, %	Melting Point Observed	Melting Point Reported	Procedure	Remarks
XLVII	C_6H_5-	C_6H_5-	Benzene-ligroin	85 75	99–100	100–101	A B	[o]
XLVII	C_6H_5-	p-$CH_3C_6H_4$	Alcohol	70 50	82–83	80–82	A B	[o]
XLIX	C_6H_5-	p-ClC_6H_4-	Alcohol	60 55	81–82	81–82	A B	[o]
L	C_6H_5-	p-$C_6H_4CO_2H$	Alcohol	75	164–165	164–165	A	[o]
LI	p-ClC_6H_4	C_6H_5-	Alcohol	70 55	119–120	—	A B	[p]
LII	p-ClC_6H_4	p-$CH_3C_6H_4$-	Alcohol	65 50	106–107	—	A B	[q]

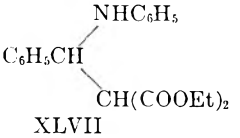
[o] E. J. Wayne and J. B. Cohen, *J. Chem. Soc.*, 127, 450 (1925).

		C	H	N
[p] $C_{20}H_{22}NO_4Cl$:	Requires	63.9	5.9	3.72
	Found	64.1	6.1	3.65[17]
[q] $C_{21}H_{24}NO_4Cl$:	Requires	N, 3.63		
	Found	N, 3.5		

then other bases may be expected to react in an analogous manner, if proper conditions are employed, and a typical equation may be assumed with diethyl malonate to become:



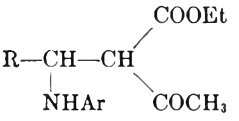
XII



XLVII

We found this reaction to proceed very well if catalytic amounts of base are employed, *e.g.*, small amounts of sodium ethoxide, piperidine, diethylamine, benzylamine, or even sodium hydroxide. The reaction may be carried out in alcohol simply by mixing the reagents as a suspension, if insoluble, or in water and stirring at room temperature for three days as necessary, when excellent yields of product are formed. Ethyl acetoacetate and acetylacetone are alkylated with equal readiness, in some instances even without the presence of the catalytic base. The products prepared by these reactions are listed in Tables IV, V, and VI. It will be noted

TABLE V



β-ARYL-β-ARYLAMINO-METHYL ACETOACETIC ESTERS

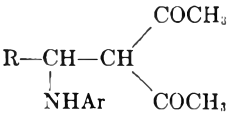
No.	R—	Ar—	Crystals from	Procedure	Yield, %	Melting Point Observed	Melting Point Reported	Remarks
LIII	C_6H_5-	C_6H_5-	Ligroin	A	85	106–107	107–108	[r]
				B	65			
LIV	C_6H_5-	p-$CH_3C_6H_4$-	Benzene–pet. ether	A	80	96–97	97	[r]
				B	55			
LV	C_6H_5-	p-ClC_6H_4-	Alcohol	A	85	112–113	112	[r]
				B	65			
LVI	p-ClC_6H_4	C_6H_5-	Alcohol	A	80	116–117	—	
				B	70			
LVII	p-ClC_6H_4-	p-$CH_3C_6H_4$	Benzene–pet. ether	A	65	112–113	—	[t]

[r] Siegfried Rohemann, *J. Chem. Soc.*, 85, 1177, 1452 (1904).

		C, %	H, %	N, %
[s] $C_{19}H_{20}NO_3Cl$:	Requires	66.07	5.797	4.057
	Found	65.87	5.78	3.95[17]

[t] $C_{20}H_{22}NO_3Cl$: Requires: N, 3.91. Found: N, 4.12.

TABLE VI



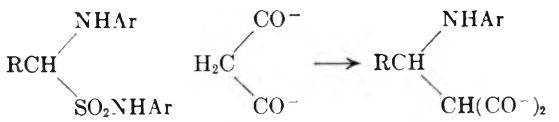
β-ARYL-β-ARYLAMINOMETHYL ACETYLACETONES

No.	R—	Ar—	Crystals from	Procedure	Yield, %	Melting Point Observed	Melting Point Reported	Remarks
LVIII	C_6H_5-	C_6H_5-	Alcohol	A	65	112–113	113	[u]
				B	50			
LIX	C_6H_5-	p-$CH_3C_6H_4$-	Alcohol	A	75	96–97	96	[u]
LX	C_6H_5-	p-ClC_6H_4-	Alcohol	A	70	99–100	99	[u]
LXI	p-ClC_6H_4-	C_6H_5-	Alcohol	A	75	118–119	—	[v]
				B	55			
LXII	p-ClC_6H_4-	p-$CH_3C_6H_4$-	Alcohol	A	55	106–107	—	[w]

[u] S. Ruhemann and E. R. Watson, *J. Chem. Soc.*, 85, 466 (1904). [v] $C_{17}H_{17}NO_2Cl$ requires N, 4.43, found N, 4.48 [w] $C_{18}H_{19}NO_2Cl$ requires N, 4.3, found N, 4.15.

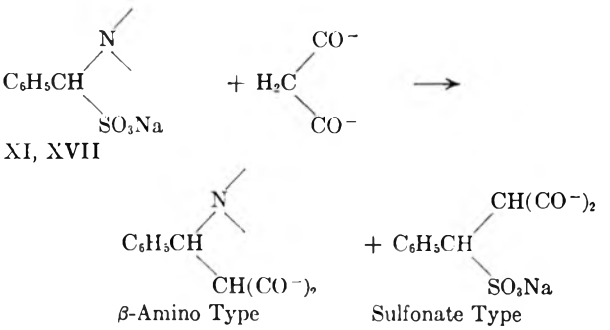
that some of these compounds have been prepared by previous investigators employing other procedures. We have not yet examined these products to determine whether they behave in the manner characteristic for β-amino ketones or β-amino esters.

We have further observed that the alkylation proceeds also with sulfonamides, affording products identical with those obtained *via* the sulfonates. Also only catalytic amounts of base are required to promote the reaction with:



active methylene reagents.

When the amino group of the sulfonate is unsubstituted or bears a nonaromatic substituent, it reacts with diethyl malonate in two directions, *e.g.*:



XI, XVII

β-Amino Type Sulfonate Type

The primary amino sulfonate reacts with diethyl malonate to form 5 to 10% β-amino type and 60% sulfonate type; but with ethyl acetoacetate only product of sulfonate type was isolated. A compound

of this type is known from the work of Raschig[16] who allowed ethyl acetoacetate to react with formaldehyde - bisulfite in the presence of sodium hydroxide. The piperidino sulfonate (XVII) reacts with ethyl acetoacetate as does the primary amino sulfonate; and ethyl cyanoacetate reacts as does ethyl acetoacetate.

The mechanism of these alkylation reactions is not yet clear. It is hoped that studies now under way will shed more light on the pathway by which these products are formed.

EXPERIMENTAL

The laboratory procedures employed for synthesizing the various compounds are adaptations and improvements on published directions. Below are given typical examples. By appropriate selection of reagents a large number of compounds become possible. The pertinent data for the present series are summarized in the respective Tables.

Sodium α-anilinophenylmethanesulfonate (XII). One-tenth mol. of benzaldehyde, 10.6 g., was stirred with a solution of 0.1 mol. of bisulfite, 10.5 g., in 50 ml. of water for 1 hr., after which 0.1 mol. aniline, 9.3 g., was added; the mixture was stirred and carefully warmed on a water bath, forming in a few minutes a clear solution; this was cooled and yielded a crystalline product, which was collected on a Buchner funnel, washed with cold water, dried, and recrystallized from alcohol.

One-tenth mol. of benzylidineaniline, 18.1 g., was warmed in a solution of 0.14 mol. sodium bisulfite, 15 g., in 100 ml. water to 60°, and after about an hour a clear solution resulted. On cooling, a colorless crystalline product was obtained, which was washed with cold water, dried, and recrystallized from alcohol.

α-Anilinophenylmethanesulfonanilide (XXVII). One-tenth mol. benzaldehyde, 10.6 g., was stirred for an hour with a solution of 0.2 mol. sodium bisulfite, 20.8 g., in 100 ml. of water, after which 0.2 mol. aniline, 18.6 g., was added; the mixture was stirred and heated on a water bath for 15 min. and then boiled for 10 min.: on standing, the solution formed colorless slender needles, which may be recrystallized from hot water or from ethanol.

α-Aminophenylacetonitrile. One-tenth mol. of sodium α-aminophenylmethanesulfonate (XI), 20.9 g., in 50 ml. of water treated with a solution of 0.1 mol. sodium cyanide, 5.0 g., in a small amount of water and stirred for about 5 min. at room temperature; an oil separated, which, on standing at 0° for 2 hr. solidified. The product was collected, washed with cold water, dried, and recrystallized from ligroin.

(16) F. v. Raschig and W. Prahl, *Ann.*, **448**, 265 (1926).

α-Anilinophenylacetonitrile (IXL). One-tenth mol. of sodium α-anilinophenylmethanesulfonate (XII), 28.5 g., and 0.1 mol. potassium cyanide, 6.5 g., were heated to reflux in 100 ml. alcohol for 1 hr. The mixture was then cooled, inorganic salt filtered off, and the filtrate concentrated under reduced pressure to about 40 ml. On cooling, a crystalline mass formed, which was recrystallized from alcohol, yielding colorless crystals.

One-twentieth mol. of α-anilinophenylmethanesulfonanilide (XXVII), 17.5 g., and 0.05 mol. potassium cyanide, 3.3 g., were refluxed in 60 ml. of alcohol for 1 hr.; the solution was then concentrated to about 35 ml. under reduced pressure; on cooling a crystalline product formed, which was purified as described above.

α-Aminoalkanesulfonates and derivatives with active methylene compounds. Procedure A. One-tenth mol. of sodium α-anilinophenylmethanesulfonate (XII), 20.9 g., 0.1 mol. diethyl malonate, 16 g., and 2 drops of piperidine was stirred for 3 days in 100 ml. water at room temperature. An oily solid formed; this was extracted with benzene, the benzene volatilized in a current of air, and a crystalline solid remained; this was crystallized from ethanol. The reaction may be expedited by refluxing rather than allowing it to proceed at room temperature. Ethyl acetoacetate or acetylacetone may be employed instead of diethyl malonate with equally favorable alkylation yields.

Procedure B. One-tenth mol. of α-anilinophenylmethanesulfonanilide (XXVII), 35.0 g., 0.1 mol. diethyl malonate, 16 g., 2 drops of piperidine, and 150 ml. of alcohol were heated to reflux for about 1 hr.; the solution was then concentrated by a current of air to about half its volume and poured into 300 ml. of ice water; after a day the crystalline product was removed, dried, washed with petroleum ether, and recrystallized from alcohol. The reagents may also be suspended or dissolved in water, stirred for 3 days at room temperature, and the products isolated and purified in the usual manner.

Procedure C. One-tenth mol. of sodium α-aminophenylmethanesulfonate (XI), 20.9 g., in 60 ml. of water was treated with 0.1 mol. of ethyl acetoacetate, 13 g., and 2 drops of piperidine. After stirring for 15 min. it formed a clear solution, but stirring was continued for a day and then placed in the refrigerator for 12 hr., whereupon a colorless crystalline substance formed; this was collected on a Buchner funnel, washed with a little water and then cold alcohol, and then recrystallized from alcohol, giving 29 g., 90%, of pure product, m.p. 182–183° (dec.), which was identified as sodium 1-phenyl-2-acetyl-2-carbethoxyethane-1-sulfonate.

Anal. Calcd. for $C_{13}H_{15}O_6SNa.H_2O$: C, 45.87; H, 5.0. Found:[17] C, 45.45; H, 5.4.

The test for presence of nitrogen was negative.

RICHMOND, VA.

(17) Analyses by Messrs. Weiler and Strauss, Oxford, England.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, EX-LAX, INC., BROOKLYN 17, N. Y.]

Bis(*p*-hydroxyphenyl)acetic Acid

MAX H. HUBACHER

Received June 24, 1959

The preparation of bis(*p*-hydroxyphenyl)acetic acid from phenol and glyoxylic acid is described. As a by-product of this condensation 3-(*p*-hydroxyphenyl)-2-coumaranone is formed. It is shown that the bis(*p*-hydroxyphenyl)acetic acid described by Kaufmann and Schierholt is actually 4,4′-dihydroxybenzil.

Recently Kaufmann and Schierholt[1] published a paper on the preparation of the previously unknown bis(*p*-hydroxyphenyl)acetic acid (I). This same acid was prepared in our laboratory. However, since our acid has properties entirely different from those of the acid described by the two German investigators, it seems appropriate to publish our results.

The acid was prepared for use as an intermediate in the synthesis of compounds having the grouping $(p)HOC_6H_4—\underset{|}{\overset{|}{C}}—C_6H_4OH(p')$ and was expected to have laxative properties.[2]

First, an attempt was made to synthetize I by the same method which Kaufmann and Schierholt had used with apparent success, namely by heating the 1,1,1-trichloro-2,2-bis(*p*-hydroxyphenyl)ethane (II) with aqueous alkali. No acid was isolated from the reaction mixture, only the following three phenols: 4,4′-dihydroxybenzil (III), 1,1-dichloro-2,2-bis(*p*-hydroxyphenyl)ethylene (IV) and 4,4′-dihydroxytolan (V). In the formation of III and of V, a rearrangement must have taken place similar to that observed by Zincke and Fries[3] who, when reducing the unsymmetrical II, obtained the symmetrical 4,4′-dihydroxystilben. When II was reacted with methanolic potassium hydroxide, then IV was obtained in 72% yield.

From the scant description of their acid which Kaufmann and Schierholt give, having made no derivatives, it is clear that their alleged acid is 4,4′-dihydroxybenzil. The properties of their acid, the melting point of 247°, its light yellow color, its elementary analysis and the solubilities all check with those of 4,4′-dihydroxybenzil (III), a compound having acidic properties. Unfortunately, I could not make a direct comparison because Dr. Kaufmann wrote that he did not have a trace of the acid left.

In the second method tried, the acid I was obtained by demethylating the bis(*p*-anisyl)acetic acid (VII) with pyridine hydrochloride. However, this method has the drawback that acid VII could be obtained only in small yields, by heating the 1,1-dichloro-2,2-bis(*p*-anisyl)ethylene (VI) with alcoholic sodium ethylate at higher temperature. No acid was obtained by heating IV under the same conditions.

The third method, which failed in the hands of Kaufmann and Schierholt, was the most successful in our hands. Phenol was condensed with glyoxylic acid, whereby acid I was obtained in yields of 45–58%. As a by-product of this reaction, a phenol was isolated, namely 3-(*p*-hydroxyphenyl)-2-coumaranone (VIII). This formed by *ortho-para* condensation and lactone formation of the primarily formed (*o*-hydroxyphenyl)-(*p*-hydroxyphenyl)acetic acid. The dimethylether of this acid, obtained by methylation of VIII, yielded the 2,4′-dimethoxybenzophenone on oxidation.

EXPERIMENTAL[4]

1,1,1-Trichloro-2,2-bis(p-hydroxyphenyl)ethane (II). This compound was made by the following improved procedure. One dropping funnel was filled with a solution of 37.6 g. of phenol, 33.1 g. of chloral hydrate and 20 ml. acetic acid; the other with 30 ml. concentrated sulfuric acid. The contents of these were added simultaneously, over a period of 1 hr., into a reaction flask, keeping the exothermic reaction at 50–55°. The red mixture was poured into ice water the next day. The crystalline mass was washed free of sulfate and dried at 50°. It was purified by dissolving it in 60 ml. of warm ethanol, adding 240 ml. of benzene and letting the solution stand overnight at room temperature. The crystals contained one mole of solvate benzene, which they lost at 110°. Calcd. for $C_{14}H_{11}O_2Cl_3 \cdot C_6H_6$: Benzene: 19.7; loss in weight 19.9 ± 0.5.

The compound, free of solvent, melted at 199–204°.

Reaction of II *with aqueous potassium hydroxide.* A solution of 31.7 g. of II in 200 ml. of 3*N* potassium hydroxide was refluxed for 30 min., then cooled, 400 ml. water was added and the solution saturated with CO_2. The dried, brown precipitate was extracted by refluxing with 2 portions of 200 ml. each of benzene. The crystals (3.2 g.) consisted of needles as well as granules. The observation that the thin needles dissolve first on reheating with benzene is helpful in their separation.

The needles, recrystallized from 20% ethanol, melted at 211–214° and were proven to be identical with compound IV.

The granular crystals (V) melted at 214.6–215.1°. They did not contain chlorine and gave the red color and the

(1) H. P. Kaufmann and J. Schierholt, *Pharm. Zentralhalle*, 96, 443 (1957).

(2) M. H. Hubacher, S. Doernberg, and A. Horner, *J. Am. Pharm. Assoc.*, 42, 23 (1953).

(3) Th. Zincke and K. Fries, *Ann.*, 325, 26 (1902).

(4) All melting points are corrected. Molecular weights were determined by the Signer method, as described by E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, 13, 820 (1941).

red compound described by Zincke and Münch[5] for 4,4'-dihydroxytolan, and analyzed.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 79.96; H, 4.79; mol. wt. 210. Found: C, 80.21; H, 5.23; mol. wt. 215.

The acetylderivative of V, crystallized from ethanol, melted at 199.3–201.4°.

4,4'-Dihydroxybenzil (III). The aqueous, alkaline solution from the reaction of II with 3*N* potassium hydroxide, after removal of the phenolic part, yielded a precipitate on acidification (2.8–4.6 g.). This was purified by sublimation at 220° and 10 microns pressure, then the yellowish sublimate was crystallized from 41% ethanol. The pale yellow crystals melted at 250.2–251.4°[6] and proved to be 4,4'-dihydroxybenzil[6] (III).

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.13; mol. wt. 242. Found: C, 69.79; H, 4.63; mol. wt. 240.

The diacetylderivative of III, pale yellow crystals from 41% ethanol, melted at 88.0–89.2°,[7] the dibenzoylderivative at 168.9–169.6°.[8]

When III was reacted with *o*-phenylendiamine, a yellow compound melting at 330.4–331.0° was obtained. This compound, when mixed with 2,3-bis(*p*-hydroxyphenyl)quinoxaline (m.p. 326–328°) kindly furnished by Dr. H. Gilman,[9] melted at 327–330°.

Dipropionylderivative of III. This compound, prepared from above III as well as from authentic 4,4'-dihydroxybenzil, formed pale yellow needles (from ethanol) and melted at 77.1–77.5°.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.77; H, 5.15; mol. wt. 354. Found: C, 67.48; H, 5.36; mol. wt. 363.

1,1-Dichloro-2,2-bis(p-hydroxyphenyl)ethylene (IV). A solution of 15.9 g. of II in 100 ml. 3*N* methanolic potassium hydroxide was refluxed for 30 min. After adding 300 ml. ice water, the purple solution was acidified. The precipitate was crystallized from 500–600 ml. 20% ethanol, yielding 9.8 to 10.4 g. (70–74%) crystals (m.p. 210–213° dec.) of pale yellow color. The pure compound (IV), which may also be crystallized from benzene (1 g. in 70 ml.) formed colorless needles, melting at 214–215° with slight dec., when introduced into the bath at 211°, raising the temperature of the latter 1° a minute. The solution of IV in concentrated sulfuric acid is red.[10]

Anal. Calcd. for $C_{14}H_{10}O_2Cl_2$: C, 59.81; H, 3.59; Cl, 25.23; mol. wt. 281. Found: C, 59.90; H, 3.60; Cl, 24.76; mol. wt. 283.

Diacetyl derivative of IV. Crystallized from a considerable amount of ethanol, it melted at 141.7–142.0°.

Anal. Calcd. for $C_{18}H_{14}O_4Cl_2$: C, 59.18; H, 3.83; Cl, 19.45; mol. wt. 365. Found: C, 59.07; H, 3.96; Cl, 19.24; mol. wt. 382.

This acetyl derivative, when oxidized in acetic acid solution with CrO_3, yielded 4,4'-diacetoxybenzophenone, m.p. 152.1–152.6°.

Dipropionyl derivative of IV. This compound, colorless crystals from ethanol, melted at 82.0–82.6°.

Anal. Calcd. for $C_{20}H_{18}O_4Cl_2$: C, 61.06; H, 4.58; Cl, 18.04. Found: C, 61.16; H, 4.95; Cl, 18.01.

1,1-Dichloro-2,2-bis(p-anisyl)ethylene (VI). Two-tenths mole (69.1 g.) of 1,1,1-trichloro-2,2-bis(*p*-anisyl)ethane (m.p. 83–86°) made by a procedure similar to the one by which II was prepared, was refluxed for 1 hr. with 200 ml. of 3*N* methanolic potassium hydroxide. The resulting compound, crystallized from 600 ml. of ethanol, melted at 110–112° (literature 113°[11a]); yield 48–55 g. (77–89%).

Bis(p-anisyl)acetic acid (VII). A solution of 15.5 g. of VI in 100 ml. of absolute ethanol containing 6.9 g. metallic sodium dissolved (ratio 1 mole to 6 g.-atom) was heated in an all-nickel autoclave for 8 hr. to 180°. Only a small part of VI reacted to the acid VII (2.5 g.). The latter, crystallized from 41% ethanol and then sublimed at 105° and 16 microns pressure, melted at 110.0–110.8°.[11]

Various changes in the experimental conditions did not improve the yield; at higher reaction temperature, tarry matter was formed.

Bis(p-hydroxyphenyl)-acetic acid (I). a. *By demethylation of* VII. Conventional demethylation methods yielded only tars. The Prey method,[12] however, gave good results. A mixture of 1.0 g. of VII and 3.0 g. of pyridine hydrochloride was heated for 40 min. to 210°. The reaction mixture was dissolved in water, acidified, and extracted with ether. The oil, on digestion with a small quantity of benzene, became crystalline. These crystals of the acid I, contained 1 mole of solvate benzene and were found to be identical in every respect to those obtained by method b.

b. *By condensing glyoxylic acid with phenol.* A solution of 37.6 g. (0.2 mole) of phenol and 2 ml. water was placed in a small flask fitted with a stirrer and thermometer. Also added was half of a solution made from 16.1 g. (0.1 mole) of glyoxylic acid (92%; Kay-Fries Chemicals, Inc., West Haverstraw, N. Y.) and 10 ml. 10*N* sulfuric acid. The mixture was heated to 30° and the heat source withdrawn. The exothermic reaction will start slowly, only after 10 to 60 min. The temperature must not go above 50°. When it has fallen to 40°, then the second half of the solution is added.

Experience has shown that when the reaction is done at higher temperature (70°), then it may easily go out of control and heat to its boiling point (110°). In such case, the crude acid is more difficult to purify, since it contains more gummy matter.

The homogeneous, almost colorless reaction mixture becomes turbid and viscous on cooling to 20°. After standing a few days at room temperature, it will usually solidify to a white crystal mass. It may be worked up before crystallization sets in. It is dissolved in 100 ml. water, extracted by ether and the ether extract in turn by 240–280 ml. of 2*N* sodium carbonate.

The phenolic part, an oil, yields 3.5–6.4 g. of phenol on distillation. The oily residue in the distillation flask is refluxed with a small amount of benzene and on cooling, crystals of VIII form (0.6–1.3 g., m.p. 145–165°).

The acid, left after the evaporation of the ether, is a light tan oil which, after shaking with 50 ml. warm benzene, will very slowly yield fine white needles. They are filtered off and washed with benzene, sucked free from oily matter and dried at 50–60°.

The crude acid (39–44 g.) is recrystallized from 3.7–4.4 l. of 1,2-dichloroethane. The acid will crystallize in the form of long, white needles sticking to the walls of the flask. They contain 1 mole of solvent, which they lose at 125°. The yield of solvent free acid (I) is 22.1–28.3 g. (45–58%), m.p. 146.5–151.0°.

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(5) Th. Zincke and S. Münch, *Ann.*, **335**, 184 (1904) give a m.p. of 220–225° for 4,4'-dihydroxytolan and a m.p. of 198° for its acetylderivative.

(6) The melting point of 4,4'-dihydroxybenzil is given in the literature variously from 235–252°.

(7) R. E. Vanderlinde, F. D. Vasington, and W. W. Westerfield, *J. Am. Chem. Soc.*, **77**, 4178 (1955) give a m.p. of 87° for the 4,4'-diacetoxybenzil.

(8) A. Schönberg and O. Krämer, *Ber.*, **55**, 1189 (1922) give a m.p. of 170° for the dibenzoylcompound of 4,4'-dihydroxybenzil.

(9) H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **70**, 2621 (1948).

(10) After this work was finished, it was found that this compound was mentioned by M. Trojna and J. Hubacek, *Chem. Abstr.*, **51**, 11297d (1957). They obtained it in a yield of 35% by heating II with aqueous sodium hydroxide. Their compound melted at 210°.

(11) (a) P. Fritsch and F. Feldmann, *Ann.*, **306**, 78, 83 (1899). (b) R. Quelet and J. Gavarret, *Chem. Abstr.*, **44**, 5331i (1950). (c) E. Buchta and H. Weidinger, *Chem. Abstr.*, **48**, 3938h (1954), a m.p. of 111°.

(12) V. Prey, *Ber.*, **74**, 1219 (1941); **75**, 445 (1942).

The acid may also be recrystallized by dissolving it in pure ether (1 g. in 2 ml.), then adding 5 ml. benzene; or from chloroform, in which it is scarcely soluble, by extracting it with that solvent in a modified Soxhlet. The crystals thus obtained contain 1 mole of solvent:

Formula	Theory for Solvent Content	Found: Loss in Weight at 110°, %
$C_{14}H_{12}O_4 \cdot CHCl_3$	32.85	31.9
$C_{14}H_{12}O_4 \cdot (ClCH_2)_2$	28.86	27.6 ± 1.0
$C_{14}H_{12}O_4 \cdot C_6H_6$	24.22	23.9 ± 0.4

The pure acid (I) melts at 148–151°, then usually solidifies again and now melts at 157.9–159.1°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95; mol. wt. 244. Found: C, 68.80; H, 4.95; neut. equiv. 245.

This acid is very soluble in water, ethanol, ether, acetone, and acetic acid. By heating a mixture of I with $CaCO_3$ (1 g. and 5 g.) to 250°, a small quantity of 4,4′-dihydroxydiphenylmethane was obtained.

By treatment of I in pyridine with acetic anhydride, a noncrystalline acetylderivative was obtained, which on oxidation with CrO_3 in acetic acid, yielded 4,4′-diacetoxybenzophenone, m.p. 153°.

Methylester of I. By treating I with ethereal diazomethane solution an oil was obtained which, on rubbing with benzene, became crystalline. After crystallizations from benzene (1 g. in 100 ml.), this ester melted at 150.5–152.6°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.74; H, 5.50. Found: C, 70.10; H, 5.36.

The monomethyl ether of this ester has only recently been described.[13]

Methyl ester of VII. By treating the acid (I) dissolved in 5*N* sodium hydroxide with an excess of dimethyl sulfate and recrystallizing the insoluble reaction product from methanol, crystals were obtained which melted at 65.0–65.5° (lit. 66–67°[11a]). By hydrolyzing this methylester, acid VII was obtained.

Ethyl ester of I. This ethyl ester, made from 10 g. of I, 50 ml. ethanol and 1 ml. concentrated sulfuric acid, was purified by dissolving it in the minimum amount of warm acetone and then adding benzene; or by crystallization from a considerable quantity of benzene. Colorless crystals, m.p. 163.3–165.7°. They were very soluble in acetone and ethanol.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.81; H, 5.85.

3-(p-Hydroxyphenyl)-2-coumaranone (VIII). This phenol, formed as a by-product in the condensation of phenol with glyoxylic acid, can be purified by sublimation at 150° at 10 microns pressure, followed by crystallizations from benzene (1 g. in 27 ml.); fine needles melting at 168.8–169.5°.[14]

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.42; mol. wt. 226. Found: C, 74.59; H, 4.87; mol. wt. 233.

The initially colorless solution of this phenol in 0.1*N* sodium hydroxide slowly turns to yellow and then to brown.

Acetyl derivative of VIII. The acetylderivative, crystallized from 41% ethanol, melted at 94.6–95.8°.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.47. Found: C, 71.60; H, 4.59.

(p-Methoxyphenyl)-(o-methoxyphenyl)acetic acid (IX). A solution of 3.0 g. of VIII in 30 ml. 5*N* sodium hydroxide was treated with 3 portions of 5 ml. each of dimethyl sulfate, keeping the mixture alkaline by addition of 40 ml. 5*N* sodium hydroxide. The alkali insoluble oil solidified on cooling (3.0 g.) and is the methyl ester of IX. On acidification of the alkaline solution, an oil fell out, which soon solidified (0.6 g., m.p. 139–140°). This acid, after crystallizations either from 50% acetic acid or benzene, formed white crystals melting at 140.0–141.0° (IX).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.58; H, 5.89; —OCH_3, 22.8; mol. wt. 272. Found: C, 71.17; H, 5.98; —OCH_3, 24.4; neut. equiv. 275.

The methyl ester of IX. This ester may be recrystallized from 41% ethanol, or better yet by dissolving it out of a Soxhlet thimble with petroleum ether. It forms colorless crystals, m.p. 70.3–71.0°. On alkaline hydrolysis the acid IX is obtained.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.33; H, 6.29; —OCH_3, 32.5; mol. wt. 286. Found: C, 71.95; H, 6.31; —OCH_3, 33.3; mol. wt. 281.

Oxidation of IX. To a solution of 0.4 g. of IX in 10 ml. acetic acid was added at 25° 0.2 g. of CrO_3. The colorless crystals were washed with 0.1*N* sodium hydroxide and water (0.18–0.21 g.). After sublimation at 100° and 10 microns pressure, followed by cryst. from 80% ethanol, they melted at 77.2–78.0°. The compound is insoluble in *N* sodium hydroxide.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.37; H, 5.78; —OCH_3, 25.6; mol. wt. 242. Found: C, 74.48; H, 5.76; —OCH_3, 25.6; mol. wt. 262.

The melting point of 2,4′-dimethoxybenzophenone is given in the literature as 99–100°.[15] When 2,4′-dihydroxybenzophenone (m.p. 146–147°) made by two different methods[16] was methylated with dimethyl sulfate, the resulting 2,4′-dimethoxybenzophenone, crystallized from 80% ethanol, was found to melt at 77.8–78.9°. They had the properties of the oxidation product and the mixture melted at 77.5–78.1°.

Later it was found that this is the dimorphic, less stable form of 2,4′-dimethoxybenzophenone. After several months, samples of the compound of m.p. 78° were found to melt at 97.8–98.1°. A mixture of the latter with a sample of 2,4′-dimethoxybenzophenone (m.p. 97.9–98.2°), kindly sent by Dr. Sunagawa,[15] melted at 98°.

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(13) O. E. Schultz and J. Schnekenburger, *Arch. Pharm.* **291/63**, 361 (1958).

(14) S. Yukawa, *Chem. Abstr.*, **23**, 832[9] (1929) gives a m.p. of 158° for a compound believed to have this structure.

(15) R. Stoermer, *Ber.*, **41**, 323 (1908); P. Pfeiffer, *Ann.*, **398**, 168 (1913); G. Sunagawa, *Pharm. Bull. (Japan)*, **3**, 123 (1955).

(16) A. Baeyer, *Ann.*, **354**, 177 (1907); W. R. Orndorff and W. R. Barrett, *J. Am. Chem. Soc.*, **46**, 2488 (1924).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Synthesis of Reserpine Analogs[1,2]

FRED A. TURNER AND JAMES E. GEARIEN

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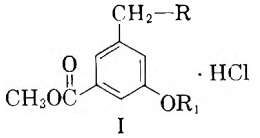
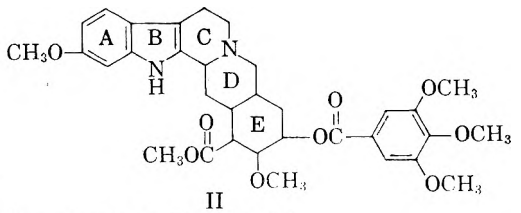
Esters of methyl 3-hydroxy-5-piperidinomethylbenzoate and of methyl 3-hydroxy-5-diethylaminomethylbenzoate were prepared and subjected to pharmacological testing. These compounds, resembling in structure a portion of the reserpine molecule, failed to show appreciable pharmacological activity. Esters of 3-piperidinomethylphenol, 3-diethylaminomethylphenol, 3-piperidinomethylbenzoic acid, and 3-diethylaminobenzoic acid were also prepared and were without pharmacological activity. All compounds were obtained as their hydrochlorides.

Esters of methyl 3-hydroxy-5-piperidinomethylbenzoate and of methyl 3-hydroxy-5-diethylaminomethylbenzoate (I) may be regarded as analogs of a portion of the reserpine molecule (II). The above



I



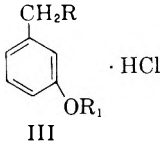
II

Ia. R = piperidino, R_1 = acetyl
Ib. R = diethylamino, R_1 = benzoyl
Ic. R = piperidino, R_1 = 3,4,5-trimethoxybenzcyl
Id. R = diethylamino, R_1 = 3,4,5-trimethoxybenzoyl

compounds possess ring E of the reserpine molecule as an aromatic ring, a portion of ring D, and all or a portion of ring C. The aromatic ring is substituted similarly to ring E of the reserpine molecule, except that the C-17 methoxyl group has been omitted. The presence of this group was deemed unnecessary to pharmacological activity since 17-desmethoxydeserpidine[3] has been shown to possess both the hypotensive and tranquilizing action of the naturally occurring alkaloids. The indole ring system, absent in the reportedly active diethylaminopropyl ester of 3,4,5-trimethoxybenzoic acid,[4] was also omitted.

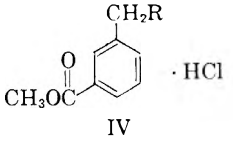
In an attempt to prepare compounds of simple chemical structure that possess both the tranquilizing and hypotensive activity of reserpine, the acetic acid ester (Ia) and the 3,4,5-trimethoxybenzoic acid ester (Ic) of methyl 3-hydroxy-5-piperidinomethylbenzoate, the benzoic acid ester (Ib) and the 3,4,5-trimethoxybenzoic acid ester (Id) of methyl 3-hydroxy-5-diethylaminomethylbenzoate were prepared as their hydrochlorides.

In the hope of observing the effects of further modification of molecular structure upon pharmacological activity, similar esters of 3-piperidinomethylphenol (IIIa and IIIc) and 3-diethylaminomethylphenol (IIIb and IIId), as well as the methyl esters of 3-piperidinomethylbenzoic acid (IVa) and 3-diethylaminomethylbenzoic acid (IVb), were also synthesized as their hydrochlorides.



III

IIIa. R = piperidino, R_1 = acetyl
IIIb. R = diethylamino, R_1 = acetyl
IIIc. R = piperidino, R_1 = 3,4,5-trimethoxybenzoyl
IIId. R = diethylamino, R_1 = 3,4,5-trimethoxybenzoyl



IV

IVa. R = piperidino
IVb. R = diethylamino

The esters of the 3-(*N*-substituted)aminomethylphenol (III) were prepared by photobrominating *m*-cresyl acetate to yield slightly impure 3-bromomethylphenyl acetate. This compound when reacted with piperidine or diethylamine yielded 3-piperidinomethylphenyl acetate and 3-diethylaminomethylphenyl acetate, respectively. The 3,4,5-trimethoxybenzoyl derivatives were prepared from the corresponding acetyl compounds by hydrolysis followed by esterification with 3,4,5-trimethoxybenzoyl chloride in a two phase Schotten-Baumann reaction.

The methyl esters of 3-(*N*-substituted)aminomethylbenzoic acids were similarly prepared from methyl *m*-toluate.

Esters of methyl 3-hydroxy-5-diethylaminomethylbenzoic acid and methyl 3-hydroxy-5-piperidinomethylbenzoic acid were somewhat more difficult to prepare and required the synthesis of 3-hydroxy-5-methylbenzoic acid (VII). The preparation of this

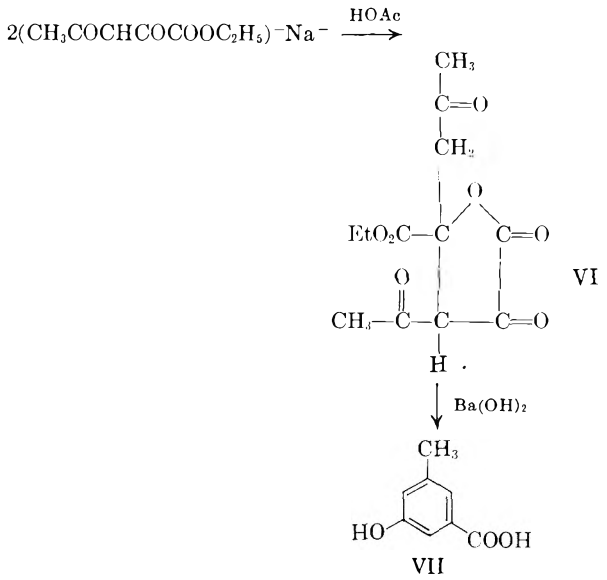
(1) Presented before the Medicinal Division at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958.

(2) Abstracted from a thesis submitted by Fred A. Turner to the faculty of the University of Illinois in partial fulfillment of the requirement for the degree of Master of Science.

(3) F. Weisenborn, *J. Am. Chem. Soc.*, **79**, 4818 (1957).

(4) F. M. Miller and M. S. Weinberg, abstracts of papers, 130th Meeting, American Chemical Society, Atlantic City, N. J., Sept. 16–21, 1956.

compound from ethyl sodioacetopyruvate (V) by the following series of reactions was first reported by Claisen.[5] Unfortunately specific directions for carrying out the reactions which were later reported by Meldrum and Perkins[6] did not prove to be satisfactory for the synthesis of relatively large amounts of the compound. Difficulty was encountered in the isolation of Claisen's compound (VI) from the acetic acid used in its preparation. It was only after acetic acid was replaced with a mixture of equal volumes of water and acetic acid that a satisfactory yield of the compound was obtained. Conversion of Claisen's compound (VI) to 3-hydroxy-5-methylbenzoic acid (VII) also proved difficult. While Meldrum and Perkins reported that satisfactory yields of this acid were obtained by warming Claisen's compound with an aqueous suspension of barium hydroxide, we were able to obtain yields of only 20% of the theoretical. In attempts to substitute barium oxide, calcium oxide, and magnesium oxide for the prescribed barium hydroxide, magnesium oxide proved to be the most effective giving yields up to 50% of the theoretical.



VI

VII

In the preparation of the desired reserpine analogs, 3-hydroxy-5-methylbenzoic acid was then esterified with methyl alcohol, and the resulting ester acetylated. This diester was photobrominated to give slightly impure methyl 3-acetoxy-5-bromomethylbenzoate. When either diethylamine or piperidine was treated with methyl 3-acetoxy-5-bromomethylbenzoate, the products were methyl 3-hydroxy-5-diethylaminomethylbenzoate and methyl 3-hydroxy-5-piperidinomethylbenzoate rather than the expected acetyl derivatives. These compounds were identified as their hydrochlorides.

Attempts to prepare the acetate and the 3,4,5-trimethoxybenzoates of methyl 3-hydroxy-5-diethylaminomethyl or methyl 3-hydroxy-5-piperidinomethylbenzoate by a two phase Schotten-Baumann reaction failed, probably due to the hydrolysis of the carbomethoxyl group. Esterification was accomplished by warming the phenolic compounds with acetic anhydride and pyridine or with 3,4,5-trimethoxybenzoyl chloride and pyridine. Acetylation of methyl 3-hydroxy-5-diethylaminomethylbenzoate followed by treatment with hydrogen chloride yielded an oil which would not crystallize. In order to obtain a solid derivative for pharmacological testing the benzoate was prepared from benzoyl chloride in the presence of pyridine. None of these compounds when subjected to pharmacological testing showed appreciable pharmacological activity.

EXPERIMENTAL[7]

γ-Lactone of 2,6-diketo-3-acetyl-4-carboethoxy-4-hydroxyheptanoic acid (Claisen's compound). A mixture of 321 g. (1.78 mol.) of ethyl sodioacetopyruvate,[8] 400 ml. of acetic acid, and 400 ml. of water was stirred for 2 hr. During this time the solid dissolved and the solution became gray. The contents of the flask was poured over 1 kg. of crushed ice in 150 ml. of sulfuric acid. The resulting acid, which was filtered and washed with cold water, weighed 205 g. (80%). It melted after recrystallization from water at 89–91°, lit. 90°.[5]

3-Hydroxy-5-methylbenzoic acid. To 1.5 l. of water, previously warmed on a steam bath, were added with stirring 190 g. (0.660 mol.) of Claisen's compound and 120 g. (3.0 mol.) of magnesium oxide. The mixture immediately became a deep reddish orange color which turned light brown in about 15 min. The stirring and heating was continued for about 30 min. after the addition of the solids.

The magnesium oxalate and excess magnesium oxide were removed by filtration, washed with warm water, and the filtrate was concentrated under vacuum to 200 ml. This concentrated solution was placed in an ice bath and treated with 150 ml. of 1:1 hydrochloric acid to precipitate the crude 3-hydroxy-5-methylbenzoic acid. The solid was filtered and washed with cold water. After recrystallization from water, 42.3 g. (42%) of a white solid melting at 206–207° was obtained (lit. 207–208°).[5]

Methyl 3-hydroxy-5-methylbenzoate. A solution of 41.6 g. (0.27 mol.) of 3-hydroxy-5-methylbenzoic acid, 100 ml. of methanol, and 10.0 ml. of sulfuric acid was refluxed on a steam bath for 5 hr. The excess methanol was removed by distillation and the residue was poured over 300 g. of crushed ice to precipitate the ester. The excess sulfuric acid was neutralized by the addition of sodium bicarbonate. The methyl 3-hydroxy-5-methylbenzoate was collected by filtration and washed with cold water. After drying, 41.5 g. (91%) of crude product was obtained. Upon recrystallization from ethanol-water, the white solid melted at 96–97°. The reported melting point is 97°.[9]

Methyl 3-acetoxy-5-methylbenzoate. A mixture of 41.5 g. (0.25 mol.) of methyl 3-hydroxy-5-methylbenzoate, 85 ml. of acetic anhydride, and 5 ml. of phosphoric acid was heated on a steam bath for 15 min. Then 100 ml. of water was carefully added to the hot solution to destroy the excess acetic anhydride. The resulting solution was poured over 500 g. of cracked ice to yield an oil which solidified after scratching

(5) L. Claisen, *Ber.*, **22**, 3271 (1889).

(6) A. N. Meldrum and W. H. Perkins, *J. Am. Chem. Soc.*, **95**, 1889 (1909).

(7) All melting points are uncorrected. The carbon and hydrogen analyses were performed by Weiler and Strauss Analytical Laboratories, Oxford, England.

(8) *Org. Syntheses*, **Coll. Vol. I**, 238 (1941).

(9) E. Bernatek, *Acta Chem. Scand.*, **5**, 1318 (1951).

the side of the beaker. The solid was collected by filtration and washed with cold water. The crude methyl 3-acetoxy-5-methylbenzoate was purified by distillation under reduced pressure. A colorless oil boiling at 105–110°/0.2 mm. was obtained. It crystallized upon cooling. Yield 46.5 g. (91%). A sample after recrystallization from ethanol-water melted at 67°.

Anal. Calcd. for $C_{11}H_{12}O$: C, 63.45; H, 5.81. Found: C, 63.65; H, 5.64.

Photobromination of methyl 3-acetoxy-5-methylbenzoate. A 500-ml. ground glass three necked flask was equipped with an addition funnel containing 100 ml. of a 2*M* bromine solution in carbon tetrachloride and a reflux condenser connected to a gas adsorption trap. The third neck was closed with a glass stopper. A 500-watt clear glass tungsten lamp was placed about 1 in. from the flask. A solution of 41.6 g. (0.2 mol.) of methyl 3-acetoxy-5-methylbenzoate in 100 ml. of carbon tetrachloride was placed in the flask and gently refluxed upon the steam bath. The bromine solution was added at such a rate that the reaction mixture just retained a red color. The reaction was completed when all of the bromine solution had been added and the red color of the reaction mixture disappeared. This required from 20–30 min. The carbon tetrachloride was removed under vacuum and the residue was fractionally distilled. A colorless viscous oil consisting chiefly of methyl 3-acetoxy-5-bromomethylbenzoate was obtained. Yield 34.1 g. (59%) b.p. 158–164°/0.2 mm.

Photobromination of methyl m-toluate. Thirty g. (0.2 mol.) of methyl *m*-toluate[10] was photobrominated in the same manner as described above. A colorless oil boiling between 100–109° at 0.2 mm. pressure was collected. The yield of impure methyl 3-bromomethylbenzoate was 24.3 g. (53%).

Photobromination of m-cresyl acetate. Starting from 30.0 g. (0.20 mol.) of *m*-cresyl acetate,[11] 3-bromomethylphenyl acetate was prepared in the same manner as that described for the photobromination of methyl 3-acetoxy-5-methylbenzoate. The yield of impure colorless product boiling between 98–102° at 0.2 mm. pressure was 24.5 g. (54%).

Methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride. To a solution of 17.2 g. (0.06 mol.) of methyl 3-acetoxy-5-bromomethylbenzoate in 150 ml. of dry benzene, was added a solution of 10.2 g. (0.12 mol.) of redistilled piperidine in 150 ml. of dry benzene. Almost immediately piperidine hydrobromide precipitated. The reaction mixture was refluxed for 1 hr. and then cooled in an ice bath. The piperidine hydrobromide was removed by filtration and washed with benzene.

The benzene was distilled under vacuum and the brown liquid residue taken up in anhydrous ether. A small amount of additional piperidine hydrobromide precipitated from the ether and was removed by filtration. After drying over anhydrous magnesium sulfate, the ether solution was treated with hydrogen chloride gas and a gummy solid was obtained. The ether was decanted and the remaining gum was then dissolved in 20 ml. of cold methanol and anhydrous ether added until a faint turbidity was produced. Upon cooling, a white crystalline solid was obtained. The solid gave a purple color with ferric chloride solution and was soluble in an excess of 10% sodium hydroxide solution indicating that the 3-acetoxy group was hydrolyzed during the reaction. The yield of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride was 9.9 g. (58%), m.p. 234–235° (dec.).

Anal. Calcd. for $C_{14}H_{20}O_3NCl$: C, 58.85; H, 7.06; Cl, 12.41. Found: C, 58.45; H, 7.25; Cl, 12.34.

Methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride. From 17.2 g. (0.06 mol.) of methyl 3-acetoxy-5-bromomethylbenzoate and 8.8 g. (0.12 mol.) of redistilled diethylamine, methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride was prepared in the same manner as described above. Yield 8.9 g. (54%), m.p. 177–178°.

Anal. Calcd. for $C_{13}H_{20}O_3NCl$: C, 57.02; H, 7.36; Cl, 12.95. Found: C, 56.73; H, 7.19; Cl, 12.80.

3-Piperidinomethylphenyl acetate hydrochloride (IIIa). The condensation of 10.2 g. (0.12 mol.) of piperidine and 13.7 g. (0.06 mol.) of 3-bromomethylphenyl acetate was carried out in a manner similar to that described for the preparation of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride. In this reaction the white crystalline hydrochloride did not give a purple color with ferric chloride solution and was insoluble in an excess of sodium hydroxide solution, indicating that hydrolysis did not occur during the reaction. The yield of 3-piperidinomethylphenyl acetate hydrochloride was 6.7 g. (41%), m.p. 215–216°.

Anal. Calcd. for $C_{14}H_{20}O_2NCl$: C, 62.34; H, 7.48; Cl, 13.15. Found: C, 62.06; H, 7.49; Cl, 13.01.

3-Diethylaminomethylphenyl acetate hydrochloride (IIIb). From 13.7 g. (0.06 mol.) of 3-bromomethylphenyl acetate and 8.8 g. (0.12 mol.) of diethylamine, 6.12 g. (39%) of 3-diethylaminomethylphenyl acetate hydrochloride was prepared following the procedure for the preparation of 3-piperidinomethylphenyl acetate hydrochloride, m.p. 172–173°.

Anal. Calcd. for $C_{13}H_{20}O_2NCl$: C, 60.56; H, 7.82; Cl, 13.75. Found: C, 60.40; H, 7.70; Cl, 13.72.

Methyl 3-piperidinomethylbenzoate hydrochloride (IVa). The reaction between 10.2 g. (0.12 mol.) of piperidine and 13.7 g. (0.06 mol.) of methyl 3-bromomethylbenzoate was carried out in a manner identical to that used for the preparation of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride. The yield of methyl 3-piperidinomethylbenzoate hydrochloride was 6.25 g. (38%), m.p. 214–215°. A mixed melting point with 3-piperidinomethylphenyl acetate hydrochloride showed a marked depression 187–192°.

Anal. Calcd. for $C_{14}H_{20}O_2NCl$: C, 62.34; H, 7.48; Cl, 13.15. Found: C, 61.97; H, 7.41; Cl, 13.04.

Methyl 3-diethylaminomethylbenzoate hydrochloride (IVb). Starting with 13.7 g. (0.06 mol.) of methyl 3-bromomethylbenzoate and 8.8 g. (0.12 mol.) diethylamine, methyl 3-diethylaminomethylbenzoate hydrochloride was prepared following the procedure previously described for the preparation of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride. Yield 8.6 g. (55%), m.p. 147–148°.

Anal. Calcd. for $C_{13}H_{20}O_2NCl$: C, 60.56; H, 7.82; Cl, 13.75. Found: C, 60.92; H, 8.03; Cl, 13.72.

3-Piperidinomethylphenol hydrochloride. Ten g. (0.037 mol.) of 3-piperidinomethylphenyl acetate and 100 ml. of a 5% solution of hydrogen chloride in methanol were refluxed for 1 hr. The excess methanol was removed by distillation and the viscous residue was dissolved in 10 ml. of methanol. Anhydrous ether was added until a faint turbidity was produced. Upon cooling, the desired 3-piperidinomethylphenol hydrochloride crystallized. Yield 7.1 g. (84%), m.p. 163–164°.

Anal. Calcd. for $C_{12}H_{18}ONCl$: C, 63.40; H, 7.98; Cl, 15.60. Found: C, 63.29; H, 8.01; Cl, 15.49.

3-Diethylaminomethylphenol hydrochloride. The methanolysis of 10.0 g. (0.39 mol.) of 3-diethylaminomethylphenyl acetate hydrochloride was carried out in a similar manner to that described above. The yield of 3-diethylaminomethylphenol hydrochloride was 6.9 g. (82%), m.p. 133–134°.

Anal. Calcd. for $C_{11}H_{18}ONCl$: C, 61.25; H, 8.41; Cl, 16.44. Found: C, 61.03; H, 8.30; Cl, 16.33.

3,4,5-Trimethoxybenzoyl chloride. The method used for the preparation of 3,4,5-trimethoxybenzoyl chloride was that of Marsh and Stephen.[12] Twenty g. (0.9 mol.) of 3,4,5-tri-

(10) P. N. Raikow and P. Tischkow, *Chem. Ztg.*, **29**, 1269 (1905).

(11) A. Claus and J. Hirsch, *J. prakt. Chem.*, (2) **39**, 62 (1889).

(12) J. T. Marsh and H. Stephen, *J. Chem. Soc.*, **127**, 1633 (1925).

methoxybenzoic acid yielded 20.4 g. (94.2%) 3,4,5-trimethoxybenzoyl chloride, m.p. 79–80°, lit. 76–78.[13]

Methyl 3-acetoxy-5-piperidinomethylbenzoate hydrochloride (Ia). To a mixture of 7.0 g. (0.025 mol.) of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride and 150 ml. of pyridine contained in a 250-ml. glass-stoppered flask was added 15 ml. of acetic anhydride. The mixture after shaking for 3 hr. yielded a homogeneous solution which was allowed to stand overnight at room temperature. The pyridine was removed by distillation under reduced pressure and the residue dissolved in methanol. Anhydrous ether was added to the methanol solution until a faint turbidity was produced. The product then crystallized upon cooling, to yield 6.3 g. (78%) of methyl 3-acetoxy-5-piperidinomethylbenzoate hydrochloride, m.p. 177–178°.

Anal. Calcd. for $C_{16}H_{22}O_4NCl$: C, 58.62; H, 6.77; Cl, 10.82. Found: C, 58.47; H, 6.72; Cl, 10.92.

Methyl 3-benzoyloxy-5-diethylaminomethylbenzoate hydrochloride (Ib). Five g. (0.018 mol.) of methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride, 150 ml. of pyridine and 5 ml. of benzoyl chloride were placed in a glass-stoppered flask, shaken for 30 min. and allowed to stand for 24 hr. at room temperature. After removal of the pyridine under pressure, the residue was dissolved in isopropyl alcohol and anhydrous ether was added to produce a faint turbidity. Upon cooling, the product crystallized and 4.7 g. (68%) of methyl 3-benzoyloxy-5-diethylaminomethylbenzoate hydrochloride was obtained, m.p. 167–168° (dec.).

Anal. Calcd. for $C_{20}H_{24}O_4NCl$: C, 63.58; H, 6.40; Cl, 9.39. Found: C, 63.28; H, 6.13; Cl, 9.50.

Methyl 3-(3′,4′,5′-trimethoxybenzoyloxy-5-piperidinomethylbenzoate hydrochloride) (Ic). A mixture of 5.0 g. (0.018 mol.) of methyl 3-hydroxy-5-piperidinomethylbenzoate hydrochloride, 8.1 g. (0.036 mol.) of 3,4,5-trimethoxybenzoyl chloride and 250 ml. of pyridine was shaken for 4 hr. The homogeneous solution was then allowed to stand at room temperature for one day. Upon the removal of the pyridine under reduced pressure, a red solid was obtained. After recrystallization of the solid from methanol and ether, 6.3 g. (75%) of colorless methyl 3-(3′,4′,5′-trimethoxybenzoyloxy)-5-piperidinomethylbenzoate hydrochloride was obtained, m.p. 202–203° (dec.).

Anal. Calcd. for $C_{24}H_{30}O_7NCl$: C, 60.05; H, 6.30; Cl, 7.39. Found: C, 59.80; H, 6.21; Cl, 7.34.

Methyl 3-(3′,4′,5′-trimethoxybenzoyloxy-5-diethylaminobenzoate hydrochloride) (Id). From 5.0 g. (0.018 mol.) of methyl 3-hydroxy-5-diethylaminomethylbenzoate hydrochloride, 8.5 g. (0.036 mol.) of 3,4,5-trimethoxybenzoyl chloride, and 250 ml. of pyridine, 4.95 g. (58%) of methyl 3-(3′,4′,5′-trimethoxybenzoxy)-5-diethylaminomethylbenzoate hydrochloride was obtained when the procedure described for the preparation of methyl 3-(3′,4′,5′-trimethoxybenzoyloxy-5-piperidinomethylbenzoate hydrochloride) was followed, m.p. 191–192°.

Anal. Calcd. for $C_{23}H_{30}O_7NCl$: C, 59.04; H, 6.46; Cl, 7.58. Found: C, 59.34; H, 6.42; Cl, 7.48.

3′-Piperidinomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride (IIIc). A solution of 6.1 g. (0.026 mol.) of 3,4,5-trimethoxybenzoyl chloride in 50 ml. of ether was added to a solution of 3.0 g. (0.013 mol.) of 3-piperidinomethylphenol hydrochloride in 25 ml. of 10% sodium hydroxide and the mixture was vigorously shaken for 20 min. The ether layer was separated and the aqueous layer was extracted with two 25-ml. portions of ether which were combined with the original ether solution. The combined ether extract was washed with 20 ml. of water and dried over anhydrous magnesium sulfate. Anhydrous hydrogen chloride when passed through the ether solution produced a white solid. After recrystallization of the solid from methanol and ether, 3.5 g. (53%) of 3′-piperidinomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride was obtained, m.p. 163–164°. A mixed melting point with the starting hydroxyl compound showed a marked depression (142–147°).

Anal. Calcd. for $C_{22}H_{23}O_5NCl$: C, 62.63; H, 6.69; Cl, 8.40. Found: C, 62.74; H, 6.60; Cl, 8.32.

3′-Diethylaminomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride (IIId). From 2.0 g. (0.009 mol.) of 3-diethylaminomethylphenol hydrochloride, and 4.3 g. (0.018 mol.) of 3,4,5-trimethoxybenzoyl chloride, 3.0 g. (79%) of 3′-diethylaminomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride was prepared in a manner analogous to that described for 3′-piperidinomethylphenyl 3,4,5-trimethoxybenzoate hydrochloride, m.p. 166–167°.

Anal. Calcd. for $C_{21}H_{28}O_5NCl$: C, 61.53; H, 6.89; Cl, 8.65. Found: C, 61.47; H, 7.29; Cl, 8.77.

Acknowledgment. The authors are grateful to Abbott Laboratories for screening the compounds for pharmacological activity.

CHICAGO, ILL.

(13) J. Koo, *J. Am. Chem. Soc.*, **75**, 720 (1953).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Some Acetate Migration and Participation Reactions in Steroids[1]

ROBERT G. SCHULTZ[2]

Received June 29, 1959

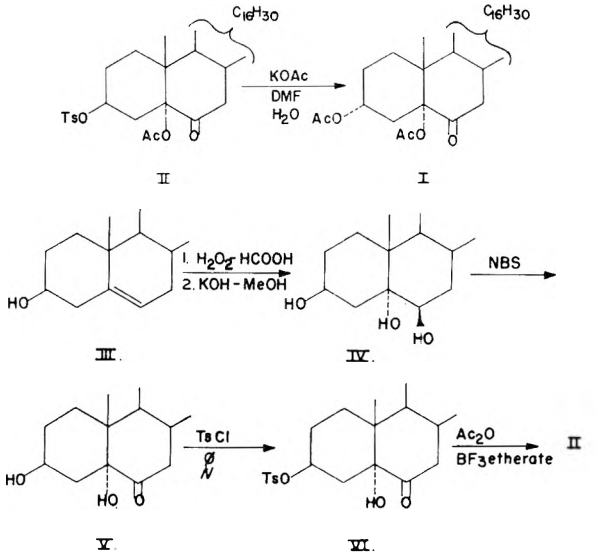
In an attempt to produce cholestan-3α,5α-diol-6-one-3,5-diacetate by solvolysis of cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate in dimethylformamide, water, and potassium acetate, cholestan-3α,5α-diol-6-one-3-acetate was the only product isolated. When the reaction was carried out without added potassium acetate the product was cholestan-3α,5α-diol-6-one-5-acetate. The 5-acetate rearranged to the 3-acetate by treatment with dimethylformamide, water, and potassium acetate.

In the course of other synthetic studies, it became necessary to synthesize cholestan-3α,5α-diol-6-one diacetate (I). The route selected involved as a last step solvolysis of cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate (II) with potassium acetate in a dimethylformamide-water system. The tosylate (II) was synthesized as shown.

Cholesterol (III) was oxidized to cholestan-3β,5α-diol-6-one (V) in a two-step procedure described by

(1) Presented in part at the 135th Meeting of the American Chemical Society, Boston, April 1959; Abstracts p. 23-0.

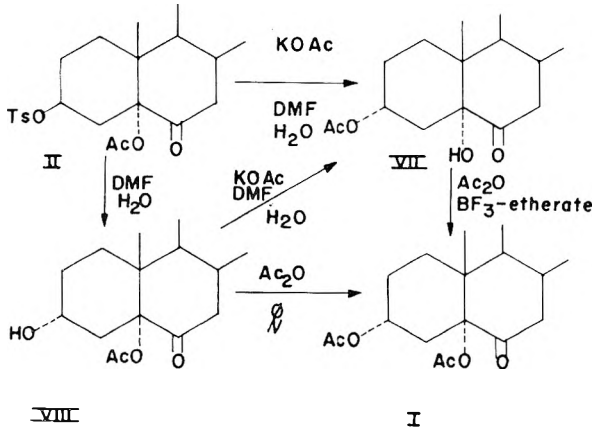
(2) Present address: Central Research Laboratories, Monsanto Chemical Co., Dayton 7, Ohio.



Fieser and Rajagopalan[3] and the diolone (V) was then treated successively with *p*-toluenesulfonyl chloride in pyridine and acetic anhydride with boron trifluoride–etherate catalyst to give the desired cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate (II).

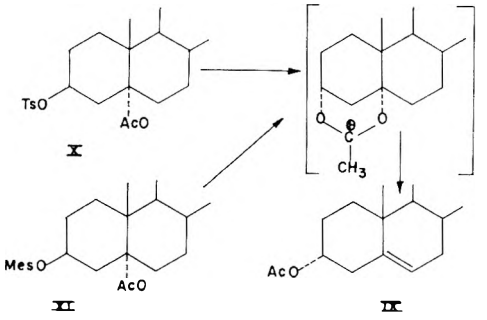
Solvolysis of II in dimethylformamide-water with added potassium acetate afforded a material which proved to be cholestan-3α,5α-diol-6-one-3-acetate (VII). Its structure was established by elemental analysis and acetylation to the desired diacetate (I) with acetic anhydride and boron trifluoride–etherate catalyst. On attempted acetylation with pyridine catalyst, only starting material (VII) was recovered.

In contrast, solvolysis of II in dimethylformamide-water *without* added potassium acetate afforded cholestan-3α,5α-diol-6-one-5-acetate (VIII). This compound could be converted to the diacetate (I) by acetylation with pyridine catalyst and rearranged to cholestan-3α,5α-diol-6-one-3-acetate (VII) on treatment with potassium acetate in a dimethylformamide-water system.

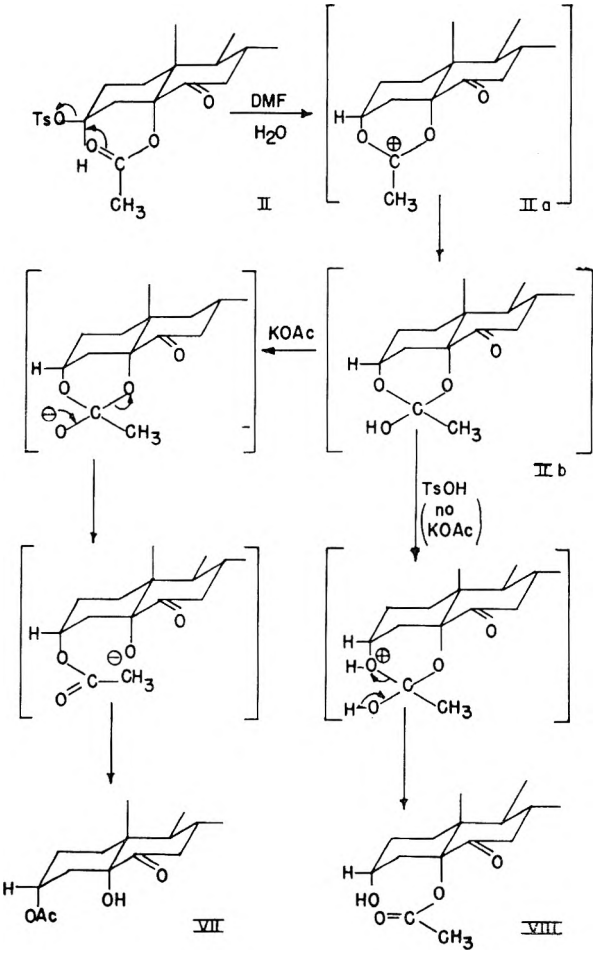


(3) L. F. Fieser and S. Rajagopolan, *J. Am. Chem. Soc.*, 71, 3938 (1949).

A somewhat similar internal 1,3-acetate rearrangement was noted by Plattner, who obtained epicholesterol (IX) by solvolysis of either cholestan-3β,5α-diol-3-tosylate-5-acetate (X)[4a] or cholestan-3β,5α-diol-3-mesylate-5-acetate (XI).[4b] He postulated a 3,5-bridged intermediate.



A possible explanation for the rearrangements in the cholestan-diolone series involves the cyclic ortho ester structure (IIb). When potassium acetate is present, it may, in addition to acting as a buffer for the *p*-toluenesulfonic acid formed, also act as a base to remove the proton from the hydroxyl of the ortho ester. The anion so formed could then col-



(4) (a) P. A. Plattner and W. Lang, *Helv. Chim. Acta*, **27**, 1872 (1944). (b) P. A. Plattner, A. Furst, F. Koller, and W. Lang, *Helv. Chim. Acta*, **31**, 1455 (1948).

lapse to an acetate and the alkoxide of greater stability, which in this case by electrostatic considerations would be the one alpha to the carbonyl group. This alkoxide would then form cholestan-3α,5α-diol-6-one-3-acetate (VII).

In the absence of acetate buffer, the *p*-toluenesulfonic acid formed in the displacement is free to protonate one of the oxygens of the ortho ester, probably the one attached to carbon-3, since this oxygen has a greater electron density than the one attached to carbon-5. This would then account for the formation of cholestan-3α,5α-diol-6-one-5-acetate (VIII).

EXPERIMENTAL

All melting points are corrected. Microanalyses by Mr. J. Nemeth and associates.

Cholestan-3β,5α-diol-6-one (V). The procedure used was a modification of that of Fieser and Rajagopolan.[3] A suspension of 40.0 g. of cholesterol in 400 ml. of 88% formic acid was heated on a steam bath until all the solid disappeared and an oil formed. The mixture was allowed to cool to room temperature, the lumpy mass was broken up, and 40 ml. of 30% hydrogen peroxide was added. The mixture was kept at room temperature with occasional stirring for 5.5 hr. Boiling water (600 ml.) was then added and the suspension was cooled to room temperature. The solid (cholestan-3β,5α,6β-triol-3,6-diformate) was filtered, washed with water, partially air-dried, and dissolved in 1200 ml. of methanol, and 40 ml. of 25% potassium hydroxide was added. The solution was heated on the steam bath for 10 min., acidified with hydrochloric acid, diluted with 400 ml. water, and the resulting suspension was cooled and filtered. The crude cholestan-3β,5α,6β-triol, m.p. 226–232°, was washed with water and air-dried.

The crude triol was suspended in a mixture of 1 l. of ether, 150 ml. of methanol, and 150 ml. of water in a separatory funnel, and 19.6 g. of *N*-bromosuccinimide was added. The mixture was shaken until solution was complete. During this time the reaction mixture turned orange. One l. of water was added to precipitate the diolone. The ether suspension of the crystalline diolone was washed with a dilute solution of sodium bisulfite for decolorization, with sodium hydroxide solution and twice with water. The crystals were then filtered, washed with ether and air-dried, yielding 41.2 g. (95%) of cholestan-3β,5α-diol-6-one, m.p. 220–225° crude (lit. m.p. 232–233°). This material could be recrystallized from chloroform to give pure diolone, m.p. 229–231°, $[\alpha]_D^{27}$ −31.9°, M_D −133°.

Cholestan-3β,5α-diol-6-one-3-tosylate (VI). To a solution of cholestan-3β,5α-diol-6-one (15 g.) in a minimum amount (50 ml.) of dry pyridine, 11.5 g. of *p*-toluenesulfonyl chloride was added and the solution allowed to stand at room temperature for 2 days. The solution was then poured into ice and concentrated hydrochloric acid and the solid extracted with ether. The ether solution was washed with water, 5% hydrochloric acid, water, dilute potassium bicarbonate, and water. Ethanol was then added, the ether was evaporated, and crystallization from ethanol water-yielded 18.0 g. (87.8%) of cholestan-3β, 5α-diol-6-one-3-tosylate, m.p. 139–140° (dec.). Crystallization several times from ethanol-water gave pure tosylate, m.p. 135.5–136.5°, $[\alpha]_D^{27}$ −48.4°, M_D −273°, infrared bands at 3500, 1713, 1194, 1180 cm.$^{-1}$ in chloroform.

Anal. Calcd. for $C_{34}H_{52}O_5S$: C, 71.29; H, 9.15. Found: C, 71.50; H, 9.16.

This compound has been previously reported[5] and the melting point recorded as 161–163° when recrystallized from acetone-hexane. The lower melting form on recrystallization twice from acetone-hexane gave the higher melting form.

Cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate (II). Cholestan-3β,5α-diol-6-one-3-tosylate (18.0 g.) was suspended in 150 ml. of acetic anhydride, 1 ml. of boron trifluoride–etherate complex was added, and the suspension was heated on a steam bath until solution occurred (about 5 min.). After the solution had cooled to room temperature, the crystals that formed were filtered, washed with acetic acid and acetic acid–water and air-dried, yielding 14.4 g. (74.2%) of cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate, m.p. 147.5–149° (dec.). The filtrate on addition of water afforded additional solid, which was filtered, washed with water, and recrystallized from ethanol-water, yielding 1.95 g. of product, m.p. 145–146° (dec.). The total yield was 16.3 g. (84.5%). A sample was recrystallized from methylene chloride–hexane three times to give pure cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate, m.p. 146.5–147°, $[\alpha]_D^{27}$ 3.6°, M_D 22.2°, infrared bands at 1742, 1723, 1238, 1195, 1182 cm.$^{-1}$ in chloroform.

Anal. Calcd. for $C_{36}H_{54}O_6S$: C, 70.32; H, 8.85. Found: C, 70.40; H, 8.86.

Cholestan-3α,5α-diol-6-one-3-acetate (VII). (a) *From Cholestan-3β,5α-diol-6-one-3-tosylate-5-acetate* (II). Cholestan-3β, 5α-diol-6-one-3-tosylate-5-acetate (1.23 g.) was dissolved in 25 ml. of dimethylformamide and 2 ml. of water, 2 g. of potassium acetate was added, and the solution was heated on a steam bath for 16 hr. Water was added, the suspension was cooled and the resulting solid was filtered, washed with water, air-dried, and recrystallized from ethanol-water, to yield 0.675 g. (73.4%) of cholestan-3α,5α-diol-6-one-3-acetate, m.p. 142–147°. An analytical sample, recrystallized three times from ethanol-water, had m.p. 155–156°, and infrared bands at 3580, 1743, 1723 cm.$^{-1}$ in chloroform.

Anal. Calcd. for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.45; H, 10.55.

(b) *From Cholestan-3α,5α-diol-6-one-5-acetate* (VIII). A solution containing cholestan-3α,5α-diol-6-one-5-acetate (100 mg.) and potassium acetate (200 mg.) in 6 ml. of dimethylformamide and 1 ml. of water was heated on a steam bath for 17 hr. Water was added, the suspension was cooled, and the resulting solid was filtered, washed with water, and air-dried to yield 73 mg. of crude solid, m.p. 120–122°. This solid was chromatographed on 1.5 g. of Florisil. The material eluted by 6:1 hexane-benzene was combined (crude wt. 45 mg.) and crystallized from ethanol-water, yielding 41.5 mg. (41.5%) of cholestan-3α,5α-diol-6-one-3-acetate, m.p. 156–157°. Mixed melting point with that prepared by method (a) is undepressed.

Cholestan-3α,5α-diol-6-one-5-acetate (VIII). Cholestan-3β, 5α-diol-6-one-3-tosylate-5-acetate (615 mg.) was dissolved 15 ml. of dimethylformamide and 2 ml. of water and heated on a steam bath for 16 hr. Water was added, the suspension was cooled, and the resulting solid was filtered, washed with water, and air-dried, to yield 467 mg. of solid material, m.p. 137–141°. Recrystallization of this solid from ethanol water yielded 430 mg. (93.5%) of cholestan-3α,5α-diol-6-one-5-acetate, m.p. 137–140°, infrared bands at 3500, 1735, 1721 cm.$^{-1}$ in carbon disulfide.

Cholestan-3α,5α-diol-6-one-3,5-diacetate (I) (a) *from Cholestan-3α,5α-diol-6-one-3-acetate* (VII). Cholestan-3α,5α-diol-6-one-3-acetate (30 mg.) suspended in 15 ml. of acetic anhydride and 10 drops of boron trifluoride–etherate complex was heated on a steam bath for 5 min. and then allowed to cool to room temperature and to stand for 2 hr. Water was added to decompose excess acetic anhydride and precipitate the diacetate. The suspension was cooled, filtered, washed with water and air-dried, yielding 29.5 mg. (90.2%) of cholestan-3α,5α-diol-6-one-3,5-diacetate, m.p. 186.5–187°, infrared bands at 1743, shoulder at 1728, 1268, and 1255 cm.$^{-1}$ in carbon tetrachloride. Three recrystallizations from ethanol-water yielded pure diacetate, m.p. 187–188°.

(5) H. Reich, F. E. Walker, and R. W. Collins, *J. Org. Chem.*, 16, 1753 (1951).

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.02. Found: C, 74.03; H, 9.94.

(b) *From Cholestan-3α,5α-diol-6-one-5-acetate* (VIII). Cholestan-3α,5α-diol-6-one-5-acetate (50 mg.) was dissolved in 10 ml. of acetic anhydride and 3 ml. of pyridine and allowed to stand at room temperature for 18 hr. Water was then added, the suspension cooled, and the resulting solid was filtered, washed with water, air-dried, and recrystallized from ethanol-water, yielding 39 mg. (71.5%) of cholestan-3α,5α-diol-6-one-3,5-diacetate, m.p. 180–182°. Recrystallization from ethanol-water gave pure diacetate, m.p. 186–187°, mixed m.p. undepressed with that prepared in (a) above.

URBANA, ILL.

[CONTRIBUTION FROM THE SUMMIT RESEARCH LABORATORIES, CELANESE CORP. OF AMERICA]

Some 3,9-Dicarboxylic Acids of 2,4,8,10-Tetroxaspiro[5.5]undecane

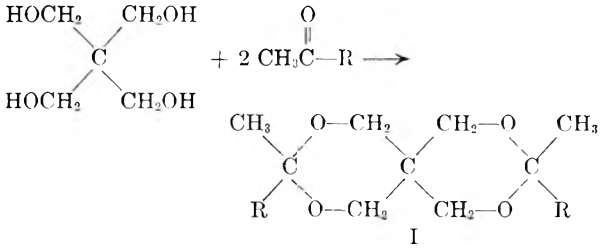
JOHN B. CLEMENTS AND LEONARD M. RICE[1]

Received July 1, 1959

A series of 3,9-disubstituted 2,4,8,10-tetroxaspiro[5.5]undecanes has been prepared by the condensation of pentaerythritol with aldehydes and acetals which contain other functions such as nitrile or ester groups. Hydrolysis of the derived nitriles and esters has led to a variety of 3,9-dicarboxylic acids. Attempts to prepare the desired acids by replacement of the halogens of 3,9-bis(halomethyl)-2,4,8,10-tetroxaspiro[5.5]undecane with appropriate nucleophiles were unsuccessful because of the extreme inertness of the halide. Finally, a very convenient method for removing dipentaerythritol from commercial pentaerythritol has been developed.

In connection with another project, it was necessary to prepare a series of 3,9-dibasic acids of 2,4,8,10-tetroxaspiro[5.5] undecane upon which we would like to report at this time. These spiro acids were prepared from pentaerythritol and a suitable aldehyde or its corresponding acetal.

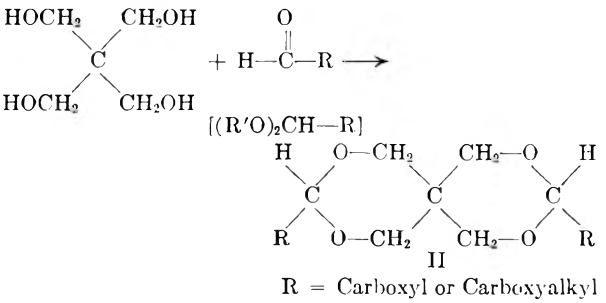
Some 30 years ago, Boeseken and Felix[2] condensed pentaerythritol with various keto esters to obtain a series of diesters (I).



I

In all of these products, positions 3 and 9 were substituted with a methyl group in addition to the fatty acid ester residue, R.

For the purpose of our investigation we were interested in the spiro acids where the 3,9 positions were not substituted by alkyl and possessed only a carboxyl or carboxyalkyl group. We took advantage in our syntheses of the condensation of pentaerythritol with aldehydes or acetals as shown in the following figure:



II

R = Carboxyl or Carboxyalkyl

The preparation of the 3,9-disubstituted 2,4,8,10-tetroxaspiro[5.5]undecanes (II) was realized by condensing pentaerythritol with a variety of aldehydes and acetals which also had an ester or nitrile function in their molecule. Thus, pentaerythritol was condensed with methyl dimethoxyacetate, ethyl 2,2-diethoxypropionate, 1,1-diethoxy-3-cyanopropane, 1,1-dimethyl-3-cyanobutyraldehyde, and 1,1-diethyl-3-cyanobutyraldehyde to give the corresponding diester or dinitrile, all in good yields. Each diester or dinitrile was hydrolyzed to the corresponding diacid. The various diesters, dinitriles, and dicarboxylic acids are listed in Table I together with pertinent data.

The condensation of methyl dimethoxyacetate with pentaerythritol to give ester V and its hydrolysis to acid VI is worthy of special note. Even though the conditions for carrying out the condensation are rather drastic, *i.e.*, 3 hr. reflux with concentrated hydrochloric acid, the ester itself is somewhat water sensitive. Thus, the diester is hydrolyzed completely to the diacid by short reflux with water alone and this was the most convenient method of preparation of the diacid. Except for this water sensitivity, the ester is not otherwise labile and remains unchanged at ordinary room conditions using no special precautions.

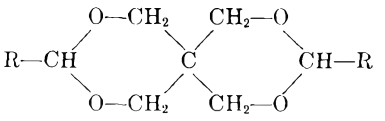
In all of the other condensations a small amount of *p*-toluene sulfonic acid was used as a catalyst. For the condensation of the acetals with pentaerythritol the reactants were refluxed until homogeneous and for the aldehydes the reactions were performed in refluxing toluene using a Dean-Stark trap for removal of the water as it formed. Dinitriles XI and XIII were hydrolyzed with potassium hydrox-

(1) Present address: Wyeth Laboratories, Radnor, Pa.

(2) J. Boeseken and B. B. C. Felix, *Ber.*, 61B, 787 and 1855 (1928).

TABLE I

3,9-DERIVATIVES OF 2,4,8,10-TETROXASPIRO[5.5]UNDECANE



No.	R	Formula	M.P.	Analyses					
				Carbon		Hydrogen		Acid No.	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
V	$-COOCH_3$	$C_{11}H_{16}O_8$	135–136	47.82	47.4, 47.6	5.84	5.81, 5.96	138	138, 139[a]
VI	$-COOH$	$C_9H_{12}O_8$	234–234.5	43.55	43.4, 43.5	4.88	4.80, 4.81	124	124
VII	$-CH_2COOC_2H_5$[b]	$C_{15}H_{24}O_8$	81.5–82	54.21	54.3, 54.4	7.28	7.31, 7.40		
VIII	$-CH_2COOH$	$C_{11}H_{16}O_8$	220–221	47.82	47.9, 47.7	5.84	5.90, 6.04	138	138, 138
IX	$-CH_2CH_2CN$	$C_{13}H_{18}N_2O_4$	73–74	58.63	58.9, 58.8	6.81	6.90, 6.86	10.52	10.37, 10.44[c]
X	$-CH_2CH_2COOH$	$C_{13}H_{20}O_8$	207–208	51.31	51.6, 51.8	6.63	6.60, 6.77	152	151, 153
XI	$-C(CH_3)_2CH_2CH_2CN$	$C_{19}H_{30}N_2O_4$	103–104	65.11	65.3, 65.2	8.63	8.56, 8.56		
XII	$-C(CH_3)_2CH_2CH_2COOH$	$C_{19}H_{32}O_8$	257–258	58.74	58.5, 58.7	8.30	8.49, 8.45	194	195, 196
XIII	$-C(C_2H_5)_2CH_2CH_2CN$	$C_{23}H_{38}N_2O_4$	89.5–90.5	67.94	67.7, 67.8	9.42	9.52, 9.55		
XIV	$-C(C_2H_5)_2CH_2CH_2COOH$	$C_{23}H_{40}O_8$	164–165	62.14	61.6, 61.7	9.07	8.90, 9.03	222	222

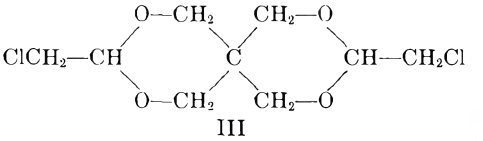
[a] Saponification No. [b] See Ref. 7. [c] Nitrogen analysis.

ide in 85% aqueous ethyl Cellosolve. All other esters and nitriles were hydrolyzed in aqueous base.

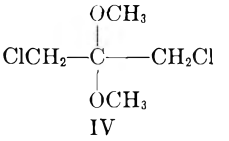
Attention is directed to the unexpected differences in physical properties between acids XII and XIV of Table I. The small structural difference at the carbon atom alpha to the spiran ring causes a great difference in melting point and in solubility characteristics. Replacement of the ethyls by methyls causes an increase of 93° in melting point and a large reduction in solubility in organic solvents. Acid XIV is easily soluble in many common solvents, recrystallizing very easily from methanol or ethanol, but acid XII dissolves only in the higher boiling solvents such as ethyl Cellosolve, ethylene glycol, and dimethyl formamide. Recrystallization from boiling dimethyl formamide was found to be the most suitable method for purification.

Early in this work attempts were made to utilize the readily available[3] 3,9-bis(chloromethyl)-2,4,8,-10-tetroxaspiro[5.5]undecane (III) in conventional reactions. If the halogen were replaceable by groups such as nitrile, a convenient path to the corresponding acid would be available. In spite of numerous attempts to replace the chlorine atom of this compound only limited success was achieved. Thus, cyanation with sodium cyanide and amination, both with ammonia and by the Gabriel method, resulted either in recovery of starting material or intractable products which could not be characterized. The only successful displacement reaction was the exchange iodination of the chloride using sodium iodide which required a rather high boiling solvent, ethyl Cellosolve, and extended reaction time. This diiodide was also very inert as shown by its failure to undergo cyanation.

An interesting analogy can be drawn between the halide unreactivity of III and IV, the dimethyl ketal of 1,3-dichloroacetone.



III



IV

In each case the halogen atom is located on a carbon alpha to a carbon atom carrying two alkoxy groups and peculiar unreactivity toward nucleophilic displacement has been found. Thus, chloride IV is unaffected by secondary amines under fairly drastic conditions, *i.e.*, at 100° under pressure. Also, sodium iodide fails to react with IV indicating it to be even less reactive toward displacement than either III or the corresponding iodide. At present no mechanism or explanation can be offered for these interesting observations.

Because it was thought contamination by dipentaerythritol, present to some extent in all commercially available pentaerythritol, might yield impure products in our syntheses, a very convenient procedure was developed for the preparation of monopentaerythritol free of dipentaerythritol. The procedure, an adaptation of the method of Simecek,[4] takes advantage of the facile condensation of commercial pentaerythritol with acetal for the preparation of pentaerythritol bisacetal. This bisacetal was carefully purified by vacuum distillation to give a product of sharp boiling point. The infrared spectrum of this material showed the absence of

(3) V. G. Mkhitaryan, *J. Gen. Chem.* (*U.S.S.R.*), 9, 1923 (1939); *Chem. Abstr.* **34**, 4381 (1940).

(4) J. Simecek, *Chem. Listy*, **47**, 1673 (1954); *Chem. Abstr.*, **49**, 856h (1955).

hydroxyl group indicating dipentaerythritol and dipentaerythritol condensation products to be absent. The bisacetal was hydrolyzed with dilute aqueous hydrochloric acid to give pure pentaerythritol. Subsequently in our work we found that both commercial pentaerythritol and the purified pentaerythritol gave identical results in our syntheses.

EXPERIMENTAL[5]

3,9-Dicarbomethoxy-2,4,8,10-tetroxaspiro[5.5]undecane. A mixture of 272 g. (2.0 mol.) of pentaerythritol, 590 g. (4.4 mol.) of methyl dimethoxyacetate and 500 ml. of concentrated hydrochloric acid was refluxed for 3 hr. The reaction mixture was transferred to a large evaporating dish and left overnight on a steam bath. On treating the resulting thick oil with 400 ml. of methanol a colorless semisolid cake was formed. Recrystallization of the entire cake from methanol resulted in 292 g. (52.8%) of colorless solid melting at 133.5–134.5°. The analytical sample was prepared by recrystallizing from methanol as long colorless needles.

The *diamide*, prepared by treatment of the diester with concentrated aqueous ammonium hydroxide, was recrystallized from water as colorless flakes. The melting point was above 300°.

Anal. Calcd. for $C_9H_{14}N_2O_6$: C, 43.87; H, 5.73; N, 11.38. Found: C, 44.0, 43.7; H, 6.01, 5.78; N, 11.25, 11.29.

The *bis-N-benzylamide*, prepared from benzylamine using NH_4Cl catalysis, yielded colorless flakes melting at 180–181°, after recrystallization from methanol.

Anal. Calcd. for $C_{23}H_{26}N_2O_6$: C, 64.75; H, 6.15; N, 6.57. Found: C, 64.6, 64.5; H, 6.18, 6.30; N, 6.49, 6.53.

The *dihydrazide* was prepared from the ester and hydrazine hydrate. It was recrystallized from aqueous methanol as colorless flakes melting at 208–210°.

Anal. Calcd. for $C_9H_{18}N_4O_6$: N, 20.29. Found: N, 20.10, 20.19.

3,9-Dicarboxy-2,4,8,10-tetroxaspiro[5.5]undecane. A solution of 55.3 g. (0.20 mol.) of 3,9-dicarbomethoxy-2,4,8,10-tetroxaspiro[5.5]undecane in 165 ml. of water was refluxed for 2 hr. and allowed to stand overnight. Upon cooling, 39.5 g. (79.5%) of colorless crystals, melting at 233.5–234.5° (gas evolution), precipitated. Two recrystallizations from water raised the melting point to 234–234.5°[c] (gas evolution).

3,9-Biscarbethoxymethyl-2,4,8,10-tetroxaspiro[5.5]undecane. A mixture of 36.0 g. (0.19 mol.) of ethyl β,β-diethoxypropionate,[6] 11.9 g. (0.086 mol.) of pentaerythritol and 0.2 g. of *p*-toluenesulfonic acid monohydrate was refluxed for 8 hr. Upon cooling a pasty, colorless solid appeared which was recrystallized from ethanol to give 16.6 g. (58.3%) of colorless crystals melting at 79.5–81°. Another recrystallization from ethanol raised the melting point to 81.5–82°. Croxall, Van Hook, and Luckenbaugh[7] report a melting point of 79° for this ester.

3,9-Biscarboxymethyl-2,4,8,10-tetroxaspiro[5.5]undecane. A mixture of 9.56 g. (0.029 mol.) of 3,9-biscarbethoxymethyl-2,4,8,10-tetroxaspiro[5.5]undecane, 7 g. of potassium hydroxide and 50 ml. of water was refluxed for 3 hr. The yellow solution was charcoaled, cooled, and acidified with concentrated hydrochloric acid. A colorless solid, weighing 6.13 g. (77.0%) and melting at 220–221° (gas evolution), was collected. Recrystallization from water did not raise the melting point.

3,9-Bis(2-cyanoethyl)-2,4,8,10-tetroxaspiro[5.5]undecane. A mixture of 33.1 g. (0.243 mol.) of pentaerythritol, 84.0 g. (0.535 mol.) of 1,1-diethoxy-3-cyanopropane,[8] and 0.66 g. of *p*-toluenesulfonic acid monohydrate was refluxed for 4 hr., ethanol removed on a steam bath, and the resulting red oil crystallized by cooling in ice. The reaction product was recrystallized from ethanol to give 56.8 g. (88.0%) of nearly colorless crystals melting at 67–69.5°. Several recrystallizations from ethanol raised the melting point to 73–74°.

3,9-Bis(2-carboxyethyl)-2,4,8,10-tetroxaspiro[5.5]undecane. A mixture of 37.9 g. (0.142 mol.) of 3,9-bis(2-cyanoethyl)-2,4,8,10-tetroxaspiro[5.5]undecane, 31.8 g. of potassium hydroxide, and 225 ml. of water was refluxed overnight. The reaction product was charcoaled, cooled, brought to *p*H 7 with concentrated hydrochloric acid and allowed to stand at room temperature overnight. The cloudy solution was filtered using a diatomaceous earth filter aid and made strongly acid with concentrated hydrochloric acid. The precipitate, after filtering and drying, weighed 38.1 g. (88.2%) and melted at 208–211°. The analytical sample was prepared by recrystallizing from water as glistening needles melting at 207–208°.

The *dimethyl ester*, prepared by overnight reflux of the diacid with methanol and sulfuric acid, recrystallized from methanol as thick, colorless needles melting at 92–93°.

Anal. Calcd. for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 53.8, 53.8; H, 7.47, 7.42.

3,9-Bis(1,1-dimethyl-3-cyanopropyl)-2,4,8,10-tetroxaspiro[5.5]undecane. A mixture of 104 g. (0.765 mol.) of pentaerythritol, 206 g. (1.65 mol.) of 2,2-dimethyl-4-cyanobutyraldehyde,[9] 4.25 g. of *p*-toluenesulfonic acid monohydrate, and 750 ml. of toluene was refluxed overnight under a Dean-Stark trap. The theoretical amount of water separated. The reaction product was partially cooled, neutralized with sodium methoxide, and filtered using a diatomaceous earth filter aid. Removal of the solvent from the filtrate gave an oil which readily crystallized to a light yellow solid. Recrystallization of this material from methanol yielded 218.1 g. (83.2%) of nearly colorless crystals melting at 101.5–102.5°.

3,9-Bis(1,1-dimethyl-3-carboxypropyl)-2,4,8,10-tetroxaspiro[5.5]undecane. A mixture of 156.5 g. (0.45 mole) of 3,9-bis(1,1-dimethyl-3-cyanopropyl)-2,4,8,10-tetroxaspiro[5.5]-undecane, 165 g. of potassium hydroxide, 185 ml. of water, and 380 ml. of ethyl Cellosolve was refluxed overnight. The reaction mixture was diluted with about 1 l. of water and made acid with concentrated hydrochloric acid. The pasty precipitate, after partially drying by distillating with benzene, weighed 185.3 g. and melted at 251–255°. The product was very insoluble, failing to dissolve in the following solvents (cold or hot): methanol, ethanol, *n*-propyl alcohol, water ethyl acetate, acetonitrile, methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, acetone, and nitromethane. It partially dissolved in hot dimethyl formamide, hot ethyl Cellosolve, and hot ethylene glycol. The analytical sample was prepared by leaching 30 g. of the crude product with boiling dimethyl formamide, filtering hot, and collecting 15.1 g. of brown precipitate melting at 257–258° (slight gas evolution). Two further recrystallizations from dimethyl formamide followed by a methanol wash did not raise the melting point and this material was directly analyzed.

The *dimethyl ester*, prepared by overnight reflux of the diacid with methanol and sulfuric acid, recrystallized from methanol as colorless flakes melting at 136–136.5°.

Anal. Calcd. for $C_{21}H_{36}O_8$: C, 60.55; H, 8.71. Found: C, 60.6, 60.5; H, 8.63, 8.78.

3,9-Bis(1,1-diethyl-3-cyanopropyl)-2,4,8,10-tetroxaspiro[5.5]undecane was prepared in a 96.2% yield from pentaerythritol and 2,2-diethyl-4-cyanobutyraldehyde[10] using a

(5) All melting points are corrected.

(6) A. N. Nesmeyanov, R. Kh. Freedlina, and L. I. Zakharkin, *Doklady Akad. Nauk S.S.S.R.*, 97, 91 (1954); *Chem. Abstr.*, 49, 8793e (1955).

(7) W. J. Croxall, J. O. Van Hook, and R. Luckenbaugh, *J. Am. Chem. Soc.*, 71, 2741 (1949) prepared this ester in an analogous manner using sodium bisulfate catalysis.

(8) R. H. F. Manske, *Can. J. Res.*, 5, 529 (1931).

(9) We wish to thank Eastman Chemical Products, Kingsport, Tenn., for a generous sample of this aldehyde.

(10) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, 66, 56 (1944).

procedure similar to that for the preparation of 3,9-bis(1,1-dimethyl-3-cyanopropyl)-2,4,8,10-tetroxaspiro[5.5]undecane.

3,9-Bis(1,1-diethyl-3-carboxypropyl)-2,4,8,10-tetroxaspiro[5.5]undecane was prepared in a 93.8% yield by basic hydrolysis of the dinitrile in aqueous Cellosolve. It recrystallized very easily from methanol.

3,9-Bis(iodomethyl)-2,4,8,10-tetroxaspiro[5.5]undecane. A mixture of 102.4 g. (0.40 mol.) of 3,9-bis(chloromethyl)-2,4,8,10-tetroxaspiro[5.5]undecane, 240 g. (1.60 mol.) of sodium iodide, and 1 l. of ethyl Cellosolve was refluxed for 24 hr. The reaction product, obtained by dilution with water, weighed 153.5 g. (87.5%) and melted at 144.5–145.5°. Recrystallization from ethanol gave colorless flakes melting at 146.5–147.5°.

Anal. Calcd. for $C_9H_{14}I_2O_4$: C, 24.55; H, 3.21. Found: C, 24.4, 24.6; H, 3.22, 3.29.

Attempts to cyanate the above diiodide with a three-fold excess of potassium cyanide in refluxing ethyl Cellosolve yielded only tars which could not be characterized. Use of cuprous cyanide in pyridine gave similar results.

Attempts to replace the chlorine of *3,9-bis(chloromethyl)-2,4,8,10-tetroxaspiro[5.5]undecane.* (a) *Amination.* Heating the dichloride with a saturated methanolic ammonia solution at 130° resulted in intractable tars which could not be characterized.

(b) *Cyanation.* Refluxing a solution of the dichloride with sodium cyanide and a small amount of sodium iodide in either ethanol or ethyl Cellosolve resulted in quantitative recovery of starting material.

(c) *Gabriel reaction.* Heating a mixture of the dichloride with potassium phthalimide in dimethyl formamide on a steam bath for 1 hr. resulted in recovery of the starting material. Refluxing for 20 hr. gave an oil which could not be characterized nor hydrolyzed to the amine.

Attempts to replace the chlorine of *1,3-dichloro-2,2-dimethoxypropane.* (a) *Reaction with secondary amines.* Heating a methanolic solution of the dichloride with excess dimethyl amine at 100° for 8 hr. resulted in the recovery of the starting material.

(b) *Iodination.* Attempts to replace the chlorine with iodine, using conditions similar to those used in preparing 3,9-bis(iodomethyl)-2,4,8,10-tetroxaspiro[5.5]undecane, resulted in the recovery of starting halide.

Monopentaerythritol. 3,9-Dimethyl-2,4,8,10-tetroxapiro[5.5]undecane (pentaerythritol bisacetal) was prepared from commercial pentaerythritol and acetaldehyde diethyl acetal according to the method of Mkhitaryan.[3] Three careful vacuum fractional distillations gave a product boiling at 113.0–113.5°/18 mm. The over-all yield was 56%. No hydroxyl groups could be detected in the infrared spectrum. Steam distillation of a weakly acidic (HCl) aqueous solution of the bisacetal resulted in complete hydrolysis to pentaerythritol. The pentaerythritol was isolated by evaporation of the reaction mixture to incipient crystallization, cooling thoroughly, and filtering. One recrystallization from the minimum amount of water gave 69% of product melting at 263–265°. The literature has reported melting points from 260°[11] to 269°.[12] Others[4,13] have reported intermediate values.

SUMMIT, N. J.

(11) W. Friedrich and W. Brun, *Ber.*, **63B**, 6281 (1930).

(12) G. Desseigne, *Mem. des Poudres*, **33**, 169 (1951); *Chem. Abstr.*, **48**, 1954i (1954).

(13) P. Ebert, *Ber.*, **64**, 114 (1931); B. W. Lew, M. L. Wolfrom, and R. M. Goepp, *J. Am. Chem. Soc.*, **86**, 1449 (1946).

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Synthesis of 6-Fluoro-, 7-Fluoro-, and 6-Methoxy-10-methyl-1,2-benzanthracenes[1]

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The syntheses of 6-fluoro-, 7-fluoro-, and 6-methoxy-10-methyl-1,2-benzanthracenes are described. The ratio of isomeric keto acids formed from reactions of 1,2-naphthalic anhydride with *p*-fluorophenylmagnesium bromide and with fluorobenzene in the Friedel-Crafts condensation were determined and the results are compared with those obtained with 3-methyl- and 3-chlorophthalic anhydrides. On hydrolysis of methyl 1-*p*-fluorobenzoyl-2-naphthoate with aqueous methanolic potassium hydroxide, an unexpectedly high yield of 1-*p*-methoxybenzoyl-2-naphthoic acid was obtained.

In continuation of a previously described program of synthesis designed to provide all of the monofluoro-10-methyl-1,2-benzanthracenes[2] for studies on carcinogenicity, we have prepared 6-fluoro-10-methyl-1,2-benzanthracene (III) and 7-fluoro-10-methyl-1,2-benzanthracene (IV) by routes essentially the same as those used for the synthesis of the corresponding 6- and 7-chloro analog.[3,4]

The condensation of *p*-fluorophenylmagnesium bromide with 1,2-naphthalic anhydride yielded 1-*p*-fluorobenzoyl-2-naphthoic acid (I) and 2-*p*-fluorobenzoyl-1-naphthoic acid (II) in the approximate ratio of 1 to 2.6. The ratio of product II, resulting from reaction at the unhindered carbonyl group, to that of I, arising from reaction of the hindered carbonyl group is thus similar to that ratio obtained in the reactions of *p*-chlorophenylmagnesium bromide[3] and of *m*-chlorophenylmagnesium bromide[4] with 1,2-naphthalic anhydride, and of phenylmagnesium bromide with 3-methylphthalic anhydride.[5] It appears then that in the

(1) This work was supported by a grant from the National Institutes of Health.

(2) M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959).

(3) M. S. Newman and M. Orchin, *J. Am. Chem. Soc.*, **61**, 244 (1939).

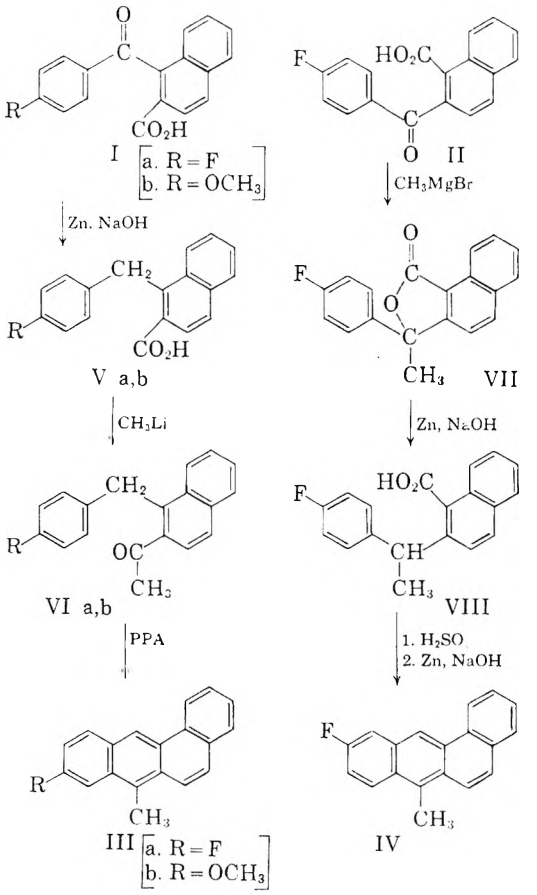
(4) M. S. Newman and M. Orchin, *J. Am. Chem. Soc.*, **60**, 586 (1938).

(5) M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1542 (1941).

Grignard reaction the steric effect of a fused aromatic ring ortho to an anhydride grouping is about the same as that of an ortho methyl group.

The keto acids I and II were prepared also by a Friedel-Crafts condensation of 1,2-naphthalic anhydride on fluorobenzene, the yields of I and II being 48% and 19%, respectively.[6] In contrast, 3-methylphthalic anhydride yields approximately equal amounts of the two isomeric acids on condensation with benzene[5] whereas 3-chlorophthalic anhydride yields exclusively 2-benzoyl-3-chlorobenzoic acid, the product of reaction at the most hindered carbonyl.[7] It thus appears that an ortho fused aromatic ring is intermediate between *o*-methyl and *o*-chloro groups in its directive influence on Friedel-Crafts condensations of anhydrides with aromatic compounds.

The acids I and II were converted into 6-fluoro-10-methyl-1,2-benzanthracene (III) and 7-fluoro-10-methyl-1,2-benzanthracene (IV), respectively, by the reactions outlined below.



(6) H. Waldman, *J. prakt. Chem.*, **127**, 195 (1930); **131**, 71 (1931) reported that 1-benzoyl-2-naphthoic acid was the main product of the Friedel-Crafts reaction of 1,2-naphthalic anhydride with benzene but no accurate estimate of the amounts of isomeric acids was given.

(7) See M. S. Newman and P. G. Scheurer, *J. Am. Chem. Soc.*, **78**, 5004 (1956) for a discussion of Grignard and Friedel-Crafts reactions of β-substituted phthalic anhydrides.

The separation of acids I and II (obtained by the Grignard or Friedel-Crafts method) was effected by the sulfuric acid method previously described.[5]

The alkaline hydrolysis of the methyl ester of Ia in aqueous methanolic potassium hydroxide for 24 hr. afforded in high yield an acid which was believed to be the expected fluoro acid, Ia. By steps analogous to those involved in the synthesis of 6-chloro-10-methyl-1,2-benzanthracene,[3] the acid thus obtained was converted into a compound believed to be IIIa. However, analysis showed that in the final compound a methoxy group was present instead of a fluorine atom. The replacement of fluorine by methoxyl was then proved to have taken place during the hydrolysis of the methyl ester of Ia in aqueous methanolic potassium hydroxide. The resulting acid was proved to be 1-*p*-methoxybenzoyl-2-naphthoic acid (Ib) and hence the final compound is 6-methoxy-10-methyl-1,2-benzanthracene (IIIb). The facile replacement of the fluorine by methoxyl in the treatment with aqueous methanolic potassium hydroxide is striking and merits further study.

When the hydrolysis of the methyl ester of Ia was carried out for 30 min. in aqueous ethanolic sodium hydroxide, the acid I was obtained in high yield. The synthesis of 6-fluoro-10-methyl-1,2-benzanthracene (IIIa) was then carried out as indicated on the chart.

EXPERIMENTAL[8]

Reactions of 1,2-naphthalic anhydride. a. Grignard reaction. The filtered Grignard reagent prepared from 22.0 g. of *p*-bromofluorobenzene[9] and 3 g. of magnesium in 150 ml. of dry ether was added during 10 min. to a warm stirred solution of 24.8 g. of 1,2-naphthalic anhydride in 275 ml. of benzene and 50 ml. of ether. After refluxing for 2 hr., the reaction mixture was cooled, treated with dilute acid, and the products were separated into a neutral and an acid fraction, 28.0 g. (76%), m.p. 138–146°. The acid fraction was separated into its components as described below.

b. *Friedel-Crafts reaction.* To a stirred mixture of 20.0 g. of fluorobenzene,[10] 40.0 g. of 1,2-naphthalic anhydride and 200 ml. of *o*-dichlorobenzene was added portionwise 65.0 g. of powdered aluminum chloride. The deep red mixture was heated at 80–90° for 4 hr. and was then cooled and decomposed with ice and 150 ml. of concentrated hydrochloric acid. An ether-benzene solution of the reaction mixture was well washed with dilute hydrochloric acid and water. Acidification of a potassium carbonate extract of the resulting solution afforded 31.5 g. (55%) of a mixture of acids (Ia and II), m.p. 140–175°, which was separated into its

(8) All melting points are corrected. Analyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Huffman Microanalytical Laboratories, Wheatridge, Colo. The term "treated in the usual manner" means that an ether-benzene solution of the organic matter was washed with saturated sodium chloride solution, filtered through a filter paper containing anhydrous magnesium sulfate, and concentrated by distillation at atmospheric pressure or under reduced pressure.

(9) Obtained from the Pierce Chemical Co., Box 117, Rockford, Ill.

(10) We are indebted to the Pennsylvania Salt Chemical Co. for a generous supply of fluorobenzene.

components as described[6] below. From the neutral fraction 8.0 g. of 1,2-naphthalic anhydride, m.p. 147–150°, was recovered.

Separation of acids, Ia *and* II. In a typical case, 28.0 g. of the acid mixture obtained from the Grignard reaction described above was esterified by refluxing for 2 hr. with methanolic hydrogen chloride solution. This ester fraction, 26.0 g., (over 1 g. of acid fraction, m.p. 140–145°, was recovered) was added slowly with cooling to 100 ml. of approximately 100% sulfuric acid (m.p. 10.4° on the less than 100% side of the f.p. maximum). The clear dark brown solution was kept at about 20–25° for 2.5 hr. and then poured on ice. The organic material was taken into ether-benzene and separated into neutral and acid fractions by extraction with potassium carbonate solution. From the acid fraction 16.0 g. (65%) of 2-*p*-fluorobenzoyl-1-naphthoic acid (II), m.p. 170–174°, was obtained. After three recrystallizations from benzene pure II, m.p. 175.0–175.8°, was obtained with little loss. The crude acid, m.p. 170–174°, was used for the next reaction.

Anal. Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.8. Found: C, 73.1; H, 3.8.

Crystallization of the neutral fraction isolated in the usual manner yielded 4.5 g. (17%) of methyl 1-*p*-fluorobenzoyl-2-naphthoate (Ia), m.p. 100–105°, sufficiently pure for the hydrolysis described below. The analytical sample, m.p. 110.5°, was obtained after three recrystallizations from methanol.

Anal. Calcd. for $C_{19}H_{13}FO_3$: C, 74.0; H, 4.3. Found: C, 74.2; H, 4.3.

Similar treatment of 44 g. of ester mixture obtained from the acid fraction resulting from the above Friedel-Crafts condensation of 1,2-naphthalic anhydride yielded 11.5 g. (27%) of II, m.p. 172–174°, and 31.6 g. (72%) of the methyl ester of Ia, m.p. 99–102°. On one crystallization from absolute methanol 28.6 g. (65%) of pure ester, m.p. 109–111°, was obtained, suitable for further reaction. In another run almost identical proportions of Ia and II were obtained.

Alkaline hydrolysis of methyl 1-p-fluorobenzoyl-2-naphthoate. Hydrolysis of 10.0 g. of the above methyl ester by heating for 30 min. in a solution containing 5 g. of sodium hydroxide, 100 ml. of water, and 100 ml. of alcohol yielded 9.2 g. of crude Ia. One recrystallization from 80% ethanol afforded 8.65 g. (90%) of Ia, m.p. 205–206°. Three crystallizations from 80% alcohol yielded the analytical sample of 1-*p*-fluorobenzoyl-2-naphthoic acid, Ia, m.p. 206.0–207.0°.

Anal. Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.8. Found: C, 73.4; H, 4.1.

On treatment with diazomethane, Ia yielded the methyl ester, m.p. 110.0–111.0°, alone and mixed with the purified sample obtained by the above described treatment with sulfuric acid. When the hydrolysis of 36.0 g. of the methyl ester of Ia was conducted for 24 hr. in a refluxing solution of 24 g. of potassium hydroxide in 180 ml. of methanol and 36 mg. of water, an almost quantitative yield of acid, m.p. 207–210°, was obtained. Recrystallization from benzene–Skellysolve B (petroleum ether, b.p. 65–70°) yielded colorless crystals of Ib, m.p. 214.5–216.5° with little loss. The analytical sample of 1-*p*-methoxybenzoyl-2-naphthoic acid, m.p. 216.0–217.0°, was obtained by two more such recrystallizations; a mixed m.p. with pure Ia, m.p. 206–207° was 175–180°.

Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.5; H, 4.6; OCH_3, 10.1. Found: C, 74.7, 74.5; H, 4.5, 4.6; OCH_3, 10.2.

When a solution of 2.0 g. of 1-*p*-fluorobenzoylnaphthalene in 40 ml. of methanol containing 2 ml. of water and 4 g. of potassium hydroxide was refluxed for one day a small yield (about 25%) of 1-*p*-methoxybenzoylnaphthalene, m.p. 100.0–101.0° alone and mixed with authentic 1-*p*-methoxybenzoylnaphthalene, was obtained. 1-*p*-Chlorobenzoylnaphthalene under similar conditions did not give 1-*p*-methoxybenzoylnaphthalene.

Proof of structure of acids, Ia, Ib, *and* II. A mixture of 1.0 g. of Ia and 0.12 g. of its copper salt[11] was heated at 240–250° for 30 min. Distillation yielded 0.5 g. of an oil which yielded an orange-red 2,4-dinitrophenylhydrazone, m.p. 230–231° alone and mixed with an authentic sample prepared from 1-*p*-fluorobenzoylnaphthalene. This ketone was prepared in 80% yield by the reaction of *p*-fluorophenylmagnesium bromide with 1-naphthonitrile. Since the ketone had a low m.p. of 32.8–33.5°, it was converted into the 2,4-dinitrophenylhydrazone, m.p. 230–231°, for identification and comparison purposes.

Anal. Calcd. for $C_{17}H_{11}FO$: C, 81.6; H, 4.4. Found: C, 81.4; H, 4.8. Calcd. for $C_{23}H_{15}FN_4O_4$: C, 64.2; H, 3.5; N, 13.0. Found: C, 64.2; H, 3.8; N, 13.2.

Similarly II was decarboxylated in high yield to 2-*p*-fluorobenzoylnaphthalene, m.p. 110.0–110.8°, alone and mixed with an authentic sample prepared from the Friedel-Crafts condensation of 2-naphthoyl chloride with fluorobenzene in 54% yield.

Anal. Calcd. for $C_{17}H_{11}FO$: C, 81.6; H, 4.4. Found: C, 81.4; H, 4.5.

In the same way, Ib was decarboxylated to 1-*p*-methoxybenzoylnaphthalene, m.p. 100.0–101.0°, m.p. alone and mixed with an authentic sample prepared in 66% yield by the reaction of *p*-methoxyphenylmagnesium bromide with 1-naphthonitrile. In addition, the 2,4-dinitrophenylhydrazones, m.p. 239.5–240.5° alone and mixed, were prepared and compared.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.4; H, 5.4. Found: C, 82.6; H, 5.2. Calcd. for $C_{24}H_{18}N_4O_5$: C, 65.2; H, 4.1; N, 12.7. Found: C, 64.8; H, 4.3; N, 12.4.

1-p-Fluorobenzyl-2-naphthoic acid, Va. A mixture of 22.0 g. of Ia, 50 g. of potassium hydroxide, 60 g. of zinc dust (activated with ammoniacal copper sulfate) and 300 ml. of water was refluxed for 34 hr. The alkaline solution was decanted and the zinc refluxed with 100 ml. of 5% potassium hydroxide for 0.5 hr. The filtered alkaline solutions were combined and acidified to yield 19.0 g. (90%) of acid, m.p. 140–146°. The analytical sample, obtained after three recrystallizations from aqueous alcohol, melted at 192.0–193.0°. Evidently polymorphic forms are present as the yields of desired product in further steps were almost as good when lower melting fractions were used as when high melting Va was used.

Anal. Calcd. for $C_{18}H_{13}FO_2$: C, 77.1; H, 4.7. Found: C, 77.3; H, 4.8.

6-Fluoro-10-methyl-1,2-benzanthracene, IIIa. To a stirred ethereal solution of 25 ml. of 0.8*N* methyllithium was added a solution of 1.6 g. of Va, m.p. 184–186°, in 150 ml. of dry ether under nitrogen. After stirring at room temperature for 1 hr. the reaction mixture was processed as usual to yield 1.4 g. of crude oily 1-*p*-fluorobenzyl-2-acetonaphthalene, VIa, and 0.2 g. of Va, m.p. 170–173°. The oily ketone was heated with 15 g. of PPA[2,12,13] at 120–130° for 5 hr. The reaction mixture was then poured into water and the organic portion treated in the usual way. Chromatography over activated alumina (heated to 170° until no more steam was evolved) afforded 0.61 g. (46%) of crude hydrocarbon, m.p. 113–115°. Further crystallization from benzene–Skellysolve B yielded 0.45 g. (35%) of almost colorless IIIa, m.p. 119.0–120.0°. The analytical sample, obtained after further recrystallization, melted at 120.0–121.0°.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; F, 7.3. Found: C, 87.8; H, 5.1.; 7.1.

In similar runs using starting acid Va melting at 140–146° and varying the time of heating in PPA to 3 hr. and

(11) See L. F. Fieser and M. S. Newman, *J. Am. Chem. Soc.*, **58**, 2376 (1936).

(12) Polyphosphoric acid, obtained from the Victor Chemical Co., to whom we are indebted for a generous gift.

(13) *Cf.* C. K. Bradsher and F. A. Vingiello, *J. Org. Chem.*, **71**, 1434 (1949). They used HBr-AcOH-H_2O mixture for this type of cyclization.

the temperature to 90–100° somewhat smaller yields (42% crude and 26% pure) of IIIa were obtained.

Lactone of 2-(α-hydroxy-α-methyl-p-fluorobenzyl)-1-naphthoic acid, VII. Reaction of 24.5 g. of II, m.p. 170–176°, with methylmagnesium bromide followed by treatment as described[4] yielded 14.2 g. (58%) of colorless VII, m.p. 105–107°, of sufficient purity for further work. An additional 6–8 g. of less pure product was obtained from the mother liquors but was not investigated further. The analytical sample, obtained after two recrystallizations from ethanol, melted at 108.0–108.5°

Anal. Calcd. for $C_{19}H_{13}FO_2$:C, 78.0; H, 4.5. Found: C, 77.7; H, 4.3.

2-(α-Methyl-p-fluorobenzyl)-1-naphthoic acid, VIII. Reduction of 13.7 g. of VII, m.p. 105–107° as described[4] yielded 12.7 g. (93%) of VIII, m.p. 174.5–175.5°. Recrystallization from benzene yielded pure VIII, m.p. 176.2–177.0°, with little loss.

Anal. Calcd. for $C_{19}H_{15}FO_2$: C, 77.6; H, 5.1. Found: C, 77.4; H, 5.1.

Reduction of crude lactone VII afforded crystalline VIII, m.p. 174.5–175.5°, in good yield also, so that it was possible to utilize noncrystalline VII directly in the preparation of VIII.

7-Fluoro-10-methyl-1,2-benzanthracene, IV. Cyclization of 13.1 g. of VIII, m.p. 174.5–175.5° with 150 ml. of concentrated sulfuric acid at 25° for 2 hr. followed by reduction of the authrone as described[4] afforded 6.3 g. (55%) of crude IV, m.p. 100–103°. The analytical sample, obtained by further chromatography and recrystallization from benzene–Skellysolve B, formed colorless needles, m.p. 102.5–103.2°.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; F, 7.3. Found: C, 87.4; H, 5.2; F, 7.5.

1-p-Methoxybenzyl-2-naphthoic acid, Vb. In the best of several reductions, a mixture of 5.0 g. of Ib, 75 ml. of 20% potassium hydroxide solution and 15 g. of zinc dust (activated as above) was refluxed for 30 hr. After a procedure similar to that for Va, 1.4 g. (29%) of crude Vb, m.p. 150–159°, was obtained. The analytical sample, obtained by two recrystallizations from benzene, formed colorless needles, m.p. 165.5–166.5°. The remainder was used in the next step.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.1; H, 5.5. Found: C, 77.8; H, 5.3.

6-Methoxy-10-methyl-1,2-benzanthracene, IIIb. To a stirred solution of 50 ml. of 0.4*N* methyllithium in ether was added during 10 min. a solution of 1.5 g. of Vb (the above crude product) in 100 ml. of ether and 50 ml. of pure dry tetrahydrofurane. A purple color developed. After 1 hr. at room temperature the reaction mixture was treated as usual and the neutral oily fraction, presumably containing 1-*p*-methoxybenzyl-2-acetonaphthalene, VIb, was heated on a steam bath with 99% PPA for 20 min. Dilution with water and the usual workup, including chromatography over alumina (activated as above) afforded 0.70 g. (50%) of crude IIIb, m.p. 169–174°. Recrystallizations from benzene afforded IIIb as pale yellow needles, m.p. 174.0–174.8°, with some loss.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.2; H, 5.9; OCH_3, 11.4. Found: C, 88.5, 88.4; H, 5.9, 6.0; OCH_3, 11.2.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

Unsymmetrical Tetraalkylmethanes. IV.[1] General Method of Synthesis of Tetraalkylmethanes

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A number of unsymmetrical tetraalkylmethanes, containing from 27 to 50 carbon atoms, have been prepared in relatively high over-all yields from unsymmetrical ketones. The latter were transformed into alkylidenecyanoacetates, which were then caused to undergo conjugate addition with Grignard reagents to give α-cyano-β,β-trialkylpropionates (I). These were hydrolyzed and decarboxylated to β,β,β-trialkylpropionitriles (III), which were converted through the branched ketones (IV) to the hydrocarbons (VII) which possessed the desired quaternary carbon atom structure.

The previous paper[1] in this series described a method for preparing unsymmetrical tetraalkylmethanes from β,β-disubstituted glutaric acids, which contained the desired center of asymmetry. In the present study it was found that the procedure failed when an attempt was made to apply it to the synthesis of high molecular weight hydrocarbons. Although the Guareschi reaction[5] affords good yields of α,α-dicyano-β,β-dialkylglutarimides with simple methyl and cyclic ketones, no condensation could be effected with 6-dodecanone. The amination reaction occurred exclusively and the ethyl cyanoacetate was converted to cyanoacetamide. Others[6] have reported limitations of the Guareschi condensation.

Alkylidenecyanoacetates, which can be obtained readily by Cope's procedure,[7] seemed to offer a general approach to the synthesis of molecules which possess quaternary carbon atoms. As the Michael addition of active methylene compounds to the alkylidene derivatives could lead to β,β-disubstituted glutaric acids of the type obtained

(1) Paper III. N. Rabjohn and H. H. Farmer, *J. Org. Chem.*, 24, 359 (1959).

(2) Abstracted in part from the Ph.D. thesis of L. V. Phillips, 1957.

(3) Supported in part by the Petroleum Research Fund of the American Chemical Society.

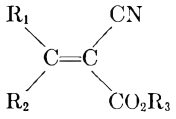
(4) Lubrizol Foundation Fellow, 1956–1958.

(5) I. Guareschi, *Gazz. chim. ital.*, 49, 124 (1919).

(6) A. I. Vogel, *J. Chem. Soc.*, 1758 (1934); A. J. Birch and R. Robinson, *J. Chem. Soc.*, 488 (1942); and S. M. McElvain and D. H. Clemens, *J. Am. Chem. Soc.*, 80, 3915 (1958).

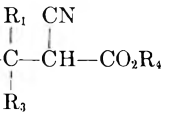
(7) A. C. Cope, C. M. Hofmann, C. Wykoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, 63, 3452 (1941).

TABLE I

ALKYLIDENE CYANOACETATES, 

							Anal.			
							Calcd.		Found	
R_1	R_2	R_3	B.P.	n_D^{25}	Yield	Formula	C	H	C	H
C_2H_5	C_3H_7	C_2H_5	100–103°/15 mm.	1.4642	59	$C_{11}H_{17}NO_2$	67.66	8.78	67.88	9.01
C_3H_7	C_4H_9	C_2H_5	158–160°/15 mm.	1.4654	74	$C_{13}H_{21}NO_2$	69.92	9.48	70.22	9.62
C_2H_5	C_7H_{15}	C_2H_5	139–142°/1 mm.	1.4651	81	$C_{15}H_{25}NO_2$	71.67	10.03	71.93	9.95
C_5H_{11}	C_6H_{13}	C_2H_5	153–156°/1 mm.	1.4652	88	$C_{17}H_{29}NO_2$	73.07	10.46	73.37	10.52
C_7H_{15}	C_8H_{17}	CH_3	208–210°/3 mm.	1.4661	68	$C_{20}H_{35}NO_2$	74.71	10.97	74.60	10.80
C_7H_{15}	$C_{10}H_{21}$	C_2H_5	199–201°/0.5 mm.	1.4660	51	$C_{23}H_{41}NO_2$	75.98	11.37	75.69	11.13
$C_{10}H_{21}$	$C_{13}H_{23}$	C_2H_5	220–222°/1.5 mm.	1.4690	69	$C_{27}H_{49}NO_2$	77.77	11.77	77.85	11.72

TABLE II

2-CYANO-3,3-DIALKYL SUBSTITUTED ESTERS, 

								Anal.			
								Calcd.		Found	
R_1	R_2	R_3	R_4	B.P.	n_D^{25}	Yield	Formula	C	H	C	H
C_2H_5	C_3H_7	$C_{12}H_{25}$	C_2H_5	195–198°/1 mm.	1.4550	60	$C_{23}H_{43}NO_2$	75.56	11.86	75.69	12.03
C_3H_7	C_4H_9	$C_{10}H_{21}$	C_2H_5	178–180°/1 mm.	1.4552	65	$C_{23}H_{43}NO_2$	75.56	11.86	75.74	11.92
C_2H_5	C_7H_{15}	C_8H_{17}	C_2H_5	190–194°/1 mm.	1.4549	81	$C_{23}H_{43}NO_2$	75.56	11.86	75.51	11.94
CH_3	C_6H_{13}	$C_{10}H_{21}$	C_2H_5	200–204°/1 mm.	1.4529	78	$C_{23}H_{43}NO_2$	75.56	11.86	75.44	11.73
C_5H_{11}	C_6H_{13}	C_7H_{15}	C_2H_5	186–190°/1 mm.	1.4549	71	$C_{24}H_{45}NO_2$	75.93	11.95	75.78	11.74
C_7H_{15}	C_8H_{17}	$C_{10}H_{21}$	CH_3	238–240°/0.5 mm.	1.4590	60	$C_{30}H_{57}NO_2$	77.69	12.39	77.83	12.22

from the Guareschi reaction, the addition of malonic ester and cyanoacetic ester to ethyl 1-pentylheptylidenecyanoacetate was attempted. In both instances unreacted starting materials and viscous residues were obtained. Hydrolysis of the residues in alcoholic potassium hydroxide solution resulted in heavy oils which neither could be distilled nor induced to crystallize.

A conjugate addition of a Grignard reagent to an alkylidenecyanoacetate then suggested itself as a way of developing a quaternary carbon atom structure. Prout and his associates,[8] in an extension of the work of Alexander, McCollum, and Paul[9] have studied the addition of organometallic compounds to several conjugated systems which possess isopropylidene or *sec*-butylidene groups. They obtained the highest yields with cyanoacetic esters and phenyl- and benzyl-magnesium halides. *n*-Alkylmagnesium halides gave 30–50% of 1,4-addition to the ethyl alkylidenecyanoacetates and 15–20% reduction of the unsaturated ester.

Some time prior to this, Hook and Robinson[10] had investigated the addition of Grignard reagents to alkylidenecyanoacetates and found that the reduction reaction was minimized by the slow inverse addition of the Grignard reagent to an ether solution of the alkylidene compound at low temperatures (14–20°). In addition, they discovered that small amounts of cuprous iodide appeared to facilitate the 1,4-type of addition.

In the present investigation a short study was made of this addition reaction, and the results supported the work of Hook and Robinson. When ethyl 1-methylheptylidenecyanoacetate was added by the normal procedure to an ether solution of decylmagnesium bromide, a 43% yield of 1,4-addition product was obtained. In contrast, the addition of the alkylidene compound to a solution of the Grignard reagent which contained cuprous iodide gave only a 29% yield of 1,4-addition product. The inverse addition of an ether solution of decylmagnesium bromide to ethyl 1-methylheptylidenecyanoacetate, however, gave quite different results. A 47% yield of 1,4-addition product was isolated from such a reaction system on the absence of cuprous iodide, whereas a 78% yield of 1,4- addition compound was obtained when cuprous iodide was present in the ethyl 1-methylheptylidenecyanoacetate solution. In the reactions described, with the exception of the latter, a considerable quantity of reduction product, ethyl α-cyano-β-methylpelargonate, was formed. The inverse addi-

(8) F. S. Prout, *J. Am. Chem. Soc.*, **74**, 5915 (1952); F. S. Prout, E. P. Y. Huang, R. J. Hartman, and C. J. Korpics, *J. Am. Chem. Soc.*, **76**, 1911 (1954).

(9) E. R. Alexander, J. D. McCollum, and D. E. Paul, *J. Am. Chem. Soc.*, **72**, 4791 (1950).

(10) W. H. Hook and R. Robinson, *J. Chem. Soc.*, 1952 (1944).

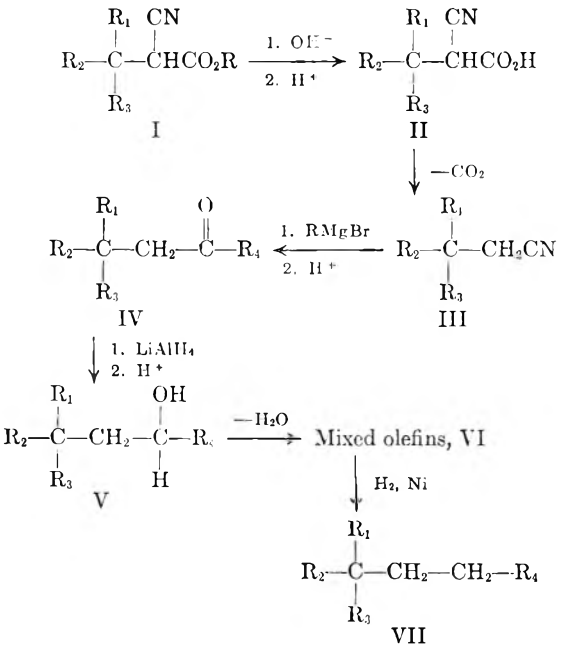
TABLE III

3,3-DIALKYL SUBSTITUTED NITRILES, $R_2-\underset{R_3}{\overset{R_1}{C}}-CH_2CN$

R_1	R_2	R_3	B.P.	n_D^{25}	Yield	Formula	Anal. Calcd. C	Anal. Calcd. H	Anal. Found C	Anal. Found H
C_2H_5	C_3H_7	$C_{12}H_{25}$	172–175°/1 mm.	1.4520	56	$C_{20}H_{39}N$	81.83	13.39	81.50	13.51
C_5H_7	C_4H_9	$C_{10}H_{21}$	168–170°/1 mm.	1.4522	69	$C_{20}H_{39}N$	81.83	13.39	81.69	13.33
C_2H_5	C_7H_{15}	C_8H_{17}	177–180°/1 mm.	1.4521	87	$C_{20}H_{39}N$	81.83	13.39	81.84	13.06
CH_3	C_6H_{13}	$C_{10}H_{21}$	181–183°/1 mm.	1.4493	86	$C_{20}H_{39}N$	81.83	13.39	82.16	13.27
C_5H_{11}	C_6H_{13}	C_7H_{15}	169–173°/1 mm.	1.4510	85	$C_{21}H_{41}N$	82.01	13.44	81.94	13.17
C_7H_{15}	C_8H_{17}	$C_{10}H_{21}$	226–228°/1 mm.	1.4570	96	$C_{28}H_{55}N$	82.88	13.66	83.12	13.66
C_7H_{15}	$C_{10}H_{21}$	$C_{12}H_{25}$	262–265°/0.5 mm.	1.4580	78	$C_{32}H_{63}N$	83.22	13.75	85.54	13.61
$C_{10}H_{21}$	$C_{11}H_{23}$	$C_{12}H_{25}$	278–281°/0.5 mm.	1.4598	36	$C_{36}H_{71}N$	83.48	13.82	83.67	13.85

tion of ether solutions of other Grignard reagents to ethyl or methyl alkylidenecyanoacetates in the presence of cuprous iodide afforded 60–81% yields of α-cyano-β,β,β-trisubstituted propionic acid esters (Table II).

The desired unsymmetrical tetraalkylmethanes (VII) were obtained from the α-cyano-β,β,β-trisubstituted propionates (I) by the following series of reactions.



The esters (I) were converted by alkaline hydrolysis to the corresponding acids with very little attack on the nitrile grouping. The cyano acids (II) were not isolated, but the crude residues from hydrolysis were transformed directly to the nitrile (III) in the presence of copper powder. The reaction was subject to an induction period and the major portion of the decarboxylation occurred over a short period of time in the temperature range of 140–160°. The nitriles, Table III, were obtained, in general, in high yields. The 3-decyl-3-undecylpentadecanonitrile resulted (36%) from thermal decarbethoxylation during attempted distillation of ethyl 2-cyano-3-decyl-3-undecylpentadecanoate.

The addition of Grignard reagents to the β,β,β-trisubstituted propionitriles gave satisfactory yields of the ketones (IV), Table IV, which were reduced then to the carbinols (V), Table V. Sodium borohydride reduction of the branched ketones, (IV), did not take place under the conditions employed. Also, catalytic reduction, even at 150° and 2500 p.s.i. in the presence of Raney nickel catalyst, was unsatisfactory because incomplete reduction made purification of the products difficult.

The dehydration of the secondary alcohols in the presence of potassium hydrogen sulfate led to mixtures of olefins (VI), Table VI. Evidence[11] has been obtained which indicates that the olefins have the expected structures, and that molecular rearrangements did not take place during the dehydration step. The mixed olefins (VI) were reduced readily to the saturated hydrocarbons (VII) with hydrogen and Raney nickel catalyst. Infrared spectra of all the compounds in the series showed the presence of the desired functional groups. Oxygen-containing and unsaturated materials could not be detected in the spectra of the tetraalkylmethanes recorded in Table VII.

EXPERIMENTAL[12]

Materials. 3-Hexanone, 2-oetanone, 4-octanone, 3-decanone, and 6-dodecanone were obtained by the oxidation of the corresponding secondary alcohols by means of sodium dichromate in sulfuric acid. The carbinols had been synthesized from the appropriate Grignard reagents and aldehydes. The ketones possessed the following physical properties: 3-hexanone, b.p. 122–126°, n_D^{20} 1.4000, lit.,[13] b.p.

(11) Norman Rabjohn and R. J. DeFeo, unpublished results.

(12) All melting points are uncorrected. The carbon and hydrogen analyses were performed by A. Mendel of this Laboratory and the Weiler and Strauss Laboratories, Oxford, England. The authors are indebted to Professor E. E. Pickett for much of the infrared data.

(13) J. M. Heilbron, "Dictionary of Organic Compounds," Vol. II, Oxford University Press, New York, 1953, p. 521.

TABLE IV

DIALKYL SUBSTITUTED KETONES, $R_2-\underset{\displaystyle R_3}{\overset{\displaystyle R_1}{\underset{|}{\overset{|}{C}}}}-CH_2-\overset{\displaystyle O}{\overset{\|}{C}}-R_4$

								Anal.			
								Calcd.		Found	
R_1	R_2	R_3	R_4	B.P.	n_D^{25}	Yield	Formula	C	H	C	H
C_2H_5	C_3H_7	$C_{12}H_{25}$	C_7H_{15}	215–216°/1 mm.	1.4551	43	$C_{27}H_{54}O$	82.16	13.79	82.09	13.66
C_3H_7	C_4H_9	$C_{10}H_{21}$	C_7H_{15}	223–225°/2 mm.	1.4540	86	$C_{27}H_{54}O$	82.16	13.79	82.08	13.84
C_2H_5	C_7H_{15}	C_8H_{17}	C_7H_{15}	212–214°/1 mm.	1.4548	83	$C_{27}H_{54}O$	82.16	13.79	82.07	13.83
CH_3	C_6H_{13}	$C_{10}H_{21}$	C_7H_{15}	202–206°/1 mm.	1.4531	75	$C_{27}H_{54}O$	82.16	13.79	82.08	13.87
C_5H_{11}	C_6H_{13}	C_7H_{15}	C_6H_{13}	195–197°/1 mm.	1.4531	42	$C_{27}H_{54}O$	82.16	13.79	82.12	13.94
C_7H_{15}	C_8H_{17}	$C_{10}H_{21}$	C_7H_{15}	253–256°/1 mm.	1.4582	88	$C_{35}H_{70}O$	82.92	13.92	82.87	13.83
$C_{10}H_{21}$	$C_{11}H_{23}$	$C_{12}H_{25}$	C_7H_{15}	270–273°/0.5 mm.	1.4613	57	$C_{43}H_{86}O$	83.41	14.00	83.32	13.95
C_7H_{15}	$C_{10}H_{21}$	$C_{12}H_{25}$	$C_{18}H_{37}$	292–295°/0.1 mm.	1.4620	71	$C_{50}H_{100}O$	83.72	14.05	83.55	13.76

TABLE V

DIALKYL SUBSTITUTED CARBINOLS, $R_2-\underset{\displaystyle R_3}{\overset{\displaystyle R_1}{\underset{|}{\overset{|}{C}}}}-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-R_4$

								Anal.			
								Calcd.		Found	
R_1	R_2	R_3	R_4	B.P.	n_D^{25}	Yield	Formula	C	H	C	H
C_2H_5	C_3H_7	$C_{12}H_{25}$	C_7H_{15}	207–210°/1 mm.	1.4592	93	$C_{27}H_{56}O$	81.74	14.23	81.80	13.95
C_3H_7	C_4H_9	$C_{10}H_{21}$	C_7H_{15}	221–223°/2 mm.	1.4588	95	$C_{27}H_{56}O$	81.74	14.23	81.83	14.37
C_2H_5	C_7H_{15}	C_8H_{17}	C_7H_{15}	193–195°/0.5 mm.	1.4591	97	$C_{27}H_{56}O$	81.74	14.23	81.49	13.99
CH_3	C_6H_{13}	$C_{10}H_{21}$	C_7H_{15}	200–204°/1 mm.	1.4572	96	$C_{27}H_{56}O$	81.74	14.23	81.87	14.51
C_5H_{11}	C_6H_{13}	C_7H_{15}	C_6H_{13}	199–203°/1 mm.	1.4580	97	$C_{27}H_{56}O$	81.74	14.23	81.62	14.00
C_7H_{15}	C_8H_{17}	$C_{10}H_{21}$	C_7H_{15}	256–260°/0.5 mm.	1.4610	96	$C_{35}H_{72}O$	82.60	14.26	82.30	14.27
$C_{10}H_{21}$	$C_{11}H_{23}$	$C_{12}H_{25}$	C_7H_{15}	290–293°/0.5 mm.	1.4633	77	$C_{43}H_{88}O$	83.14	14.28	82.91	14.43
C_7H_{15}	$C_{10}H_{21}$	$C_{12}H_{25}$	$C_{18}H_{37}$	305–306°/0.1 mm.	1.4636	91	$C_{50}H_{102}O$	83.48	14.29	83.17	14.32

TABLE VI

ALKENES, $R_2-\underset{\displaystyle R_3}{\overset{\displaystyle R_1}{\underset{|}{\overset{|}{C}}}}-CH{=}CHCH_2R_4$ AND $R_2-\underset{\displaystyle R_3}{\overset{\displaystyle R_1}{\underset{|}{\overset{|}{C}}}}-CH_2-CH{=}CH-R_4$

								Anal.			
								Calcd.		Found	
R_1	R_2	R_3	R_4	B.P.	n_D^{25}	Yield	Formula	C	H	C	H
C_2H_5	C_3H_7	$C_{12}H_{25}$	C_6H_{13}	189–193°/1 mm.	1.4569	91	$C_{27}H_{54}$	85.63	14.37	85.68	14.34
C_3H_7	C_4H_9	$C_{10}H_{21}$	C_6H_{13}	218–220°/2 mm.	1.4562	94	$C_{27}H_{54}$	85.63	14.37	85.76	14.17
C_2H_5	C_7H_{15}	C_8H_{17}	C_6H_{13}	200–203°/2 mm.	1.4570	92	$C_{27}H_{54}$	85.63	14.37	85.96	14.18
CH_3	C_6H_{13}	$C_{10}H_{21}$	C_6H_{13}	193–196°/1 mm.	1.4549	98	$C_{27}H_{54}$	85.63	14.37	85.59	14.24
C_5H_{11}	C_6H_{13}	C_7H_{15}	C_5H_{11}	185–187°/1 mm.	1.4559	90	$C_{27}H_{54}$	85.63	14.37	85.49	14.18
C_7H_{15}	C_8H_{17}	$C_{10}H_{21}$	C_6H_{13}	243–246°/0.5 mm.	1.4599	98	$C_{35}H_{70}$	85.63	14.37	85.66	14.30
$C_{10}H_{21}$	$C_{11}H_{23}$	$C_{12}H_{25}$	C_6H_{13}	259–261°/0.5 mm.	1.4630	92	$C_{43}H_{86}$	85.63	14.37	85.63	14.15
C_7H_{15}	$C_{10}H_{21}$	$C_{12}H_{25}$	$C_{17}H_{35}$	292–295°/0.1 mm.	1.4629	91	$C_{50}H_{100}$	85.63	14.37	85.89	14.30

123–123.5°, n_D^{22} 1.3990; 2-octanone, b.p. 72–74°/17 mm., n_D^{20} 1.4151, lit.,[14] b.p. 172.9°, n_D^{20} 1.4161; 4-octanone, b.p. 63–64°/14 mm., n_D^{20} 1.4138, lit.,[15] b.p. 165–168°; 3-decanone, b.p. 98–102°/17 mm., n_D^{20} 1.4240, lit.,[16] b.p. 203°, n_D^{20} 1.4251; and 6-dodecanone, b.p. 92–95°/2 mm., n_D^{25} 1.4270, m.p. 8–9°, lit.,[17] b.p. 112°/9 mm., m.p. 9°. The 8-octadecanone was prepared by the reaction of caprylyl chloride with decylcadmium; b.p. 178–180°/3 mm., m.p. 44–45° (from 2-butanone); lit.,[18] m.p. 44.8–46°. Similarly, the 11-docosanone was obtained from decylcadmium and lauroyl chloride; m.p. 59–60°, lit.,[18] m.p. 58.6–59.8°.

Ethyl 1-methylheptylidenecyanoacetate was synthesized by the condensation of ethyl cyanoacetate with 2-octanone

(14) N. A. Lange, "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, 1952, p. 588.

(15) L. Bouveault and R. Locquin, *Bull. soc. chim.*, **35**, 646 (1906).

(16) A. I. Vogel, *J. Chem. Soc.*, 607 (1948).

(17) L. Bouveault and R. Locquin, *Compt. rend.*, **140**, 1699 (1905).

(18) F. L. Breusch and F. Baykut, *Ber.*, **86**, 684 (1953).

TABLE VII

TETRAALKYLMETHANES, $R_2-\overset{R_1}{\underset{R_3}{C}}-R_4$

								Anal.			
								Calcd.		Found	
R_1	R_2	R_3	R_4	B.P.	n_D^{25}	Yield	Formula	C	H	C	H
C_2H_5	C_3H_7	$C_{12}H_{25}$	C_9H_{19}	195–196°/1 mm.	1.4521	84	$C_{27}H_{56}$	85.17	14.83	85.05	14.97
C_3H_7	C_4H_9	$C_{10}H_{21}$	C_9H_{19}	200–201°/1 mm.	1.4524	88	$C_{27}H_{56}$	85.17	14.83	84.96	14.69
C_2H_5	C_7H_{15}	C_8H_{17}	C_9H_{19}	189–190°/1 mm.	1.4520	93	$C_{27}H_{56}$	85.17	14.83	85.19	14.89
CH_3	C_6H_{13}	$C_{10}H_{21}$	C_9H_{19}	190–191°/1 mm.	1.4501	85	$C_{27}H_{56}$	85.17	14.83	85.37	14.52
C_5H_{11}	C_6H_{13}	C_7H_{15}	C_8H_{17}	180–182°/1 mm.	1.4508	94	$C_{27}H_{56}$	85.17	14.83	84.94	14.76
C_7H_{15}	C_8H_{17}	$C_{10}H_{21}$	C_9H_{19}	243–245°/0.5 mm.	1.4560	92	$C_{35}H_{72}$	85.28	14.72	85.42	14.69
$C_{10}H_{21}$	$C_{11}H_{23}$	$C_{12}H_{25}$	C_9H_{19}	268–270°/0.5 mm.	1.4596	82	$C_{43}H_{88}$	85.34	14.66	85.47	14.54
C_7H_{15}	$C_{10}H_{21}$	$C_{12}H_{25}$	$C_{20}H_{41}$	298–300°/0.05 mm.	1.4610	68	$C_{50}H_{102}$	85.38	14.62	85.37	14.39

according to the method of Cope, Hofmann, Wykoff, and Hardenbergh,[7] b.p. 134–137°/3 mm., n_D^{25} 1.4649; lit.,[7] b.p. 124–125°/2 mm., n_D^{25} 1.4656. The alkylidene esters listed in Table I were prepared also by this general method.

Ethyl 2-cyano-3-hexyl-3-methyltridecanoate. Method A. A Grignard reagent was prepared from 5.74 g. (0.24 g. atom) of magnesium and 52.7 g. (0.24 mol.) of decyl bromide in 100 ml. of ether. The mixture was allowed to stir for 30 min. after addition of the decyl bromide had been completed. This Grignard reagent was added dropwise to a mixture of 35 g. (0.16 mol.) of ethyl 1-methylheptylidenecyanoacetate and 0.8 g. (5 g./mol. of alkylidene) of cuprous iodide in 93 ml. (590 ml./mol.) of ether. The reaction mixture became blue-black. After the addition had been completed, the reaction mixture was refluxed with stirring for 1 hr. and stood at room temperature for 20 hr. The mixture was poured onto 47 ml. of concentrated hydrochloric acid and 100 g. of ice with rapid stirring. The resulting mixture was shaken thoroughly in a separatory funnel, and after the aqueous layer had been removed, was extracted with several small portions of ether. The ether solutions were combined, washed with water, 10% sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. After the ether had been removed by distillation, the residue was distilled to give 45.2 g. (78.5%) of ethyl 2-cyano-3-*n*-hexyl-3-methyltridecanoate; b.p. 195–202°/1 mm.; 5.66 g. of eicosane and 1.76 g. of material which boiled at 120–126°/1 mm.

Method B. The Grignard reagent was prepared as above, and the cuprous iodide was added to the Grignard reagent. To this solution was added the alkylidene compound in ether solution. All other conditions were the same as above. There were obtained 16.64 g. (29%) of ethyl 2-cyano-3-*n*-hexyl-3-methyltridecanoate, 5.23 g. eicosane, and 17.6 g. of a lower boiling material; b.p. 122–130°/1 mm.

Method C. The reaction was carried out under the same conditions as Method A without the use of cuprous iodide. There resulted 26.9 g. (46.9%) of ethyl 2-cyano-3-*n*-hexyl-3-methyltridecanoate, 6.68 g. of eicosane, and 9.38 g. of material; b.p. 115–130°/1 mm.

Method D. The conditions of Method B were employed without the use of cuprous iodide to give 24.77 g. (43%) of ethyl 2-cyano-3-*n*-hexyl-3-methyltridecanoate, 5.89 g. of eicosane and 14.85 g. of a material; b.p. 115–130°/1 mm.

The remainder of the alkylidene compound was converted to ethyl 2-cyano-3-hexyl-3-methyltridecanoate by Method A; b.p. 200–204°/1 mm., n_D^{25} 1.4529.

Anal. Calcd. for $C_{23}H_{43}NO_2$: C, 75.56; H, 11.86. Found: C, 75.44; H, 11.73.

The material which boiled at 115–130°/1 mm. was redistilled and the fraction which was collected at 118°/1 mm., n_D^{25} 1.4380, was submitted for analysis.

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29. Found: C, 69.26; H, 10.72.

An infrared spectrum of this substance showed the presence of the ester and nitrile groups, and the intensity for the double bond absorption was reduced considerably compared to that shown by the spectrum of ethyl 1-methylheptylidenecyanoacetate. The material apparently was a mixture which contained a large portion of ethyl 2-cyano-4-methyldecanoate and some of the corresponding alkylidene compound. Hook and Robinson[10] and Prout[8] have observed similar reduction products.

3-Hexyl-3-methyltridecanenitrile. The following procedure is representative of the method employed for the conversion of the 2-cyano-3,3-dialkyl substituted esters (I) to the dialkyl substituted nitriles. A mixture of 150 g. (2.4 mol.) of 85% potassium hydroxide in 660 ml. of water, 179.9 g. (0.49 mol.) of ethyl 2-cyano-3-hexyl-3-methyltridecanoate and 128 ml. of ethanol was heated at reflux for 6 hr. The alcohol was removed by distillation, 800 ml. of 20% sulfuric acid was added to the residue, and the mixture was refluxed 4 hr. After it had cooled, the organic layer was removed and the aqueous solution was extracted with several small portions of ether. The organic layer and the ether extracts were combined and the ether was evaporated.

The residue was mixed with 0.8 g. (0.005 part by weight) of copper powder and heated slowly with mechanical stirring. Decarboxylation occured at 150–160°. After the vigorous evolution of carbon dioxide had ceased, the reaction mixture was heated to 180° for a short period. The residue was distilled to give 124 g. (86%) of 3-hexyl-3-methyltridecanenitrile; b.p. 181–183°/1 mm., n_D^{25} 1.4493.

10-Ethyl-10-heptyl-8-octadecanone. The ketones listed in Table IV were synthesized in the following representative manner. A Grignard reagent was prepared from 18.7 g. (0.78 g. atom) of magnesium and 138 g. (0.77 mol.) of *n*-heptyl bromide in 400 ml. of anhydrous ether. It was stirred mechanically while 150 g. (0.51 mol.) of 3-ethyl-3-heptylundecanenitrile was added dropwise. After the addition had been completed, the reaction mixture was heated at reflux for 11 hr. It was allowed to cool and was poured onto a mixture of 180 ml. of concentrated hydrochloric acid and 280 g. of ice. The ether layer was separated, the solvent was evaporated, and a solution of 65 ml. of concentrated hydrochloric acid and 450 ml. of water was added. The mixture was heated and stirred for 1 hr., allowed to cool, and extracted with ether. The extracts were washed with water, 10% sodium bicarbonate solution, again with water and dried over anhydrous sodium sulfate. The ether was removed by distillation and the residue was distilled to give 167 g. (83%) of 10-ethyl-10-heptyl-8-octadecanone; b.p. 212–214°/1 mm., n_D^{25} 1.4548.

9-Pentyl-9-hexyl-7-hexadecanol. The carbinols listed in Table V were obtained by means of the following typical lithium aluminum hydride reduction. A solution of 14 g. (0.34 mol.) of lithium aluminum hydride in 640 ml. of

anhydrous ether was stirred mechanically while 126 g. (0.32 mol.) of 9-pentyl-9-hexyl-7-hexadecanone in 160 ml. of anhydrous ether was added at a rate sufficient to cause gentle refluxing. After the addition had been completed, the mixture was stirred at room temperature for 1 hr. and heated under reflux for an additional 5 hr. Then a 50% by volume solution of ethyl acetate in ether was added slowly until refluxing ceased. This was followed by the addition of 500 ml. of 10% sulfuric acid. The ether layer was removed, washed with water, 10% sodium bicarbonate, again with water, and was dried over anhydrous sodium sulfate. After removing the ether, the residue was distilled to give 124 g. (98%) of the carbinol; b.p. 199–203°/1 mm., n_D^{25} 1.4580.

Attempted reduction of 9-pentyl-9-hexyl-7-hexadecanone with sodium borohydride. The method of Chaikin and Brown[19] was followed. To a solution of 50 g. (0.13 mol.) of 9-pentyl-9-hexyl-7-hexadecanone in 50 ml. of methanol was added 2.4 g. (0.07 mol.) of sodium borohydride in 20 ml. of methanol. No reaction appeared to occur even when the mixture was heated to boiling for some time. It was heated then with 100 ml. of 10% sodium hydroxide solution for 1 hr. The organic layer was removed, taken up in 100 ml. of ether, washed with water and dried over anhydrous sodium sulfate. The ether was removed by distillation and the residue was distilled to give 48 g. of unchanged ketone.

(19) S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).

10-Propyl-10-butyl-7(8)-eicosene. This procedure is typical of those used to obtain the mixtures of olefins given in Table VI. A mixture of 111 g. (0.3 mol.) of 10-propyl-10-butyl-8-eicosanol and 20 g. of anhydrous potassium bisulfate was heated under reduced pressure at 150–160° for 24 hr. It was allowed to cool, the liquid was decanted, and the potassium bisulfate was extracted with several small portions of ether. The oil and extracts were combined and the ether was evaporated. The residue was distilled to give 101 g. (94%) of material which boiled between 218 and 220°/2 mm., n_D^{25} 1.4562.

10-Butyl-10-propyleicosane. The tetraalkylmethanes in Table VII were obtained by the hydrogenation of the mixtures of olefins reported in Table VI. The preparation of 10-butyl-10-propyleicosane is representative. A mixture of 51 g. of 10-butyl-10-propyl-7(8)-eicosene, 75 ml. of methylcyclohexane, and 10 g. of Raney nickel catalyst was heated, and rocked at 180° and 3200 p.s.i. of hydrogen for 7 hr. The reaction mixture was allowed to cool, was filtered and the solvent was removed by distillation. The residual oil was washed with three 100-ml. portions of cold, concentrated sulfuric acid, then with saturated sodium chloride solution, 10% sodium bicarbonate solution, and water. It was distilled to give 45 g. (88%) of a colorless liquid; b.p. 200–201°/1 mm., n_D^{25} 1.4524.

COLUMBIA, MO.

[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION, TEXTILE FIBERS DEPARTMENT, E. I. DU PONT DE NEMOURS & CO., INC.]

Synthesis of Hydrocarbon Derivatives by the Wittig Reaction II. Diarylbutadienes and Quinquephenyls[1]

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The reaction of triphenylcinnamylphosphonium chloride and *p*-xylylenebis(triphenylphosphonium chloride) with aromatic aldehydes and cinnamaldehydes has given diarylbutadienes and 1,4-bis(4-arylbutadienyl)benzenes in yields of 60–100%. 1,4-Diphenylbutadiene, 1-(*p*-tolyl)-4-phenylbutadiene, and 1,4-bis(*p*-tolyl)butadiene were converted by the method described by Lohaus into *p*-terphenyl, 4-methylterphenyl, and 4,4″-dimethylterphenyl, respectively. This technique was extended to 1,4-bis(4-phenylbutadienyl)benzene, 1,4-bis[4-(*p*-tolyl)butadienyl]benzene, and 1,4-bis(3-methyl-4-phenylbutadienyl)benzene. *p*-Quinquephenyl, 4,4′′′′-dimethylquinquephenyl, and 2′,3′′′-dimethylquinquephenyl were obtained, respectively, in good yields. This represents the best route to this aromatic hydrocarbon system reported and the latter two methyl derivatives are the first derivatives to appear in the literature. This route is considered to be unambiguous.

Diarylbutadienes and 1,4-bis(arylbutadienyl)-benzenes, ArCH=CH—CH=CH—C_6H_4—CH=CH—CH=CH—Ar, have proved relatively difficult to synthesize in good yield, particularly with functional groups on the aryl rings. The dehydrogenation of 1,4-diphenylbutene-2 with *n*-butyllithium[2] gave 1,4-diphenylbutadiene in 12% yield. The Meerwein reaction between, for example, benzenediazonium chloride and cinnamylidene acetic acid,[3] has also been employed in the synthesis of diarylbutadienes. Probably the most widely used reaction has been the Perkin or Kuhn condensation of a β-arylacrolein with an arylacetic acid in the presence of lead oxide.[4,5] This is the basis of the *Organic Syntheses* preparation of diphenylbutadiene in 25% yield.[4a] A variation of this latter method is the condensation of two molecules of an aromatic aldehyde with succinic acid in the presence of lead oxide.[5] 1,4-Bis(4-phenylbutadienyl)benzene has been prepared in low over-all yield by similar techniques.[4b]

The synthesis of 1,4-diarylbutadienes and of 1,4-bis(arylbutadienyl)benzenes may be carried out conveniently in two steps, and in high over-all yields using the Wittig synthesis in an extension of

(1) Previous paper, T. W. Campbell, and R. N. McDonald, *J. Org. Chem.*, 24, 1246 (1959).

(2) H. Gilman and C. W. Bardley, *J. Am. Chem. Soc.*, 60, 2333 (1938).

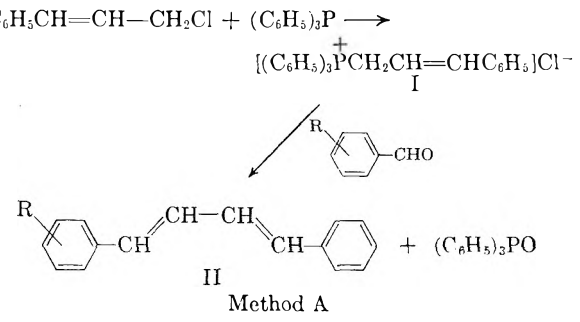
(3) C. F. Koelsch and V. Boekelheide, *J. Am. Chem. Soc.*, 66, 412 (1944).

(4) (a) B. B. Corson, *Org. Syntheses*, Coll. Vol. II, 229 (1943). (b) G. Drefahl and G. Plotner, *Chem. Ber.*, 91, 1285 (1958).

(5) S. Israelashvili, Y. Gottlieb, M. Imber, and A. Habas, *J. Org. Chem.*, 16, 1519.(1951).

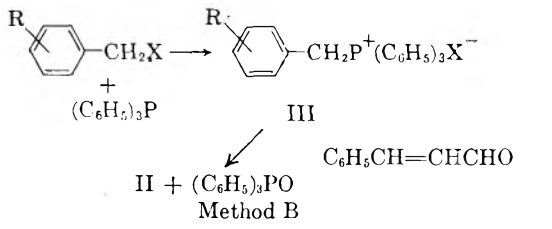
the methods used for the preparation of distyryl benzenes.[1]

One procedure (Method A) involves the preparation of triphenylcinnamylphosphonium chloride (I) from the reaction of cinnamyl chloride and triphenylphosphine. When a solution of I and benzal-



dehyde, or a substituted benzaldehyde, in ethanol is treated with a solution of lithium ethoxide in ethanol, a transient yellow-orange color forms. This is undoubtedly due to formation of the corresponding "ylide" of I, which then reacts with the aldehyde. As the color fades the product, diarylbutadiene (II), precipitates. Substitution of terephthalaldehyde for benzaldehyde gave the bisbutadiene.

In the other procedure (Method B) phosphonium salts from benzyl halides, exemplified by III, are allowed to react with cinnamaldehydes in the



ethanol-ethoxide mixture. This gives the butadienes and triphenylphosphine oxide. Starting with substituted cinnamaldehydes, a butadiene with substituents in each ring could be made. 1,4-Bis(*p*-tolyl)butadiene was prepared in this manner from the reaction of (*p*-methylbenzyl)triphenylphosphonium bromide and *p*-methylcinnamaldehyde. When R in III is another $-CH_2P^+(C_6H_5)_3Cl^-$ group, the bisbutadienes are obtained.

Diarylbutadienes. The diarylbutadienes prepared during this investigation are listed in Table I. The yields in all cases surpass those reported in the literature. A point of interest is the fact that these compounds were isolated, except in the case of the *p*-carbomethoxy and *m*-nitro derivatives, as the thermodynamically more stable *trans-trans* isomers. Generally, when two isomers were possible from the Wittig reaction, they were formed in ratios varying from a 50:50 up to an 80:20 mixture, the *trans* form predominating.

It is interesting that when the Wittig reaction is carried out in an ether solvent a temperature of about 65° is required to decompose the intermediate

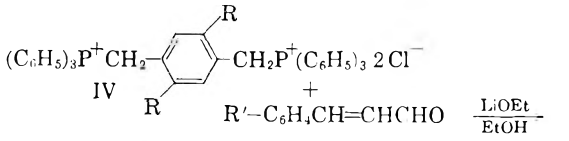
TABLE I

1,4-DIARYLBUTADIENES

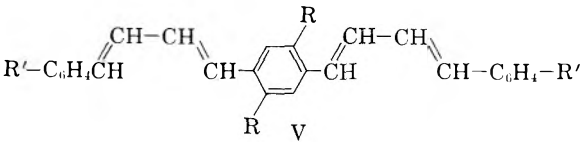
R	Yield	M.P.	Method of Preparation
H	63	154–156	A
p-CH_3	76	160–161	A
p-OCH_3	63	161–162.5	A
p-$NHCOCH_3$	61	264–265	A
p-$N(CH_3)_2$	66	177–180	B
p-CO_2CH_3	38	180–180.5	B
m-NO_2	65	181.5–182	B

to products.[6] However, using the ethanol-ethoxide system the reactions proceed rapidly in about 30–60 seconds at room temperature. This rapidity of reaction in ethanol is in line with the polar nature of the reaction intermediates.

1,4-Bis(4-arylbutadienyl)benzenes. The next obvious extension of these reactions was the synthesis of 1,4-bis(4-arylbutadienyl)benzenes (IV). In the previous paper[1] are described the preparations of *p*-xylenebis(triphenylphosphonium chloride) (IVa) and 2,5-dimethyl-*p*-xylylenebis(triphenylphosphonium chloride) (IVb). These phosphonium salts were found to react easily with benzaldehydes to produce 1,4-distyrylbenzenes in good yields. When a solution of the phosphonium salt



(a. R = H)
(b. R = CH_3)

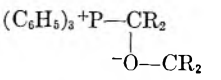


(a. R = H)
(b. R = CH_3)

(IVa) and cinnamaldehyde in ethanol was treated with a lithium ethoxide solution in ethanol, the product, 1,4-bis(4-phenylbutadienyl)benzene (Va. R′ = H) precipitated in 88% yield.[7]

This reaction was found to be general for cinnamaldehydes. The compounds Vb (R′ = H) and Va, where R′ is *m*-nitro, *p*-methyl, *p*-methoxy, and

(6) In the mechanism proposed by Wittig [*Angew. Chem.*, **68**, 505 (1956); *Experientia*, **12**, 41 (1956)] for the reaction, the betaine



is considered to be an intermediate, since in many cases a compound described as the betaine could be isolated and heating of it normally leads to olefin formation.

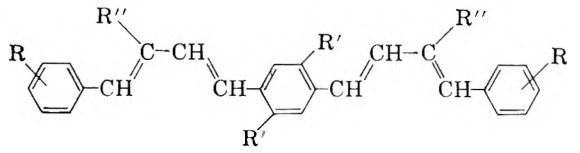
(7) This hydrocarbon was recently prepared by Drefahl and Plotner[4a] by the Perkin or Kuhn condensation in 25% yield.

p-dimethylamino have been prepared. The poor yield of the *p*-methoxy derivative is from only one experiment, and could undoubtedly be raised to the good yields as shown by the others. Another derivative of Va was obtained by replacing cinnamaldehyde in the scheme above with α-methylcinnamaldehyde to give 1,4-bis(3-methyl-4-phenylbutadienyl)benzene in 83% yield.

All of the products were obtained as mixtures of *cis* and *trans* isomers which were routinely isomerized, except for the dimethylamino derivative, to the all *trans* configuration by digestion in boiling xylene containing a trace of iodine. The dimethylamino compound, due to its reaction with iodine, could not be isomerized in this manner. It did, however, isomerize when recrystallized from dimethylformamide. The compounds obtained are listed in Table II. The yields are based on crude product, while the melting points are those of the isomerized materials, which were obtained with essentially no loss.

TABLE II

1,4-BIS(ARYLBUTADIENYL)BENZENES

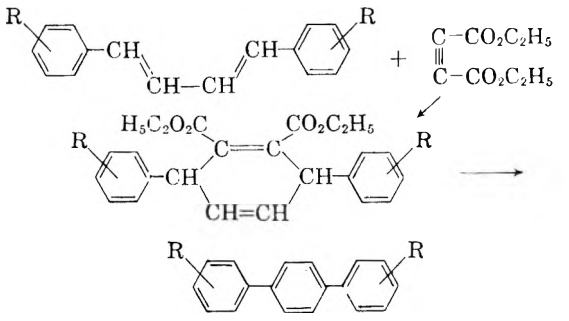


R	R′	R″	Yield, %	M.P.
H	H	H	88	290–293
p-CH_3	H	H	100	315–319
H	CH_3	H	75	246–247
H	H	CH_3	83	235–237
m-NO_2	H	H	65	260–264
p-OCH_3	H	H	13	304–306
p-$N(CH_3)_2$	H	H	100	314–315

Terphenyls and Quinquephenyls. In 1935 Lohaus[8] reported a convenient method for the preparation of *p*-terphenyl from 1,4-diphenylbutadiene. This involved the Diels-Alder reaction of the diene with diethyl acetylenedicarboxylate to give a 90% yield of diethyl 3,6-diphenyldihydrophthalate. Saponification and acidification gave the corresponding diacid. When this diacid was dissolved in aqueous carbonate and treated with a solution of potassium ferricyanide, a quantitative yield of terphenyl resulted.

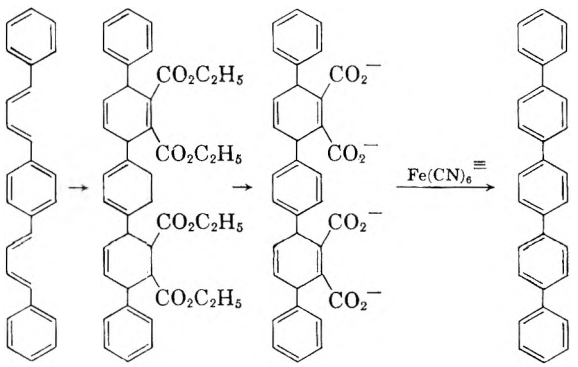
We have repeated this synthesis without isolation of intermediates and have obtained a 60% yield of terphenyl. Application of this procedure to 1-(*p*-tolyl)-4-phenylbutadiene and 1,4-bis(*p*-tolyl)-butadiene resulted in a 70% yield of 4-methylterphenyl and a 42% yield of 4,4″-dimethylterphenyl, respectively. This appears to be a fairly general route to terphenyls not containing groups attacked by ferricyanide.

(8) H. Lohaus, *Ann.*, **516**, 295 (1935).



It was of interest to see if this technique could be extended to the bisbutadienyl system to obtain *p*-quinquephenyls.[9] Previous methods of synthesis of this interesting polyphenyl have been laborious and have resulted in the production of trace amounts or, at best, very poor yields. These have included the reaction of biphenyllithium with cyclohexandione-1,4 followed by dehydration and air oxidation,[10] the Gatterman coupling reaction of benzenediazonium formate with copper[11]; the Ullmann coupling of 4-iodoterphenyl and 4-iodobiphenyl with silver[11]; the catalytic reduction of *p*-dibromobenzene[12]; and the Friedel-Crafts reaction of cyclohexene with terphenyl followed by dehydrogenation.[13]

The synthesis of quinquephenyl was carried out as follows. 1,4-Bis(4-phenylbutadienyl)benzene was condensed with two equivalents of diethyl acetylenedicarboxylate in boiling *o*-dichlorobenzene. The resulting mixture was saponified with alcoholic potassium hydroxide to give a brilliant yellow solution of the potassium tetrahydroquinquephenyl tetracarboxylate. This solution was readily decarboxylated and aromatized by reaction with potassium ferricyanide to give quinquephenyl. The product from four experiments was combined and sublimed to give a 52% yield of pure hydrocarbon. This rep-



(9) This material has been previously published in a Communication, T. W. Campbell and R. N. McDonald, *J. Org. Chem.*, **24**, 730 (1959).

(10) E. Miller and T. Topel, *Chem. Ber.*, **72B**, 273 (1939).

(11) O. Gerngrass and M. Dunkel, *Chem. Ber.*, **57B**, 739 (1924).

(12) M. Busch, W. Weber, C. Darboven, W. Renner, H. J. Hahn, G. Mathauser, F. Stratz, K. Zitzmann, and H. Engelhardt, *J. prakt. Chem.*, **146**, 1 (1936).

(13) Buu-Hoï and P. Cagniant, *Compt. rend.*, **216**, 381 (1943).

resents by far the best synthesis of this polyphenyl of which we are aware.

Applying this synthesis to 1,4-bis[4-(*p*-tolyl)butadienyl]benzene and 1,4-bis(3-methyl-4-phenylbutadienyl)benzene gave 4,4′′′′- and 2′,3′′′-dimethylquinquephenyl, respectively.

These two methylated derivatives of *p*-quinquephenyl represent the first derivatives of the hydrocarbon reported in the literature. It is also worth noting that they were synthesized under mild conditions and in what we consider an unambiguous manner.

When 1,4-bis[4-(3-nitrophenyl)butadienyl]benzene was used, none of the 3,3′′′′-dinitroquinquephenyl, resulted. It is felt that the nitro groups deactivated the diene system sufficiently so that the Diels-Alder reaction did not occur as expected.

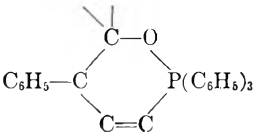
The condensation of 1,4-bis[4-(4-*N*,*N*-dimethylaminophenyl)butadienyl]benzene with diethyl acetylenedicarboxylate and saponification seemed to proceed as expected. But, on subsequent treatment with potassium ferricyanide, a black, unidentified material was obtained. Apparently the dimethylamino groups were oxidized along with the anticipated decarboxylation and aromatization. However, little effort was expended in attempted identification of this material.

Miscellaneous. In continuing the extension of the Wittig reaction to higher polyenes, 1,6-diphenylhexatriene and 1-(3-nitrophenyl)-6-phenylhexatriene were prepared by reaction of triphenylcynnamylphosphonium chloride with cinnamaldehyde and *m*-nitrocinnamaldehyde, respectively. Since the yields of these reactions reported are from single experiments with little care taken to insure proper conditions, these do not by any means represent the maximum yields obtainable. A single attempt to prepare 1,6-diphenylhexatriene by reaction of 1,4-bis(triphenylphosphonium chloride)butene-2 and benzaldehyde gave only a brown resin as product. A similar product was obtained when the synthesis of 1,10-diphenyldecapentaene from the butene-bisphosphonium salt and cinnamaldehyde was attempted.

In connection with triphenylcinnamylphosphonium chloride, it is interesting to consider what the structure of the intermediate phosphonium ylide

$$\underset{a}{C_6H_5CH}=CH-\underset{b}{\overset{(-)}{C}H}-\overset{(+)}{P}-(C_6H_5)_3 \longleftrightarrow C_6H_5\overset{(-)}{C}H-CH=CH-\overset{(+)}{P}-C_6H_5)_3$$

might be. When prepared in alcohol solution in the absence of aldehyde, it is brilliant red-orange and stable for long periods. It is evident from the color that the ylide can resonate as indicated, in a manner similar to cinnamyl anion.[14] Such being the case, reaction can occur with the carbonyl group at both positions (a) and (b); *via* an intermediate such as;



as well as the conventional 4-ring intermediate. Evidence for such intermediates has not been observed in the products, hence it must not be capable of collapsing to products other than the original ylide and carbonyl compound.[15]

EXPERIMENTAL

Melting points were determined on the Kofler Hot Stage.

Preparation of (p-nitrobenzyl)triphenylphosphonium bromide. A mixture of 25.0 g. (0.12 mol.) of *p*-nitrobenzyl bromide and 33.0 g. (0.13 mol.) of triphenylphosphine in 300 ml. of xylene was refluxed and stirred for 26 hr. The tan crystalline solid was filtered, washed with xylene, and dried. The yield was 51.2 g. (95%) of a product melting at 275 to 275.5°.

Anal. Calcd. for $C_{25}H_{21}NO_2Br$: C, 63.0; H, 4.0; N, 2.93. Found: C, 62.6, 62.7; H, 4.4, 4.5; N, 3.14, 3.24.

The tan solid was readily soluble in alcohol. Treatment of an alcoholic solution of the phosphonium salt with lithium ethylate solution gave a very intense cherry-red color which persisted in the solution for nearly an hour.

Preparation of (p-methylbenzyl)triphenylphosphonium bromide. A mixture of 80.0 g. (0.43 mol.) of α-bromo-*p*-xylene and 140 g. (0.54 mol.) of triphenylphosphine in 500 ml. of dimethylformamide was heated under reflux for 3 hr. After cooling to room temperature the salt was filtered, washed with ether, and dried under reduced pressure at 65°. The dry weight was 147.4 g. (76%), m.p. 277–277.5°. An analytical sample was recrystallized from dimethylformamide to give clusters of colorless crystals, m.p. 276–277°.

Anal. Calcd. for $C_{26}H_{24}BrP$: C, 69.80; H, 5.41; Br, 17.87. Found: C, 69.96, 69.91; H, 5.96; Br (ionic), 17.86, 17.41; Br (total), 17.95, 18.09.

1,4-Bis(triphenylphosphonium chloride)butene-2. A mixture of 1400 ml. of xylene, 200 g. (0.75 mol.) of triphenylphosphine, and 30 g. (0.24 mol.) of 1,4-dichlorobutene-2 was refluxed for 60 hr. The slightly discolored crystalline solid was refluxed for 60 hr. The slightly discolored crystalline solid was filtered, dried, and recrystallized from a mixture of isopropanol and ether. The nicely crystalline product was obtained in a yield of 102 g. (65%). For analysis the sample was dried for 3 hr. at 110° in a high vacuum.

Anal. Calcd. for $C_{40}H_{36}P_2Cl_2$: C, 73.9; H, 5.5; Cl, 10.9. Found: C, 73.6, 73.9; H, 5.5, 5.7; Cl, 10.92, 10.88.

Preparation of ethylene-bis(triphenylphosphonium bromide). To a solution of 37.8 g. (0.201 mol.) of ethylene bromide in 300 ml. of benzene was added a solution of 140.0 g. (0.534 mol.) triphenylphosphine dissolved in 400 ml. of benzene. The mixture was heated at reflux for 4 days. The solid was filtered, washed with benzene, and dried in the vacuum oven at 60°. The dry weight was 37.4 g. An analytical sample of this material was recrystallized twice from ethanol-ether mixture to give colorless crystals, m.p. 280–295°.

Anal. Calcd. for $C_{38}H_{34}Br_2P_2$: C, 64.06; H, 4.81; Br, 22.44. Found: C, 64.1, 64.2; H, 4.83, 5.11; Br (ionic) 22.62.

The benzene filtrate was evaporated and on dilution with ether yielded considerably more product.

Preparation of triphenylcinnamylphosphonium chloride. To a solution of 40 g. (0.263 mol.) of (3-chloropropenyl)-benzene in 200 ml. of xylene was added a solution of 92 g.

(14) T. W. Campbell and W. G. Young, *J. Am. Chem. Soc.*, 69, 688 (1947); 69, 3066 (1947); 71, 296 (1949); 74, 608 (1952).

(15) Compare F. Bohlmann, *Chem. Ber.*, 89, 2191 (1956).

(0.350 mol.) of triphenylphosphine in 300 ml. of xylene. The mixture was heated at reflux with stirring overnight. The colorless crystalline product was filtered, washed with xylene, and dried in the vacuum oven. The dry weight was 99–101 g. (91–93%), m.p. 224–226°. A sample was recrystallized twice from ethanol ether to give colorless rosettes of needles, m.p. 224–226°.

Anal. Calcd. for $C_{27}H_{24}ClP$: C, 78.15; H, 5.83; Cl, 8.55. Found: C, 76.58, 76.58; H, 6.13, 6.26; Cl (ionic) 8.22, 8.36; O, 3.54 (direct analysis).

The poor analyses, plus presence of oxygen, suggest solvation.[1]

A solution of triphenylcinnamylphosphonium chloride in absolute ethanol gave an intense red color when treated with lithium ethoxide, which persisted for some time. In the following reactions, it was noted that reaction of the cinnamyl "ylide" with aromatic aldehydes was qualitatively much slower than the corresponding reaction of the bis "ylide" from *p*-xylylene-bis(triphenylphosphonium chloride).[1]

In addition to the products described in more detail below, triphenylcinnamylphosphonium chloride underwent the following reactions. Eight g. of this salt was condensed with 2.9 g. of *p*-nitrobenzaldehyde to give 3.1 g. of pure 1-(4-nitrophenyl)-4-phenylbutadiene melting at 181–182°. In addition, 0.82 g. of a yellow, crystalline solid melting at 165–175° was obtained from the filtrate as well as some unidentified oil.

Similarly, reaction of the cinnamyl phosphonium salt with terephthalaldehyde gave the previously known 1,4-bis-(4-phenylbutadienyl)benzene, m.p. 276–281. The yield was only 0.8 g. from 1.2 g. of terephthalaldehyde (27%).

Preparation of 1,4-diphenylbutadiene. A solution of 60 g. (0.145 mol.) of triphenylcinnamylphosphonium chloride and 16.4 g. (0.155 mol.) of benzaldehyde in 200 ml. of alcohol was treated with 760 ml. of 0.2*M* lithium ethoxide in ethanol. After allowing this mixture to stand over the week end at room temperature, 700 ml. of water was added and the solid filtered, washed with 150 ml. of 60% alcohol, and dried in a vacuum oven at 65°. The yield of product was 17.9–19.9 g. (60–66%). Recrystallization from cyclohexane gave colorless needles, m.p. 154–155° (reported[4a] m.p. 152.5–153.5°). The product is in the *trans-trans* form of the diene.

Preparation of 1-(4-methoxyphenyl)-4-phenylbutadiene. To a solution of 15.0 g. (0.0363 mol.) of triphenylcinnamylphosphonium chloride and 5.26 g. (0.0387 mol.) of anisaldehyde in 50 ml. of alcohol was added 190 ml. of 0.2*M* lithium ethoxide in ethanol. After standing at room temperature over the week end, 150 ml. of water was added and the crystalline solid filtered, washed with 100 ml. of 60% alcohol, and dried in the vacuum oven at 60°. The dry weight was 5.4 g. (63%). The solid was recrystallized from benzene-cyclohexane mixture to give colorless crystals, m.p. 162–162.5°. An analytical sample was recrystallized from the same solvent mixture to give colorless crystals, m.p. 162–162.5°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.3, 86.5; H, 6.89, 6.91.

Preparation of 1-(4-acetamidophenyl)-4-phenylbutadiene. To a solution of 15.0 g. (0.0363 mol.) of triphenylcinnamylphosphonium chloride and 6.4 g. (0.392 mol.) of *p*-acetamidobenzaldehyde in 50 ml. of alcohol was added 190 ml. of 0.2*M* lithium ethoxide in ethanol. After standing overnight at room temperature, 150 ml. of water was added and the solid filtered, washed with 100 ml. of 60% alcohol and dried in the vacuum oven at 60°. The dry weight was 5.8 g. (61%). Recrystallization from dimethylformamide-ethanol mixture gave light yellow needles (4.9 g.), m.p. 264–265°. An analytical sample was recrystallized from the same solvent mixture, m.p. 267–268°.

Anal. Calcd. for $C_{18}H_{17}ON$: C, 82.09; H, 6.51; N, 5.32. Found: C, 82.31, 82.33; H, 6.55, 6.58; N, 5.32, 5.38.

Preparation of 1-(p-tolyl)-4-phenylbutadiene. To a solution of 60 g. (0.145 mol.) of triphenylcinnamylphosphonium chloride and 19.2 g. (0.16 mol.) of *p*-tolualdehyde in 200 ml. of alcohol was added 760 ml. of 0.2*M* lithium ethoxide in ethanol. After 24 hr., an equal volume of water was added, and the crystalline product was filtered, washed with 60% aqueous ethanol, and dried in a vacuum at 60°. The yield was 24.3 g. (76%). After recrystallization from cyclohexane, colorless needles resulted, m.p. 160–161° (reported[4b], m.p. 159–160°).

Anal. Calcd. for $C_{17}H_{16}$: C, 92.70; H, 7.30. Found: C, 92.44, 92.41; H, 7.36, 7.37.

Preparation of 1-(4-dimethylaminophenyl)-4-phenylbutadiene. To a solution of 20.0 g. (0.051 mol.) of triphenylcinnamylphosphonium chloride and 9.5 g. (0.053 mol.) of *p*-dimethylaminobenzaldehyde in 200 ml. of ethanol was added 260 ml. of 0.2*M* lithium ethoxide. In about 4 min. a yellow-tan crystalline precipitate appeared. After standing overnight 250 ml. of water was added, the solid filtered, washed with 100 ml. of 60% ethanol and dried at reduced pressure and 60°. The dry weight was 8.5 g. (66%). This was recrystallized from a benzene-cyclohexane mixture to give golden needles, m.p. 177–180°. An analytical sample was recrystallized from dimethylformamide, m.p. 180–182°.

Anal. Calcd. for: $C_{18}H_{19}N$: C, 86.7; H, 7.8; N, 5.6. Found: C, 86.6, 86.9; H, 7.8, 7.6; N, 5.7, 5.7.

Preparation of 1-(4-carbomethoxyphenyl)-4-phenylbutadiene. A solution of 47.4 g. (0.11 mol.) of (4-carbomethoxybenzyl)triphenylphosphonium chloride[1] and 16.0 g. (0.12 mol.) of cinnamaldehyde in 100 ml. of ethanol was treated with 60 ml. of a 0.2*M* solution of lithium ethoxide. Immediately, a nearly colorless crystalline precipitate separated. After 0.5 hr., 100 ml. of water was added, the solution was filtered and dried to give 10.4 (37%) of product which on recrystallization from benzene-cyclohexane mixture (50/50) in the presence of a trace of iodine gave a product melting at 180–180.3°.

Anal. Calcd. for: $C_{18}H_{16}O_2$: C, 81.8; H, 6.07. Found: C, 81.8, 81.9; H, 6.10, 6.32.

Preparation of 1-(4-nitrophenyl)-4-phenylbutadiene. To a solution of 45.8 g. (0.96 mol.) of (*p*-nitrobenzyl)triphenylphosphonium bromide and 15.0 g. (0.114 mol.) of cinnamaldehyde in 250 ml. of ethanol was added a solution of 0.78 g. (0.114 mol.) of lithium wire dissolved in 400 ml. of ethanol. The mixture turned to a deep wine which faded as yellow crystals formed. After standing overnight, 250 ml. of water was added, the solid was filtered, washed with 100 ml. of 60% ethanol, and dried. The dry weight was 18.7 g. (72%). This was recrystallized from benzene-cyclohexane mixture containing a trace of iodine. The yield of product was 16.5 g., m.p. 181.5–182°.

Anal. Calcd. for: $C_{16}H_{13}NO_2$: C, 76.49; H, 5.18. Found: C, 76.26, 76.45; H, 5.17, 5.33.

Preparation of 1,4-bis(p-tolyl)butadiene. To a solution of 50.0 g. (0.11 mol.) of (*p*-methylbenzyl)triphenylphosphonium bromide and 17.3 g. (0.12 mol.) of *p*-methylcinnamaldehyde in 75 ml. of ethanol was added 550 ml. of a 0.2*M* lithium ethoxide solution. After standing overnight 400 ml. of water was added, and the crystals were filtered, washed with 100 ml. of 60% ethanol, and dried at reduced pressure and 65°. The dry weight was 17.1 g. (68.5%), m.p. 198–200°.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.50, 92.51, H, 7.71, 7.73.

Preparation of 1,4-bis(4-phenylbutadienyl)benzene. To a solution of 70.0 g. (0.10 mol.) of *p*-xylylene-bis-(triphenylphosphonium chloride)[1] and 35.0 g. (0.26 mol.) of cinnamaldehyde in 250 ml. of ethanol was added a solution of 1.74 g. (0.25 mol.) of lithium wire dissolved in 1 l. of ethanol. After standing overnight the yellow solid was filtered, washed with 300 ml. of 60% ethanol, and dried under reduced pressure at 70°. The dry weight was 29–32 g. (87–95%). The solid was dissolved in boiling xylene, treated with decolorizing carbon, filtered, and the filtrate digested for 3 hr. in the presence of a trace of iodine. Bright yellow leaflets were obtained (23–25 g.), m.p. 285–287°. An analytical sample

was recrystallized from dimethylformamide, m.p. 290–293° (reported[4b] m.p. 288°).

Preparation of 1,4-bis-(4-phenylbutadienyl)-2,5-dimethylbenzene. To a solution of 72.7 g. (0.10 mol.) of 2,5-dimethyl-*p*-xylylenebis(triphenylphosphonium chloride)[1] and 30.4 g. (0.23 mol.) of cinnamaldehyde in 1050 ml. of ethanol was added 1150 ml. of 0.2*M* lithium ethoxide. After standing overnight, 600 ml. of water was added, the yellow precipitate filtered, washed with 400 ml. of 60% ethanol, and dried at reduced pressure and 65°. The dry weight was 27.1 g. (75%). This was recrystallized from xylene containing a trace of iodine to give the all *trans* product, m.p. 246–247°.

Anal. Calcd. for: $C_{28}H_{26}$: C, 92.8; H, 7.18. Found: C, 92.9, 92.8; H, 7.13, 7.15.

The preparation of 1,4-bis[4-(3-nitrophenyl)butadienyl]-benzene. To a solution of 70.0 g. (0.1 mol.) of *p*-xylylene-bis-(triphenylphosphonium chloride)[1] and 37.0 g. (0.209 mol.) of *m*-nitrocinnamaldehyde in 500 ml. of absolute alcohol was added 1 l. of 0.2*M* lithium ethoxide in ethanol. After standing overnight at room temperature, 200 ml. of water was added and the solid filtered. It was washed with 100 ml. of 60% alcohol. The yellow precipitate was dried in the vacuum oven at 60°. The dry weight was 27.7 g. (65%). The yellow solid was isomerized in boiling xylene with a trace of iodine. The resulting orange-brown crystals weighed 17.5 g., m.p. 260–264° (dec.). An analytical sample was recrystallized twice from dimethylformamide, m.p. 267–267.5°.

Anal. Calcd. for: $C_{26}H_{20}O_4N$: C, 73.5; H, 4.75; N, 6.60. Found: C, 73.77, 73.78; H, 4.90, 4.75; N, 6.59, 6.64.

Preparation of 1,4-bis[4-(p-tolyl)butadienyl]benzene. To a solution of 70.0 g. (0.10 mol.) of *p*-xylylene-bis(triphenylphosphonium chloride)[1] and 32.4 g. (0.22 mol.) of *p*-methylcinnamaldehyde in 250 ml. of alcohol was added 1100 ml. of 0.2*M* solution of lithium ethoxide in ethanol. After standing overnight, 680 ml. of water was added and the light yellow solid filtered, washed with 250 ml. of 60% alcohol, and dried in the vacuum oven. The weight of product was 36.0 g. (99%). This was recrystallized from xylene with a trace of iodine. The resulting crystals were filtered and washed with benzene to give 26.1 g. of product, m.p. 315–319°. An analytical sample was recrystallized from dimethylformamide to give yellow leaflets, m.p. 315–320°.

Anal. Calcd. for: $C_{28}H_{26}$: C, 92.8; H, 7.23. Found: C, 92.6, 92.7; H, 7.14, 7.52.

Preparation of 1,4-bis(3-methyl-4-phenylbutadienyl)benzene. To a solution of 35.0 g. (0.050 mol.) of *p*-xylylene-bis(triphenylphosphonium chloride)[1] and 16.4 g. (0.11 mol.) of α-methylcinnamaldehyde in 150 ml. of alcohol was added 500 ml. of a 0.2*M* lithium ethoxide solution. After standing overnight 400 ml. of water was added and the yellow solid was filtered, washed with 150 ml. of 60% ethanol, and dried in a vacuum oven at 65°. The dry weight was 15.1 g. (83%). This was recrystallized from a mixture of benzene cyclohexane containing a trace of iodine after digesting for 5 hr. The resulting yellow leaflets weighed 12.0 g., m.p. 217–218°. An analytical sample was recrystallized from dimethylformamide, m.p. 235–237°.

Anal. Calcd. for: $C_{28}H_{26}$: C, 92.8; H, 7.23. Found: C, 92.8, 92.8; H, 7.50, 7.31.

Preparation of 1,4-bis[4-(4-N,N-dimethylaminophenyl)-butadienyl]benzene. To a solution of 30.0 g. (0.043 mol.) of *p*-xylylene-bis(triphenylphosphonium chloride)[1] and 17.5 g. (0.10 mol.) of *p*-*N*,*N*-dimethylaminocinnamaldehyde in 350 ml. of alcohol was added 500 ml. of a 0.2*M* lithium ethoxide solution. After standing overnight 500 ml. of water was added and the orange precipitate was filtered, washed with 200 ml. of 60% alcohol, and dried in a vacuum oven at 70°. The dry weight was 17.7 g. (100%). This was not isomerized except for the analytical sample which apparently did so when recrystallized from dimethylformamide to give red-orange leaflets, m.p. 314–315°.

Anal. Calcd. for: $C_{30}H_{32}N_2$: C, 85.6; H, 7.67; N, 6.66. Found: C, 85.5, 85.3; H, 7.87, 7.78; N, 6.66, 6.65.

Preparation of 1,4-bis[4-(4-methoxyphenyl)butadienyl]-benzene. To a solution of 23.0 g. (0.033 mol.) of *p*-xylylene-bis(triphenylphosphonium chloride)[1] and 11.0 g. (0.068 mol.) of *p*-methoxycinnamaldehyde was added a solution prepared by dissolving 0.236 g. (0.033 mol.) of lithium dissolved in 100 ml. of alcohol. After standing over the week end, the lemon yellow precipitate was filtered, washed with 50 ml. of 60% alcohol, and dried in the vacuum oven at 60°. The weight of product was 1.7 g. (13%).

This yellow solid was recrystallized from xylene with a trace of iodine after digesting for 3 hr. The resulting yellow plates were filtered, washed with benzene, and dried in the vacuum oven. Weight 1.0 g., m.p. > 300°. A sample was recrystallized from dimethylformamide, m.p. 304–306.

Anal. Calcd. for $C_{28}H_{26}O_2$: C, 85.25; H, 6.65. Found: C, 84.82, 84.99; H, 6.58, 6.73.

The infrared spectrum shows aromatic ether present and the butadiene system as *trans-trans*.

Preparation of p-terphenyl. The conversion of 1,4-diphenylbutadiene to *p*-terphenyl was repeated following the method of Lohaus.[8] The yield of *p*-terphenyl without isolation of intermediates was 1.5 g. (60% from diphenylbutadiene), m.p. 211–212° (reported by Lohaus,[8] m.p. 211° on recrystallized material).

Preparation of 4-methyl-p-terphenyl. A mixture of 2.2 g. (0.01 mol.) of 1-(*p*-tolyl)-4-phenylbutadiene and 1.7 g. (0.01 mol.) of diethyl acetylenedicarboxylate was heated in an oil bath maintained at 140–150° for 5 hr. Fifty ml. of alcohol along with 2 g. of potassium hydroxide was added and the mixture was refluxed for 11 hr. Most of the solvent was evaporated under nitrogen on the steam bath, the damp residue dissolved in water, some insoluble material was extracted with ether, and the aqueous layer was acidified with dilute hydrochloric acid. The solid acid was filtered, washed until neutral with water, and dried in the vacuum oven at 60°. Weight 3.2 g. (97% yield).

The acid was dissolved in a solution of 7 g. sodium carbonate in 200 ml. of water. To the filtered solution was added a solution of 20.0 g. of potassium ferricyanide in 50 ml. of water. The solid methylterphenyl separated almost at once. After heating on the steam bath for 0.5 hr. and allowing to stand at room temperature overnight, the product was filtered, washed with water, and dried in the vacuum oven at 80°, weight 1.7 g. (70% based on the butadiene). The solid was recrystallized from alcohol plus a small amount of dimethylformamide to give colorless crystals, m.p. 209–209.5° (reported,[16] m.p. 207–208°).

Preparation of 4,4″-dimethyl-p-terphenyl. A mixture of 4.68 g. (0.020 mol.) of 1,4-bis(*p*-tolyl)butadiene and 3.50 g. (0.020 mol) of diethyl acetylenedicarboxylate in 20 ml. of *o*-dichlorobenzene was heated under reflux for 4 hr. To this was added 100 ml. of ethanol and 5.0 g. of potassium hydroxide and the mixture was heated under reflux for 6 hr. The solvent was practically evaporated on the steam bath under nitrogen and the residual solid dissolved in 200 ml. of water. Extraction of the solution twice with ether removed a trace of solid and the *o*-dichlorobenzene. The aqueous solution was treated with dilute hydrochloric acid until just cloudy and then 5.0 g. of sodium carbonate was added. Thirty g. of potassium ferricyanide was dissolved in 200 ml. of water and this was added to the above solution. The mixture became turbid almost at once. After standing overnight it was centrifuged, the solid washed once with water by centrifugation and then dried in a vacuum oven at 80°. The dry weight was 2.2 g. (42%). This was sublimed at 220° and 0.02 mm. to give an almost colorless sublimate, m.p. 255–257°.

Anal. Calcd. for: $C_{20}H_{18}$: C, 92.98; H, 7.02. Found: C, 92.84, 92.88; H, 7.08, 7.08.

Synthesis of quinquephenyl. A mixture of 3.40 g. (0.02 mol.) of diethyl acetylenedicarboxylate and 3.34 g. (0.01

(16) H. France, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 1283 (1939).

mol.) of 1,4-bis-4(phenylbutadienyl)benzene was refluxed with 20 ml. of o-dichlorobenzene for 3 hr. The mixture was cooled and a trace of crystalline solid was filtered and discarded. The filtrate was refluxed with 100 ml. of absolute alcohol containing 5 g. of potassium hydroxide. The solvent was practically evaporated under nitrogen and the damp residue was extracted with water. The aqueous layer was separated from water insoluble matter by the addition of a little ether. The intense yellow aqueous phase was treated with a little decolorizing carbon, filtered, and the filtrate was then neutralized with dilute hydrochloric acid and then made basic again by the addition of 5 g. of sodium carbonate. Thirty g. of potassium ferricyanide was dissolved in 200 ml. of water and the two solutions were mixed. The mixture rapidly turned milky, but the very finely divided precipitate could not be satisfactorily filtered. The suspension was centrifuged and the deposited solid was washed several times by centrifugation. The precipitated solid was dried in a vacuum oven to give 3.6 g. (theory 3.8 g.) of a green tinged solid. An analytical sample was prepared by subliming 0.3 g. at 0.2 mm. and 300°. The yellowish solid melted at 380–390° on the hot bar. Further purification was carried out by recrystallizing the product from dimethylsulfoxide from which it was obtained as large well defined leaflets. The infrared and ultraviolet spectra were consistent with the structure of quinquephenyl. No carbonyl bands could be detected in the infrared.

Anal. Calcd. for $C_{30}H_{22}$: C, 94.24; H, 5.76. Found: C, 94.19, 94.27; H, 5.95, 5.96.

The over-all yield of sublimed quinquephenyl in several preparations was 50% based on 1,4-bis(4-phenylbutadienyl)benzene.

Preparation of 4,4''''-dimethylquinquephenyl. This synthesis was carried out as described for the preparation of quinquephenyl only using 3.63 g. (0.010 mol.) of 1,4-bis[4-(*p*-tolyl)butadienyl]benzene instead of 1,4-bis(4-phenylbutadienyl)benzene. The total products (17.3 g.) from four experiments on this scale were combined and sublimed at 350° and 0.07 mm. The light yellow crystalline sublimate weighed 6.9 g. (42%), m.p. > 400°. This could be recrystallized from tetramethylenesulfone to give light yellow leaflets.

Anal. Calcd. for $C_{32}H_{26}$: C, 93.62; H, 6.38. Found: C, 93.59, 93.65; H, 6.48, 6.57.

Preparation of 2',3''''-dimethylquinquephenyl. The synthesis of this compound was carried out as described for the preparation of quinquephenyl only using 3.63 g. (0.010 mol.) of 1,4-bis(3-methyl-4-phenylbutadienyl)benzene in place of 1,4-bis(4-phenylbutadienyl)benzene. The yield of crude product was 4.7 g. This was sublimed at 210° and 0.05 mm. The colorless sublimate weighed 3.5 g. (85%), m.p. 217–218°.

Anal. Calcd. for $C_{32}H_{26}$: C, 93.62; H, 6.38. Found: C, 93.57, 93.61; H, 6.43, 6.48.

Attempted nitration of p-quinquephenyl. One-half g. of *p*-quinquephenyl was heated for 1 hr. with 100 ml. of concentrated nitric acid under reflux. Five ml. of concentrated sulfuric acid was added and heating continued for 26 hr. At the end of this time there was some crystalline solid present which was removed by filtration. It was washed with water and a little acetone and dried in the vacuum oven. Weight 0.1 g. (A).

The mother liquor was poured into water and the resulting fluffy precipitate filtered, washed with water and dried in the vacuum oven. Weight 0.4 g (B).

The infrared spectra of both A and B are quite similar both showing nitro groups present, but impossible to determine sites of substitution since both *m*- and *p*-substitution appear. (B) shows some carbonyl (probably acid) present.

Preparation of 1,6-diphenylhexatriene. A mixture of 8.0 g. (0.019 mol.) of triphenylcinnamylphosphonium chloride, 2.6 g. (0.020 mol.) of cinnamaldehyde, 50 ml. of ethanol, and 100 ml. of 0.2*M* lithium ethoxide reacted rapidly with separation of a pastel pink solid. This product was recrystallized from xylene in the presence of iodine to give the all-*trans*-diphenylhexatriene as pale yellow leaflets, m.p. 206–207° (hot bar). The yield of pure product was 0.90 g. and product of lesser purity (m.p. 180–185°) was 2.2 g. An analytical sample melting at 203° was obtained by recrystallization from cyclohexane-benzene mixture.

Anal. Calcd. for $C_{18}H_{16}$: C, 93.07; H, 6.93. Found: C, 93,10, 93.09; H, 7.00, 7.01.

Preparation of 1-(3-nitrophenyl)-6-phenylhexatriene. A mixture of 5.3 g. (0.013 mol.) of triphenylcinnamylphosphonium chloride and 2.4 g. (0.013 mol.) of *m*-nitrocinnamaldehyde in 50 ml. of ethanol was treated with 80 ml. of 0.2*M* lithium ethoxide. The reaction proceeded normally and after 1 hr it was diluted with an equal volume of water and the solid was filtered. The solid was dissolved in boiling xylene and the wet solution was dried with magnesium sulfate, decolorized, and cooled. Approximately 0.9 g. of an offcolor, yellow crystalline solid separated which was filtered and the filtrate was rejected. The solid melted in the range of 175–180°. It was recrystallized from 20 ml. of xylene to give 0.3 of stubby yellow needles, m.p. 182–184°. An analytical sample was obtained by recrystallizing again from boiling xylene followed by drying at 110° for 4 hr. This product melted at 184–185.5°.

Anal. Calcd. for: $C_{18}H_{15}NO$: C, 78.0; H, 5.4. Found: C, 78.36, 78.48; H, 5.68, 5.65.

Reaction of benzaldehyde with 1,4-bis(triphenylphosphonium chloride)butene-2. In the reaction of benzaldehyde and the subject phosphonium salt, a low melting crystalline solid was obtained which was dissolved in benzene to give a lemon yellow solution. A crystal of iodine was then added which brought about the immediate precipitation of a crystalline solid of a more orange color. This was allowed to stand in the air for a short time. However, the next day only a brown gum remained in the dish.

Only a brown resin was obtained with cinnamaldehyde.

WILMINGTON 98, DEL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CHICAGO AND THE ARGONNE NATIONAL LABORATORY]

Beckmann Rearrangement in Hydrogen Fluoride

K. D. KOPPLE AND J. J. KATZ

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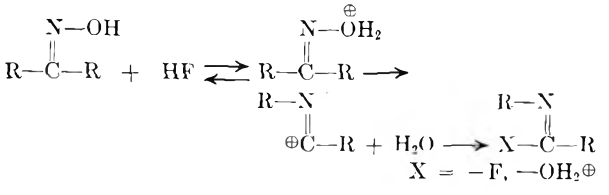
In contrast to benzophenone oxime, cyclohexanone oxime does not undergo the Beckmann rearrangement in hydrogen fluoride solution. The *O*-benzoyl derivatives of both oximes rearrange readily.

Most of the reagents that are commonly used to effect the Beckmann rearrangement of oximes, *e.g.*, concentrated sulfuric acid, polyphosphoric acid, and acid chlorides, are capable of producing

esters, $R_2C{=}N{-}O{-}X$, prior to rearrangement, but whether ester formation is a necessary prelude to rearrangement is not an entirely settled question.[1] The rearrangement of benzophenone oxime by hydrogen chloride in an inert solvent probably proceeds at least in part *via* a mechanism in which water, rather than another acid, is the leaving group.[2] Although water is probably also the leaving group in the same rearrangement as carried out in concentrated aqueous hydrochloric acid,[2,3] prior ester formation is not excluded in other cases.[1,4]

We wish to report experiments in which Beckmann rearrangements are carried out in anhydrous hydrogen fluoride, a highly polar and strongly acidic solvent. The results of these experiments can be described briefly: Cyclohexanone oxime, on storage in hydrogen fluoride for 24 hr. at room temperature, does not rearrange detectably; the corresponding *O*-benzoyl derivative is converted to caprolactam. Benzophenone oxime is about 60% rearranged on 2-hr. storage in hydrogen fluoride; its benzoate reacts quantitatively in a similar period.

The immediate inference from these results is that oxime esters rearrange more readily than the oximes themselves, a conclusion which is in agreement with much previous work.[4] The difference in reactivity between the two unacylated oximes is worth discussion. It is unlikely that the reaction of benzophenone oxime proceeds through *slow* formation of *N*-fluoroimine, for there is no obvious reason for cyclohexanone oxime to react in this sense so much less readily than benzophenone oxime. In addition, since *N*-chloroimines have been shown not to rearrange,[5] fluoroimines are also apt to be relatively stable once formed. The most likely path for rearrangement of benzophenone oxime in hydrogen fluoride is the obvious one.



In this formulation the protonated oxime is an intermediate, and water is lost. That cyclohexanone oxime does not rearrange under the conditions used (while benzophenone oxime does) can be ascribed to a requirement of anchimeric assistance by the phenyl group when the leaving group is water. It has been reported that in 94.5% sulfuric acid cyclohexanone oxime and benzophenone oxime rearrange at about the same rate[6]; in this case, where a sulfuric ester may be the rearranging species and sulfuric acid is lost during rearrangement, the assistance provided by the migrating phenyl group is less important. In the transition state, N—O bond breaking has proceeded farther and migration is less complete than in the hydrogen fluoride catalyzed reaction where water is the departing species.

We are indebted to Mr. Lloyd A. Quarterman for his assistance in parts of this work.

EXPERIMENTAL

Materials and method. Cyclohexanone oxime, m.p. 91–92°, and benzophenone oxime, m.p. 142°, were prepared by standard procedures. *O*-benzoyl cyclohexanone oxime, m.p. 62–63°[7] and *O*-benzoyl benzophenone oxime, m.p. 100°[8] were obtained by treatment of the oximes with benzoyl chloride in pyridine, precipitation of the benzoylated products with excess water, and recrystallization from ethanol water.

Commercial hydrogen fluoride was purified in a metal-free apparatus as described elsewhere and was determined by conductivity measurements to be of purity greater than 99.95%. Reactions using hydrogen fluoride were carried out in molded poly(chlorotrifluoroethylene) tubes attached to an appropriate vacuum line.[9]

Rearrangement of O-benzoyl benzophenone oxime. Samples of this substance (1 g.) were treated at room temperature with hydrogen fluoride (about 3 ml. liquid) for 2 and 24 hr.; complete reaction was observed in each case. The tan powder obtained after removal of volatile material was triturated with aqueous sodium bicarbonate and then with water; dried, this crude product had m.p. 155–160° and corresponded to a 90% yield (0.6 g.) of crude benzanilide. Recrystallization from ethanol water afforded pure benzanilide, m.p. 163°.

Rearrangement of benzophenone oxime. A solution of benzophenone oxime, 1.00 g., in 3 ml. of hydrogen fluoride was stored 2 hr. at room temperature before removal of the solvent. The resulting powder was washed with sodium bicarbonate solution and with water, then dried. Benzanilide (0.21 g., 53%) was obtained by fractional crystallization of an aliquot (0.40 g.) from ethanol water. Another sample (0.48 g.) was boiled 20 min. with 6 ml. of 50% ethanol 3*N* in hydrochloric acid, diluted to 20 ml. with ethanol, and mixed with 15 ml. of 2,4-dinitrophenylhydrazine reagent.[10] After 20 min. at reflux there was obtained 0.27 g. (31%) of benzophenone 2,4-dinitrophenylhydrazone, m.p. 237–239°.

Rearrangement of O-benzoyl cyclohexanone oxime. The oxime benzoate (1.00 g.) was dissolved in 3 ml. of hydrogen fluoride at room temperature for 24 hr. The oil remaining after pumping off solvent was washed with bicarbonate solution and extracted into methylene chloride. After drying over magnesium sulfate, the methylene chloride solution was

(1) D. E. Pearson and F. Ball, *J. Org. Chem.*, **14**, 118 (1949).
(2) A. W. Chapman, *J. Chem. Soc.*, 1223 (1935).
(3) A. Lachman, *J. Am. Chem. Soc.*, **47**, 260 (1925).
(4) B. Jones, *Chem. Revs.*, **35**, 335 (1944).
(5) J. Stieglitz and P. P. Peterson, *Ber.*, **43**, 782 (1910); P. P. Peterson, *Am. Chem. J.*, **46**, 325 (1911).
(6) P. T. Scott, D. E. Pearson, and L. J. Bircher, *J. Org Chem.*, **19**, 1815 (1954).
(7) W. Hückel and M. Sachs, *Ann.*, **498**, 166 (1952).
(8) A. W. Chapman and C. C. Howis, *J. Chem. Soc.*, 806 (1933).
(9) K. D. Kopple and J. J. Katz, *J. Am. Chem. Soc.*, **78**, 6199 (1956).
(10) R. L. Shriner, R. C. Fuson, and D. V. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, 1956, p. 219.

concentrated and the residue distilled in vacuum to give 0.38 g. (72%) of crystalline caprolactam. The product had infrared spectrum identical to that of an authentic sample of caprolactam.

Effect of hydrogen fluoride on cyclohexanone oxime. A sample of cyclohexanone oxime (1.01 g.) was subjected to the same treatment as its benzoate as described above. In this case, the methylene chloride soluble fraction crystallized *immediately on removal of solvent to give* 0.23 g. (23%) of crude cyclohexanone oxime, m.p. 87°. No traces of caprolactam were detected. Since removal of hydrogen fluoride was accomplished by 150 hr. pumping at near 1μ pressure, sublimation of the oxime may account for the poor recovery.

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[CONTRIBUTION FROM CHEMISTRY DEPARTMENT, STATE UNIVERSITY COLLEGE OF FORESTRY AT SYRACUSE UNIVERSITY]

Periodate Oxidation of Compounds Related to Malondialdehyde

HERMAN L. MARDER[1] AND CONRAD SCHUERCH

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The methylene carbon of malondialdehyde bis(dimethyl)acetal and 2-deoxy-D-glucose (D-arabino-2-deoxyhexose) is oxidized to carbon dioxide *via* malondialdehyde, hydroxymalondialdehyde, and mesoxdialdehyde. Evidence is presented that this is the common oxidation route for compounds producing malondialdehyde and hydroxymalondialdehyde.

In a study of the periodate oxidation of polyvinyleneglycol (polyhydroxymethylene) and vinylene glycol–vinyl alcohol copolymers, (derived from the hydrolysis of vinylene carbonate–vinyl acetate copolymer) it became necessary to clarify the overoxidation of malondialdehyde and hydroxymalondialdehyde by periodate solutions. Although overoxidations have been studied, there are few data which show the simultaneous formation of products and consumption of periodate and some inconsistencies appear in the literature.

For orientation, we investigated the periodic acid oxidation of glucose, mannitol, inositol, glycerol and tartaric acid, and in addition, studied the oxidation of malondialdehyde bis(dimethyl) acetal and 2-deoxy-D-glucose, two compounds the oxidation of which has not been previously reported.

Under the reaction conditions reported in the experimental section, glycerol consumed 2.0 molar equivalents of periodic acid and produced 1.0 mol. of titratable acid in 1 hr. and the product and oxidant concentrations remained unchanged over a 30 hr. period. Mannitol consumed nearly 5.0 (or 4.9) mole of periodic acid in 10 hr. but produced less than the theoretical amount of titratable acid, 3.7 mole rather than 4.0. Over a 70 hr. period the yield of acid increased slightly and the periodate consumption rose to slightly more than the theoretical amount 5.1 rather than 5.0.[2] We interpret this to mean that a slight amount of overoxidation occurs probably by the mechanism discussed below. Inositol was studied with less precision but gave evidence of overoxidation as has been reported previously and is to be discussed below. The consumption of periodate and formation of acid by glucose was quantitative in 30 hr. and unchanged over an additional 40 hr. when the reaction was carried out with periodic acid but was not quantitative with sodium periodate because of formate ester formation. The oxidation of tartaric acid (Fig. 1) consumed the theoretical 3.0 mole of periodate in

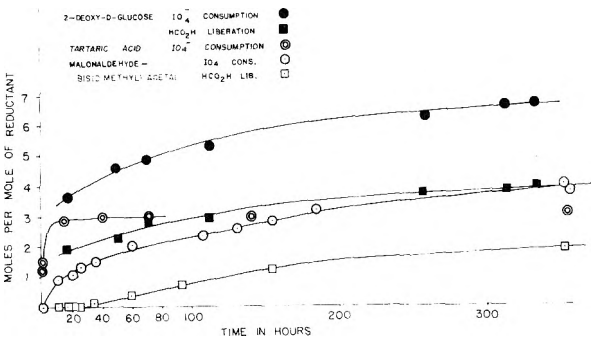


Figure 1. Oxidation of some model compounds with 0.0125*M* periodic acid

less than 20 hr. but no more over 350 hr. of reaction time. Similarly the titratable acid remained unchanged over 350 hr. In this selection of polyhydric alcohols, aldehydes and acids, there was therefore no evidence of side reactions except in those cases that might produce hydroxymalondialdehyde as an intermediate, and furthermore formic acid was stable to periodate (or more correctly, mixtures of periodate and iodate[2]) over the entire 350 hr. period of our experiments.

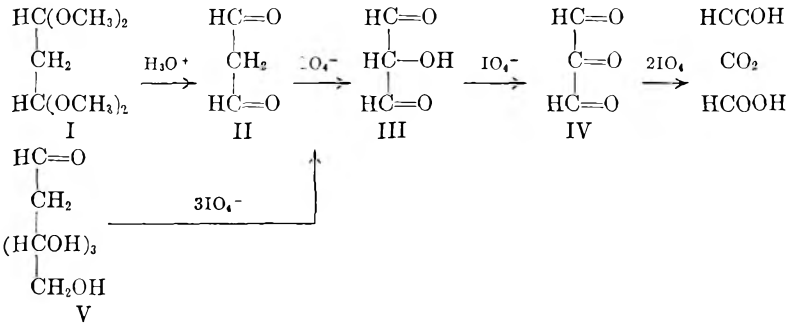
According to published data on the rate of hydrolysis of malondialdehyde bis(dimethyl) acetal

(1) Abstracted from a portion of a thesis presented by Herman L. Marder in partial fulfillment of the requirements of the Ph.D. degree at Syracuse University. Present address: Textile Fibers Dept., Pioneering Research Division, Wilmington 98, Delaware. E. I. du Pont de Nemours and Company.

(2) T. Halsall, E. Hirst, and J. Jones, *J. Chem. Soc.*, 1427 (1947).

with aqueous acid,[3] under our oxidation conditions the compound should be converted essentially completely to the free aldehyde in 5 hr. The oxidation with periodic acid, shown on Fig. 1, should therefore differ little, if at all, from that of the free aldehyde. In about 10 hr. malondialdehyde added as the bis-(dimethyl) acetal had consumed 1 mole of periodate but no formic acid was produced. Indeed no formic acid was produced until nearly 1.5 mol. of oxidant were consumed. The oxidation proceeded slowly to limiting values very close to 4 mol. of oxidant consumed and 2 mol of acid formed. These observations suggest that the periodate oxidation of malondialdehyde proceeds via the following route, and that III is not cleaved to formic acid directly.

The mechanism proposed for the oxidation of malondialdehyde by Huebner, Ames and Bubl[4] is in conflict with our results. They assumed that malondialdehyde oxidized via hydroxymalondialdehyde to 3 mole of formic acid with the consumption of 3 mole of periodate. However, their experimental data supporting this view are meager. The malondialdehyde was formed from digitoxose. A total of 6.1 mole of oxidant was consumed rather than the 5 mole required for their mechanism. It is not clear whether formic acid was determined to be present in the quantity proposed (4 mole from digitoxose) or merely assumed to be that amount. The carbon dioxide observed as a product of reaction was assumed to be the result of overoxidation of formic



The same reaction sequence explains in large measure our observations on the oxidation of 2-deoxy-D-glucose. This compound reacted very rapidly with three mole of oxidant according to the accepted mode of reaction of 1,2,3,4 tetraols, and then more slowly the oxidant consumption increased to a limiting value of about 6.7 mole per mole of reactant. At the same time the titratable acid which is near 2 mole per mole of reactant early in the reaction gradually increased to a limiting value of slightly less than 4 mole. In a separate experiment 0.82 mole of carbon dioxide per mole of reductant was produced after 600 hr. of reaction in the dark. The corresponding theoretical values for periodate consumption, formic acid liberation and carbon dioxide formation 7, 4, and 1 for the reaction sequence above are in good agreement with the experimental. It is however not possible to eliminate entirely other reaction sequences. As the methylene C_2 carbon atom is α to a hemiacetal hydroxyl, which probably complexes most readily with periodate, and is also in a six membered ring, which in the diketone series makes it more susceptible to oxidation, oxidation of the deoxysugar to glucose or mannose may compete with the glycol split of the trans 3,4-glycol group. Twenty percent of such a reaction occurring concurrently would still give limiting values of 6.8, 4.2, 0.8 mole also in fair agreement with our results.

(3) Data from Kay Fries Technical Bulletin, Kay Fries Chemical Co., N. Y.

acid, formaldehyde, or acetaldehyde, the primary products. However, these products are stable to periodate when proper reaction conditions are maintained. It is probable therefore that digitoxose actually oxidizes by the mechanism proposed above.

The proposed reaction sequence which assumes instead that the active methylene carbon of malondialdehyde is oxidized via a carbonyl oxidation state to carbon dioxide is not entirely novel. It is analogous or equivalent to that proposed by Wolfrom and Bobbitt[5] for the oxidation of cyclic β-diketones, by Potter and Hassid[6] for the overoxidation of reducing end groups in starch, cellulose and maltose, and especially by Schwarz[7] for the oxidation of myoinositol. In the last case, glyoxylic acid is shown to be an intermediate in the oxidation of the tricarbonyl compound to carbon dioxide and formic acid.

As some fraction of mannitol,[2] fructose,[8] inositose,[9] 1,2,4,5-tetrahydroxycyclohexane,[10] and do-

(4) C. Huebner, S. Ames, and E. Bubl, *J. Am. Chem. Soc.*, **68**, 1621 (1946).

(5) M. L. Wolfrom and J. Bobbitt, *J. Am. Chem. Soc.*, **78**, 2489 (1956).

(6) A. L. Potter and W. Z. Hassid, *J. Am. Chem. Soc.*, **70**, 3489 (1948).

(7) J. Schwarz, *Chem. and Ind. (London)*, 1388 (1955).

(8) Y. Khouvine and G. Arragon, *Compt. Rend.*, **212**, 167 (1941).

(9) D. Sprinson and E. Chargaff, *J. Biol. Chem.*, **164**, 433 (1946).

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decitol[11] would be expected to oxidize via malondialdehyde, or hydroxymalondialdehyde, this reaction should be considered in any interpretation of the periodate oxidation of these compounds. For example, if the simplifying assumption is made that the rate of cleavage of glycol carbon bonds is equivalent to the rate of cleavage of hydroxyaldehyde carbon bonds, 5.5% of the carbon in dodecitol should appear as carbon dioxide. Wolfrom found a consumption of 11.5 mole of periodate instead of the theoretical values of eleven and only 9.5 mole of formic acid instead of 10. His failure to find carbon dioxide is understandable if a terminal assay of the acidic solutions was used. Our results on polyvinylene glycol and its vinyl alcohol copolymer are consistent with this interpretation of the periodate oxidation and will be published elsewhere.

EXPERIMENTAL

All periodate oxidations were carried out in the dark at room temperature using paraperiodic acid (H_5IO_6) or occasionally sodium meta periodate ($NaIO_4$). Sufficient sample to reduce 1 mmol. of oxidant was weighed into a 100 ml. volumetric flask, and enough .05–.1*M* oxidant solution to give 1.25 mmol. of oxidant was added and the flask was diluted to the mark. At the same time a blank containing the identical amount of oxidant was prepared. After the sample was observed to be dissolved, aliquots were withdrawn at intervals for titration. This procedure was followed in all cases except for the oxidations of mannitol and glycerol where the initial oxidant concentrations were .0045 and .01*M* respectively, and consequently less sample was used.

Oxidant consumption was determined by the method of Malaprade.[12] A 5 ml. aliquot was added to a 125 ml. Erlenmeyer flask containing a few crystals of iodate-free potassium iodide in 20 ml. of distilled water. Two drops of 6*N* hydrochloric acid were then added and the liberated iodine was immediately titrated with .02*N* thiosulfate to a Thyodene (Fisher Scientific Co. substitute for starch indicator) endpoint. The difference between the titer of the blank and the sample, $\bar{D}$, is a measure of the oxidant consumed by the sample; Periodate consumed = $10\ \bar{D}\ N_{(thio)}$.

The formic acid liberated during the oxidation was estimated by the total acidity of the solutions according to the iodometric procedure of Hallsall, Hirst and Jones.[2] The iodometric procedure was checked by titrations with 0.02*N* barium hydroxide solutions to a phenophthalein endpoint and good agreement was obtained.

A terminal assay of the carbon dioxide evolved in periodic acid oxidations was performed using the high vacuum technique of Levy and Szwarc.[13,14]

Acknowledgment. We acknowledge with gratitude the financial support of this work by The National Science Foundation, the assistance of Dr. John Binks in certain analytical work, and the valuable cooperation of Dr. Morton Litt.

SYRACUSE 10, N. Y.

(11) M. L. Wolfrom, W. W. Binkley, C. C. Spenser, and B. W. Lew, *J. Am. Chem. Soc.*, **73**, 3357 (1951).

(12) L. Malaprade, *Compt. Rend.*, **186**, 392 (1928); *Bull. soc. chim. France*, **43**, 683 (1928).

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(14) M. Szwarc, *J. Polymer Sci.*, **16**, 367 (1955); *J. Chem. Phys.*, **22**, 1621 (1954).

[CONTRIBUTION FROM THE RADIOISOTOPE SERVICE, VETERANS ADMINISTRATION HOSPITAL, MINNEAPOLIS, AND THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF MINNESOTA]

Preparation and Properties of N^{α}-Acyl Lysine Esters[1]

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Received July 10, 1959

The syntheses of the free bases, N^{α}-tosyl-L-lysine methyl ester, m.p. 93–95°, and N^{α}-tosyl-DL-lysine benzyl ester, m.p. 104°, are described. A number of other N^{α}-acyl lysine esters, obtained as hygroscopic hydrochlorides or hydrobromides, have also been prepared.

It has recently been suggested that the proximate metabolite of the carcinogen *N*-(2-fluorenyl)acetamide which is bound to proteins is the *o*-quinone imine, 1,2-fluorenoquinone-2-imine,[2,3] and that the ϵ-amino group of lysine is implicated in the binding reaction.[4] N^{α}-acyl lysine esters in which the ϵ-amino group is free and the carboxyl and the α-amino group are protected, were therefore desired for a study of their reactions with model quinone imides.[5] A search of the literature showed that such N^{α}-acyl lysine esters have not been prepared and we have therefore undertaken the synthesis of a number of these lysine derivatives.[6] Since recent evidence indicates that peptide linkages involving

(1) Supported by grants from the National Cancer Institute, U. S. Public Health Service (C-2571), and the Minnesota Division of the American Cancer Society.

(2) H. T. Nagasawa, M. A. Morgan, and H. R. Gutmann, *Biochim. et Biophys. Acta*, **28**, 665 (1958).

(3) H. T. Nagasawa and H. R. Gutmann, *J. Biol. Chem.*, **234**, 1593 (1959).

(4) C. C. Irving and H. R. Gutmann, *Federation Proc.*, **18**, 252 (1959).

(5) H. R. Gutmann, J. G. Burtle, and H. T. Nagasawa, *J. Am. Chem. Soc.*, **80**, 5551 (1958).

(6) While this work was in progress, the synthesis of N^{α}-tosyl-L-lysine ethyl ester hydrochloride and N^{α}-tosyl-L-lysine benzyl ester hydrochloride were reported (D. L. Swallow, I. M. Lockart, and E. P. Abraham, *Biochem. J.*, **70**, 359 (1958)).

the ε-amino group of lysine are found in naturally occurring peptides[7] and in collagen,[8] these lysine derivatives would also be useful for the synthesis of ε-lysyl peptides.

The compounds prepared in the course of these studies and the synthetic routes are indicated in Fig. 1. The free bases, N^{α}-tosyl-L-lysine methyl ester (XX) and N^{α}-tosyl-DL-lysine benzyl ester (XXI) were obtained in crystalline form, but we have been unable to crystallize N^{α}-tosyl-L-lysine benzyl ester. The preparation of a number of other N^{α}-acyl lysine esters, obtained as the hydrochlorides or hydrobromides, is also described. These compounds (XII, XIII, XIV, and XV) are hygroscopic oils or hygroscopic semisolids. It is of interest that most of the compounds of the DL series obtained in these studies have higher melting points than the corresponding L isomers. This indicates that these members of the DL series are racemic compounds rather than racemic mixtures.[9]

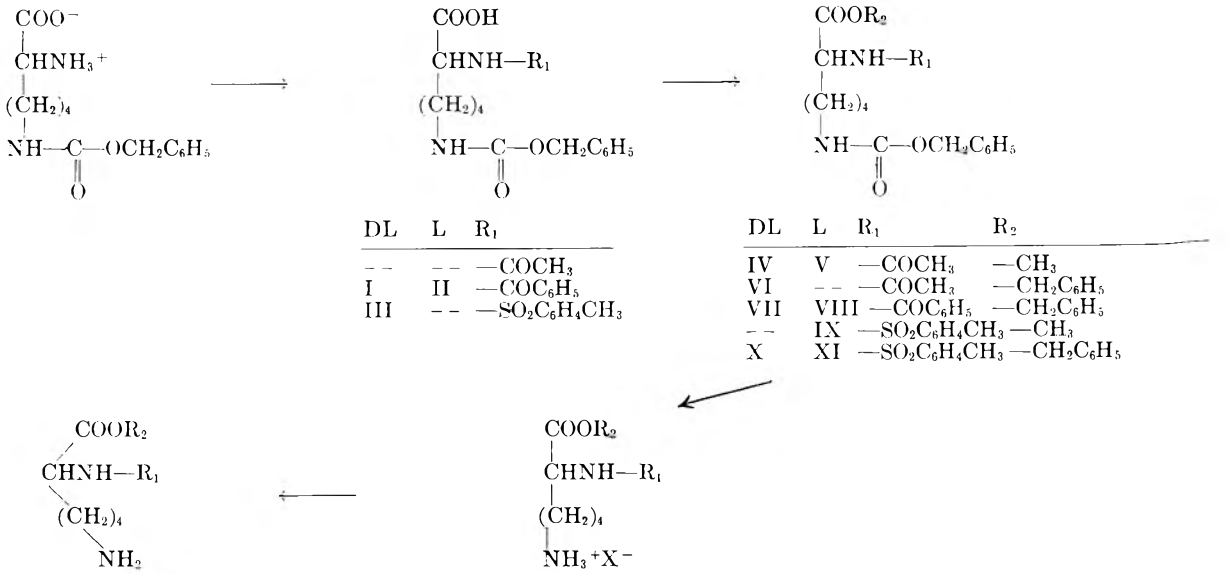

Fig. 1. $N\alpha$-acyl lysine esters and intermediates

EXPERIMENTAL

DL- and L-lysine were obtained from the Mann Research Laboratories, New York, N. Y. N^{ϵ}-carbobenzoxy lysine (DL or L) was prepared by a modification[10] of the procedure of Neuberger and Sanger.[11] All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Amino nitrogen was determined manometrically.[12] The petroleum ether used had a boiling range of 30–60°.

N^{α}-Benzoyl-N^{ϵ}-carbobenzoxy-DL-lysine (I). Crude I was obtained by benzoylation[13] of 3.00 g. of N^{ϵ}-carbobenzoxy-DL-lysine. The crude oil was purified by two extractions with 25 ml. of boiling water. The wash water was discarded and the residual oil was taken up in 20 ml. of *N* NaOH. The mixture was filtered and the filtrate was acidified with 6*N* HCl. The oil which precipitated solidified on standing overnight. The material was collected and washed with water. After drying over phosphoric anhydride *in vacuo* there was obtained 3.70 g. of I, m.p. 130–131°, 90% yield. I was recrystallized from benzene; m.p. 132–133° (reported[14] m.p. 130°).

N^{α}-Benzoyl-N^{ϵ}-carbobenzoxy-L-lysine (II). Three g. of N^{ϵ}-carbobenzoxy-L-lysine (10.7 mmol.) was benzoylated[13] yielding 4.6 g. of a gummy product after drying *in vacuo* over phosphoric anhydride. The crude product was washed with petroleum ether, dissolved in a small amount of hot acetone and the solution was filtered. The filtrate was heated to boiling and water was added dropwise to incipient turbidity. Upon standing, the compound precipitated as an oil which crystallized when left at 4° for 2 days, yielding 2.5 g. of II m.p. 132–133°, after drying *in vacuo* over sulfuric acid; 61% yield. II was recrystallized from benzene; m.p. 132–133°. For analysis, II was dried *in vacuo* at 78°. $[\alpha]_D^{23}$ +2.5° (*c* 2.4, 0.1*N* NaOH).

Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.6; H, 6.29; N, 7.29. Found: C, 65.5; H, 6.23; N, 7.18.

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(11) A. Neuberger and F. Sanger, *Biochem. J.*, **37**, 515 (1943).

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N^{α}-Tosyl-N^{ϵ}-carbobenzoxy-DL-lysine (III). III was prepared by the procedure reported by Swallow *et al.*[6] for the synthesis of the corresponding L-isomer. The yield was 86%; m.p. 130–132°. III was recrystallized from benzene[15] and dried *in vacuo* at 78°; m.p. 132–133°.

Anal. Calcd. for $C_{21}H_{26}N_2O_6S$: C, 58.1; H, 6.03; N, 6.50. Found: C, 58.1; H, 6.00; N, 6.70.

N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-DL-lysine methyl ester (IV). (a) By esterification of N^{α}-acetyl-N^{ϵ}-carbobenzoxy-DL-lysine. N^{α}-acetyl-N^{ϵ}-carbobenzoxy-DL-lysine,[16] 3.72 g. (11.5 mmol.), m.p. 119–121°, was suspended in 150 ml. of benzene and diazomethane[17] was passed through the solution. When all of the solid had dissolved and the yellow color of the diazomethane persisted, the reaction mixture was filtered and the solvent was evaporated under reduced pressure. The resulting oil crystallized upon cooling and addition of ether to give 3.55 g. of IV after drying *in vacuo* over calcium chloride; m.p. 78–80°; 85% yield. Recrystallization from benzene-petroleum ether gave pure IV, m.p. 81–83°, after drying *in vacuo* over paraffin chips.

Anal. Calcd. for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.19; N, 8.33. Found: C, 60.8; H, 7.15; N, 8.55.

(b) IV was obtained in lower yields by methanolysis[18] of N^{α}-carboxy-N^{ϵ}-carbobenzoxy-DL-lysine anhydride[19] followed by acetylation of the resulting oil. The product melted at 81–82° and the mixed melting point with authentic IV was not depressed.

N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-L-lysine methyl ester (V). N^{ϵ}-carbobenzoxy-L-lysine, 0.850 g. (3.1 mmol.), m.p. 247–250°, was acetylated according to Neuberger and Sanger.[11] The oil, which was obtained when the reaction mixture was acidified with concentrated hydrochloric acid, solidified on cooling and scratching to give 0.503 g. of N^{α}-acetyl-N^{ϵ}-carbobenzoxy-L-lysine after drying *in vacuo* over calcium chloride; m.p. 85–87°; 52% yield. In large scale preparations yields ranging from 66 to 77% were realized. Solution of this product in ethyl acetate and precipitation with petroleum ether gave amorphous N^{α}-acetyl-N^{ϵ}-carbobenzoxy-L-lysine, m.p. 82–84°.

Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.6; H, 6.88; N, 8.69. Found: C, 59.6; H, 6.93; N, 8.88.

N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-L-lysine, 0.50 g. (1.55 mmol.), m.p. 82–84°, was hydrogenolyzed[11] to give 0.27 g. of $N\alpha$-acetyl-L-lysine,[11] m.p. 250° (dec.), $[\alpha]_D^{20}$ +4.4° (*c* 2.4, water); 93% yield.

Crystalline N^{α}-acetyl-N^{ϵ}-carbobenzoxy-L-lysine, m.p. 107–110°, was obtained in poor yield by recrystallization of the amorphous product from chloroform–petroleum ether. Neuberger and Sanger[11] reported a melting point of 105–115° for N^{α}-acetyl-N^{ϵ}-carbobenzoxy-L-lysine.

N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-L-lysine, 0.52 g. (1.62 mmol.), m.p. 85–87°, was esterified with diazomethane in benzene as described for IV to yield 0.322 g. of V, m.p. 66–67°, 62% yield. In large scale preparations, yields ranging from 80 to 90% were realized. After recrystallization from ether or ether–petroleum ether, V melted from 67–68°; $[\alpha]_D^{23}$ −23.7° (*c* 3.0, methanol).

Anal. Calcd. for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.19; N, 8.33. Found: C, 60.9; H, 7.10; N, 8.43.

N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-DL-lysine benzyl ester (VI). N^{α}-acetyl-N^{ϵ}-carbobenzoxy-DL-lysine,[16] 7.72 g. (24 mmol.), was suspended in 150 ml. of benzene. Benzyl alcohol, 4.0 ml. (39 mmol.) and 0.36 g. of *p*-toluenesulfonic acid were added and the mixture was refluxed for 17 hr., the water formed being removed azeotropically.[20] The reaction mixture was cooled, filtered, and extracted twice with 50 ml. of 5% sodium bicarbonate. After drying over anhydrous sodium sulfate, the benzene layer was taken to dryness under reduced pressure (30–40°). The resulting oil crystallized when triturated with petroleum ether, yielding 9.00 g. of VI, m.p. 86–87°, 91% yield. VI was recrystallized from benzene–petroleum ether; m.p. 87–88°.

Anal. Calcd. for $C_{23}H_{28}N_2O_5$: C, 67.0; H, 6.84; N, 6.79. Found: C, 67.0; H, 7.05; N, 6.95.

N^{α}-Benzoyl-N^{ϵ}-carbobenzoxy-DL-lysine benzyl ester (VII). I, 2.40 g. (6.25 mmol.), was esterified in 600 ml. of benzene containing 1.0 ml. of benzyl alcohol (9.6 mmol.) and 0.25 g. of *p*-toluenesulfonic acid by the above procedure to give 2.44 g. of VII, m.p. 92–95°, 82% yield. VII was recrystallized from benzene-petroleum ether (activated charcoal added); m.p. 94–95°.

Anal. Calcd. for $C_{28}H_{30}N_2O_5$: C, 70.9; H, 6.37; N, 5.91. Found: C, 71.0; H, 6.38; N, 6.02.

N^{α}-Benzoyl-N^{ϵ}-carbobenzoxy-L-lysine benzyl ester (VIII). One g. of II (2.61 mmol.) in 250 ml. of benzene containing 0.40 ml. of benzyl alcohol (3.87 mmol.) and 0.10 g. of *p*-toluenesulfonic acid was esterified by the above procedure to give 1.11 g. of VIII, m.p. 93–97°, 90% yield. VIII was recrystallized from benzene–petroleum ether; m.p. 94–95°. $[\alpha]_D^{23}$ +2.2° (*c* 2.5, methanol).

Anal. Calcd. for $C_{28}H_{30}N_2O_5$: C, 70.9; H, 6.37; N, 5.91. Found: C, 71.0; H, 6.34; N, 6.01.

N^{α}-Tosyl-N^{ϵ}-carbobenzoxy-L-lysine methyl ester (IX). N^{α}-tosyl-N^{ϵ}-carbobenzoxy-L-lysine,[6] 1.50 g. (3.34 mmol.), m.p. 127–128°, was suspended in 75 ml. of benzene and esterified with diazomethane as described above. Evaporation of the benzene under reduced pressure gave an oil which was taken up in 5 ml. of benzene. Addition of petroleum ether and cooling gave 1.32 g. of crystalline material, m.p. 72–76°, 88% yield. In another run, the yield of IX, m.p. 76–78°, was 88%. The crude IX, m.p. 72–76°, was recrystallized twice from benzene–petroleum ether to give pure IX, m.p. 78–80°; $[\alpha]_D^{22}$ +4.9° (*c* 3.0, methanol).

Anal. Calcd. for $C_{22}H_{28}N_2O_6S$: C, 58.9; H, 6.29; N, 6.25. Found. C, 58.9; H, 6.26; N, 6.08.

N^{α}-Tosyl-N^{ϵ}-carbobenzoxy-DL-lysine benzyl ester (X). III, 17.4 g. (40 mmol.), was esterified in 400 ml. of benzene containing 6.4 ml. of benzyl alcohol (62 mmol.) and 0.9 g. of *p*-toluenesulfonic acid by the above procedure to give 19.5 g. of X, m.p. 91–92°, 92% yield. X was recrystallized from benzene–petroleum ether, m.p. 92°.

Anal. Calcd. for $C_{25}H_{32}N_2O_6S$: C, 64.1; H, 6.15; N, 5.34. Found: C, 63.9; H, 6.14; N, 5.42.

N^{α}-Tosyl-N^{ϵ}-carbobenzoxy-L-lysine benzyl ester (XI). One g. of N^{α}-tosyl-N^{ϵ}-carbobenzoxy-L-lysine[6] (1.95 mmol.) was esterified in 20 ml. of benzene containing 0.31 ml. of benzyl alcohol (3.00 mmol.) and 0.55 g. of *p*-toluenesulfonic acid by the above procedure to give 0.95 g. of XI, m.p. 90–91°, 93% yield. XI was recrystallized from benzene–petroleum ether (activated charcoal added) and dried *in vacuo* at 78°, m.p. 92–93°, $[\alpha]_D^{23}$ +2.3° (*c* 3.0, methanol).

Anal. Calcd. for $C_{28}H_{32}N_2O_6S$: C, 64.1; H, 6.15; N, 5.34. Found: C, 64.2; H, 6.08; N, 5.20.

N^{α}-Acetyl-DL-lysine methyl ester hydrochloride (XII). A 0.440 g. sample of IV (1.30 mmol.) was dissolved in 50 ml. of methanol and 0.2 ml. of concentrated hydrochloric acid. The solution was hydrogenolyzed in the presence of 0.06 g. of Palladium black[21] at a hydrogen pressure of 33 lb. per in.^{2} for 1 hr. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure (35–40°) to yield a clear oil. The oil was washed with ether and then dried to

(15) Swallow *et al.*[6] reported the L-isomer with 1 mole of benzene of crystallization. In contrast, the DL-isomer did not contain benzene of crystallization since the compound did not lose weight on drying *in vacuo* at 78° and the elemental analysis of the dried compound did not indicate the presence of benzene.

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(18) M. Bergmann, L. Zervas, and W. F. Ross, *J. Biol. Chem.*, **111**, 245 (1935).

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(20) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(21) H. Wieland, *Ber. deut. chem. Ges.*, **45**, 484 (1912).

constant weight (0.292 g., 98% yield) *in vacuo* over phosphoric anhydride.

Anal. Calcd. for $C_9H_{19}N_2O_3Cl$: NH_2—N, 5.87. Found: NH_2—N, 5.81.

To provide further evidence for the identity of the oil, N^{α}-acetyl-N^{ϵ}-phthaloyl-DL-lysine methyl ester was prepared.

N^{α}-Acetyl-N^{ϵ}-phthaloyl-DL-lysine methyl ester from XII. To a solution of 0.337 g. of XII (1.41 mmol.) in 6 ml. of glacial acetic acid were added 0.306 g. of phthalic anhydride (2.1 mmol.) and 0.525 g. of sodium acetate trihydrate and the mixture was heated under reflux for 15 min. After cooling, the mixture was diluted with water and allowed to stand at room temperature for 1 hr. The clear solution was then taken to dryness under reduced pressure (30–40°) and the residue was dissolved in 50 ml. of warm benzene. The benzene solution was washed with 25 ml. of 5% sodium bicarbonate and 25 ml. of water. After drying over anhydrous sodium sulfate, the benzene was evaporated under reduced pressure (30–40°) to give 0.187 g. of N^{α}-acetyl-N^{ϵ}-phthaloyl-DL-lysine methyl ester, m.p. 132–133°, after washing with petroleum ether and drying in air, 42% yield. The compound was recrystallized twice from benzene–petroleum ether to give needles, m.p. 133–134°. For analysis, the compound was dried *in vacuo* at 78° over paraffin chips for 24 hours. Drying at lower temperatures resulted in the retention of benzene.

Anal. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.4; H, 6.07; N, 8.43. Found: C, 61.5; H, 6.10; N, 8.40.

N^{α}-Acetyl-L-lysine methyl ester hydrochloride (XIII). A 0.400 g. sample of V (1.19 mmol.), m.p. 66–68°, was dissolved in 25 ml. of methanol and 0.1 ml. of concentrated hydrochloric acid. After addition of 0.075 g. of Palladium black, hydrogenolysis was carried out at atmospheric pressure. The reaction mixture was worked up as described for XII and the resulting oil was dried to constant weight (0.274 g., 98% yield) *in vacuo* over potassium hydroxide and phosphoric anhydride.

Anal. Calcd. for $C_9H_{19}N_2O_3Cl$: NH_2—N, 5.87. Found: NH_2—N, 5.87.

XIII was converted to N^{α}-acetyl-N^{ϵ}-phthaloyl-L-lysine methyl ester as described above, m.p. 126–128°, 43% yield. The product was recrystallized once from benzene and three times from benzene–petroleum ether to give needles, m.p. 127–128°.

Anal. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.4; H, 6.07; N, 8.43. Found: C, 61.7; H, 6.12; N, 8.63.

N^{α}-Acetyl-DL-lysine benzyl ester hydrobromide (XIV). Attempts to prepare XIV by treatment of VI with 35% hydrogen bromide in glacial acetic acid and isolation[20] of the product yielded gummy material which retained excess hydrogen bromide even when dried *in vacuo* over potassium hydroxide for several days. The following method gave pure XIV. VI, 0.83 g. (2.0 mmol.), was treated with 1.5 ml. of 35% hydrogen bromide in glacial acetic acid in a flask closed with a calcium chloride drying tube. After 15 min., 20 ml. of dry acetone-ether[22] (1:1, v/v) was added, the stoppered flask was shaken vigorously for 5 min. and then cooled in an ice bath for 30 min. The mother liquor was decanted and the residual oil was washed four times with 20 ml. of the acetone-ether mixture and twice with 20 ml. of ether. The resulting semisolid was dissolved in 5 ml. of methanol and treated batchwise with Amberlite IR-45 (OH) until the excess hydrogen bromide had been removed as indicated by the use of methyl yellow. The mixture was filtered and the ion-exchange resin was washed twice with 3 ml. of methanol. The combined methanolic solutions were treated with activated charcoal and filtered through Celite. The filtrate was taken to dryness under reduced pressure (40°) yielding a clear oil which, after drying *in vacuo* over calcium chloride and phosphoric anhydride, weighed 0.58 g., 80% yield.

Anal. Calcd. for $C_{15}H_{23}N_2O_3Br$: NH_2—N, 3.90. Found: NH_2—N, 3.97.

N^{α}-Benzoyl-DL-lysine benzyl ester hydrobromide (XV). VII, 0.95 g. (2.0 mmol.), was treated with 1.5 ml. of 35% hydrogen bromide in glacial acetic acid. XV was isolated and purified as described above for the preparation of XIV to yield a clear oil (0.48 g., 57% yield) after drying *in vacuo* over calcium chloride and phosphoric anhydride.

Anal. Calcd. for $C_{20}H_{25}N_2O_3Br$: NH_2—N, 3.33. Found: NH_2—N, 3.49.

N^{α}-Tosyl-L-lysine methyl ester hydrochloride (XVI). A 0.350 g. sample of IX (0.78 mmol.), m.p. 78–80°, was dissolved in 25 ml. of methanol and 0.1 ml. of concentrated hydrochloric acid. Hydrogenolysis was carried out at atmospheric pressure in the presence of 0.09 g. of 10% palladium on charcoal. The oil which remained after evaporation of the solvent under reduced pressure (30–40°) solidified on cooling and triturating with ether to give 0.235 g. of XVI, m.p. 147–148°, after drying *in vacuo* over calcium chloride and potassium hydroxide, 86% yield. In large scale runs the yields of XVI ranged from 72 to 90%. XVI was recrystallized from ethanol ether to give long needles, m.p. 148–150°; $[\alpha]_D^{22}$ −10.2° (*c* 4.0, water).

Anal. Calcd. for $C_{14}H_{23}N_2O_4SCl$: C, 47.9; H, 6.60; S, 9.14; NH_2—N, 3.99. Found: C, 48.0; H, 6.64; S, 9.13; NH_2—N, 3.95.

N^{α}-Tosyl-DL-lysine benzyl ester hydrobromide (XVII). X, 18.3 g. (35 mmol.), was treated with 26 ml. of 35% hydrogen bromide in glacial acetic acid[20] in a flask closed with a calcium chloride drying tube. After 20 min., 350 ml. of ether was added to complete the precipitation of XVII. The product was collected and washed with ether to give 15.3 g. of crude XVII, m.p. 150–160°, 93% yield. The crude hydrobromide was crystallized from water (activated charcoal added) and dried *in vacuo* over phosphoric anhydride and potassium hydroxide; m.p. 182–183°. For analysis, XVII was recrystallized from water and dried *in vacuo* at 78° over phosphoric anhydride, m.p. 184–185°.

Anal. Calcd. for $C_{20}H_{27}N_2O_4SBr$: C, 51.0; H, 5.77; N, 5.94. Found: C, 51.2; H, 5.76; N, 5.70.

N^{α}-Tosyl-L-lysine benzyl ester hydrobromide (XVIII). XI was converted to XVIII by the method used above to prepare XVII. The crude product, m.p. 156–159°, obtained in 95% yield, was recrystallized from water and dried *in vacuo* at 78° over phosphoric anhydride, m.p. 172–173°,[23] $[\alpha]_D^{23}$ +10.4° (c 2.2, 95% ethanol).

Anal. Calcd. for $C_{20}H_{27}N_2O_4SBr$: C, 51.0; H, 5.77; NH_2—N, 2.97. Found: C, 51.0; H, 5.86; NH_2—N, 2.92.

N^{α}-Tosyl-DL-lysine benzyl ester hydrochloride (XIX). XIX was prepared by esterification of N^{α}-tosyl-DL-lysine. (a) N^{α}-tosyl-DL-lysine.[24] III, 2.00 g. (4.6 mmol.), was dissolved in 25 ml. of methanol. Six ml. of water, 0.15 ml. of glacial acetic acid, and 0.10 g. of palladium black were added and the mixture was hydrogenolyzed at atmospheric pressure for 1.5 hr. After 30 ml. of water had been added, the reaction mixture was heated to boiling and filtered hot. The filtrate was taken to dryness under reduced pressure (60°), yielding 0.99 g. of N^{α}-tosyl-DL-lysine, m.p. 260–262°

(22) The acetone was dried over anhydrous calcium sulfate for several days and then distilled with careful exclusion of moisture.

(23) While this manuscript was in preparation, the syntheses of N^{α}-tosyl-N^{ϵ}-carbobenzoxy-L-lysine benzyl ester m.p. 86–87°, and N^{α}-tosyl-L-lysine benzyl ester hydrobromide, m.p. 160–161°, were reported.[8] The compounds were not characterized by elemental analysis and, as judged from the reported melting points, were not obtained in pure form.

(24) N^{α}-Tosyl-DL-lysine has been prepared by Steib according to the following sequence of reactions: N^{ϵ}-benzoyl-DL-lysine ⟶ N^{α}-tosyl-N^{ϵ}-benzoyl-DL-lysine ⟶ N^{α}-tosyl-DL-lysine. [H. Steib, Hoppe-Seyler's *Z. physiol. Chem.*, 155, 292 (1926).] However, no melting point was given for N^{α}-tosyl-DL-lysine.

(dec.), 72% yield. The compound was recrystallized from water and dried *in vacuo* at 78° over phosphoric anhydride; m.p. 262–263° (dec.).

Anal. Calcd. for $C_{13}H_{20}N_2O_4S$: C, 52.0; H, 6.71; N, 9.33. Found: C, 52.1; H, 6.76; N, 9.22.

(b) XIX from N^{α}-tosyl-DL-lysine. N^{α}-tosyl-DL-lysine, 0.765 g. (2.55 mmol.), was esterified[6] by heating at 100° for 3 hr. with 12 ml. of benzyl alcohol saturated with dry hydrogen chloride, to give 0.860 g. of XIX, m.p. 163–165° (with softening at 160–163°), 79% yield. XIX was recrystallized from 2*N* hydrochloric acid and dried *in vacuo* at 78° over phosphoric anhydride and potassium hydroxide, m.p. 176–177°.

Anal. Calcd. for $C_{20}H_{27}N_2O_4SCl$: C, 56.3; H, 6.38; N, 6.56. Found: C, 55.6; H, 6.36; N, 6.57.

N^{α}-Tosyl-L-lysine methyl ester (XX). Dry ammonia was passed through a solution of 0.431 g. of XVI (1.23 mmol.), m.p. 148–150°, in dry chloroform for 15 min. The solution was cooled in an ice bath to 0°. The reaction mixture was then washed twice with 25 ml. of water. After drying over anhydrous sodium sulfate, the chloroform was evaporated under reduced pressure (30–40°). The residual oil solidified on cooling and triturating with petroleum ether to give 0.306 g. of XX, m.p. 93–95°, after drying *in vacuo* over calcium chloride, 79% yield. Recrystallization of XX from benzene–petroleum ether gave needle clusters, m.p. 93–95°. The recrystallized XX was dried *in vacuo* at room temperature over paraffin chips for 24 hr.; $[\alpha]_D^{23}$ −5.4° (*c* 2.5, 95% ethanol).

Anal. Calcd. for $C_{14}H_{22}N_2O_4S$: C, 53.5; H, 7.05; S, 10.2; NH_2—N, 4.46. Found: C, 53.7; H, 7.06; S, 10.5; NH_2—N, 4.26.

N^{α}-Tosyl-DL-lysine benzyl ester (XXI). A suspension of 1.08 g. of XVII (2.29 mmol.) in 25 ml. of chloroform was cooled to −15° in an ice-salt mixture. Dry ammonia was passed into the suspension for 10 min. The resulting clear solution was allowed to warm slowly to room temperature and the ammonium bromide which precipitated from the reaction mixture was removed by filtration and washed with chloroform. The slightly turbid filtrate and washings were combined and extracted twice with 15 ml. of water. The chloroform solution was dried over anhydrous sodium sulfate and then taken to dryness under reduced pressure (35–40°). The residual oil crystallized when it was covered with petroleum ether and cooled, to give 0.80 g. of XXI, m.p. 103–104°, 90% yield. XXI was recrystallized from chloroform–petroleum ether, m.p. 104°.

Anal. Calcd. for $C_{20}H_{26}N_2O_4S$: C, 61.5; H, 6.71; NH_2—N, 3.59. Found: C, 61.3; H, 6.61; NH_2—N, 3.52.

Attempts to prepare N^{α}-acetyl-DL-lysine methyl ester by esterification of N^{α}-acetyl-DL-lysine[16] with diazomethane[17] yielded a basic oil which, as judged from the elemental analysis, appeared to be N^{α}-acetyl-N^{ϵ}-methyl-DL-lysine methyl ester.

Anal. Calcd. for $C_{10}H_{20}N_2O_3$: C, 55.5; H, 9.32; N, 12.96. Found: C, 54.9; H, 8.99; N, 12.84.

N-Methylation of primary amines by diazomethane is a known reaction.[25] The reaction here probably proceeds *via* the intermediate formation of N^{α}-acetyl-DL-lysine methyl ester.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Chemistry of the 1,2,4-Thiadiazine Ring System. II. A New Synthesis of 1,2,4,2*H*-Thiadiazine-3,5(4*H*,6*H*)-dione-1,1-dioxide

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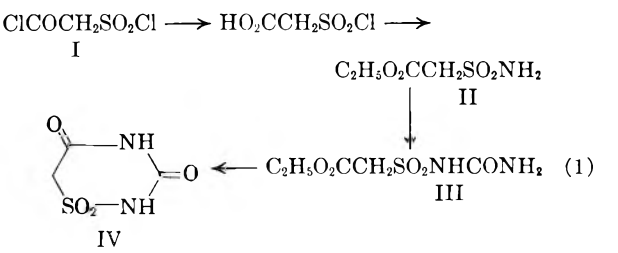
1,2,4,2*H*-Thiadiazine-3,5(4*H*,6*H*)-dione-1,1-dioxide (IV) has been synthesized in 25% over-all yield by the following sequence: sulfoacetic acid, sulfoacetic diacid chloride (I), diphenyl sulfoacetate (V), sulfamylacetamide (VI), carbamylmethanesulfonylurea (VII). The final ring closure of VII to IV was carried out in refluxing pyridine; other bases were ineffective. The same method was used to cyclize β-ureidoethanesulfonamide (XI) to 1,2,4(2*H*)-thiadiazine-3(4*H*,5*H*,6*H*)-one-1,1-dioxide (XII), an analog of dihydrouracil. Attempted ring closure of sulfamylacetylurea (IX) to IV was unsuccessful as were attempts to synthesize IV from sulfamylacetamide by reaction with ethyl carbonate, ethyl chloroformate, or urea

1,2,4(2*H*)-Thiadiazine-3,5(4*H*,6*H*)-dione-1,1-dioxide (IV) has recently been synthesized and its properties have been fully described for the first time.[2] Attention has been called to its similarity to barbituric acid, particularly its pronounced acidity (*p*Ka′ 2.7). The method used is shown in Equation 1. To circumvent difficulties in the conversion of sulfoacetic diacid chloride (I) to ethyl sulfamylacetate (II),[2] an alternative synthesis of IV was sought.



The present paper describes several new approaches to the synthesis of IV, including one new and improved method, summarized in Equation 2. Sulfoacetic diacid chloride (I) was converted to diphenyl sulfoacetate (V) which reacted with liquid ammonia in a sealed tube, forming sulfamylacetamide (VI). (Only the more reactive[2] carboxyl end of

(1) Author to whom inquiries should be addressed. Present address: Union Carbide Research Institute, 32 Depot Plaza, White Plains, N. Y.

(2) R. L. Hinman and L. Locatell, Jr., *J. Am. Chem. Soc.*, **81**, 5655 (1959). Previously reported attempts to synthesize IV are discussed in this reference.

$$\underset{\text{I}}{ClCOCH_2SO_2Cl} \longrightarrow \underset{\text{V}}{C_6H_5O_2CCH_2SO_3C_6H_5} \longrightarrow \underset{\text{VI}}{NH_2COCH_2SO_2NH_2}$$

$$\underset{\text{IV}}{} \xleftarrow[\text{2. Dowex-50}]{\text{1. refluxing pyridine}} \underset{\text{VII}}{NH_2COCH_2SO_2NHCONH_2} \quad (2)$$

V reacted with liquid ammonia at atmospheric pressure. Phenyl carbamylmethanesulfonate (VIIIa) was the product. In like manner liquid methylamine at atmospheric pressure changed V to VIIIb.[3])

$$\underset{\text{V}}{C_6H_5O_2CCH_2SO_3C_6H_5} \xrightarrow{RNH_2} \begin{cases} \xrightarrow[\text{sealed tube}]{} \text{VI} \\ \xrightarrow[\text{atm. press.}]{} \underset{\text{VIIIa. R = H; b. R = CH}_3}{RNHCOCH_2SO_3C_6H_5} \end{cases}$$

Sulfamylacetamide (VI) was readily converted to carbamylmethanesulfonylurea (VII), by taking advantage of the fact that sulfonamides are more reactive toward potassium cyanate in basic solution than are carboxamides.[4] The conditions for the reaction were similar to those used previously[2] for the conversion of ethyl sulfamylacetate (II) to carbethoxymethanesulfonylurea (III).

Initial attempts to cyclize VII to IV were unsuccessful. From treatment of VII with ethanolic sodium ethoxide (the method used for the cyclization of III to IV), or with sodamide in liquid ammonia, ethyl ether, or *N*,*N*-dimethylaniline, only salts of VII were obtained. Refluxing an aqueous solution of VII brought about hydrolysis to sulfamylacetamide (VI), as did the presence of moisture under the other conditions just described. Simple heating of a carefully dried sample of VII led only to charring and general decomposition, as did heating a mixture of VII and *N*,*N*-dimethylaniline at the reflux temperature. Cyclization was finally achieved by refluxing a solution of VII in pyridine, from which the pyridine salt of 1,2,4,2*H*-thiadiazine-3,5(4*H*,6*H*)-dione-1,1-dioxide was isolated.[5] The free acid (IV) was obtained from the salt with the aid of a cationic exchange resin. The product obtained by this synthesis was identical to that previously reported,[2] and confirms the structure assigned to IV in the previous paper of this series. Each step of the synthesis gave a good yield of product (>65%); the over-all yield of IV from sulfoacetic acid was 25%.

The success of this synthesis suggested that sulfamylacetylurea (IX), the isomer of VII, might be induced to cyclize under similar conditions, as shown in Equation 3. Compound IX was prepared from the known[6] chlorosulfonylacetylurea by reaction with ammonia. However, none of the desired product (IV) was obtained from refluxing solutions

$$\underset{\text{I}}{} \longrightarrow \underset{}{ClSO_2CH_2CONHCONH_2} \longrightarrow \underset{\text{IX}}{NH_2SO_2CH_2CONHCONH_2} \longrightarrow \text{IV} \quad (3)$$

of IX in anhydrous pyridine. Heating IX in refluxing nitrobenzene, diphenyl ether, or in the absence of solvents led only to extensive decomposition. The use of aqueous ethanolic sodium carbonate, a technique which has been used[7] for the synthesis of sulfonylureas from sulfonamides and urea, was also unsuccessful.

Although cyclization of IX to IV could not be effected, refluxing pyridine was employed successfully in the related cyclization of β-ureidoethanesulfonamide (XI) to 1,2,4,2*H*-thiadiazine-3(4*H*,5*H*,-6*H*)-one-1,1-dioxide (XII), an analog of dihydrouracil. Attempts to bring about the cyclization of XI to XII in triethylamine or tri-*n*-butylamine were unsuccessful.

$$\underset{\text{X}}{ClNHC_3H_2CH_2SO_2NH_2} \longrightarrow$$

$$\underset{\text{XI}}{NH_2CONHCH_2CH_2SO_2NH_2} \longrightarrow \underset{\text{XII}}{\begin{array}{l} \text{NH} \\ \text{CO} \\ \text{SO}_2\text{—NH} \end{array}}$$

Compound XI was prepared from tauramide hydrochloride (X) by reaction with potassium cyanate. The structure of XI was assigned on the basis of the fact that amines react readily with potassium cyanate in acidic media, whereas sulfonamides are converted to sulfonylureas in basic media. The conversion of sulfanilamide to *p*-ureidobenzenesulfonamide has been effected in the same way.[4] The infrared spectrum of XI has a strong band at 1648 cm.$^{-1}$ which is in the region where *N*-alkylureas

(3) Phenyl methanesulfonate ($C_6H_5O_3SCH_3$) was recovered unchanged after having been heated with liquid ammonia in a sealed tube at 75°, conditions under which V is converted to VI. Ammonolysis of the sulfonate group in V is apparently made possible by the activating effect of the carbonyl group in the α position.

(4) F. Kurzer, *Chem. Revs.*, **50**, 1 (1953). In our hands acetamide and benzamide did not react with potassium cyanate under the conditions employed for the reaction of sulfamylacetamide and ethyl sulfamylacetate.[2] Further proof for the structure of VII was obtained by preparation of the isomeric sulfamylacetylurea (IX) by an established method (see below).

(5) The cyclization probably takes place by way of an intermediate of the sulfonylisocyanate type ($NH_2COCH_2SO_2NCO$). Sulfonylisocyanates have been prepared [O. C. Billeter, *Ber.*, **37**, 690 (1904); J. R. Geigy, Brit. Pat. **604,259**, June 30, 1948; *Chem. Abstr.*, **43**, 1061 (1949)], and isocyanates in general are known to react with amides to form substituted ureas [see for example: P. F. Wiley, *J. Am. Chem. Soc.*, **71**, 1310, 3746 (1949)]. A sulfonylisocyanate of the type shown would react rapidly with water to give sulfamylacetamide, in accord with the facile conversion of the sulfonylurea to the amide by trace amounts of water in the pyridine.

(6) K. Bodendorf and N. Senger, *Ber.*, **72**, 571 (1939). These authors reported the synthesis of (*N*-phenylsulfamyl)-acetylurea by a method similar to that used for IX. They were unable to cyclize it by heating the dry solid.

(7) E. Haack, U. S. Patent **2,385,571**, Sept. 25, 1945; *Chem. Abstr.*, **40**, 603 (1946).

absorb.[8a] Carbonyl absorption in sulfonylureas occurs at higher frequencies, as shown by carbamylmethanesulfonylurea (VII) (1686 cm.$^{-1}$), XII (1700 cm.$^{-1}$), and methanesulfonylurea (1710 cm.$^{-1}$).[8b]

The product of cyclization (XII) is a considerably weaker acid than IV, since the former was isolated directly from the pyridine solution, rather than in the form of the pyridine salt. Compound XII could nevertheless be titrated to a satisfactory end point with dilute sodium hydroxide. The neutralization equivalent agreed closely with that calculated for formula XII. The infrared spectrum of XII has a strong band at 1700 cm.$^{-1}$, near that of methanesulfonylurea, and at 1148 and 1324 cm.$^{-1}$. The spectrum of methanesulfonylurea has a band at 1150 cm.$^{-1}$ as well as two bands in the sulfonyl region at 1318 and 1331 cm.$^{-1}$

Although the methods commonly used for the preparation of barbituric acid (*i.e.*, urea and the diester or diacid chloride of malonic acid) cannot be used for the synthesis of 1,2,4,2*H*-thiadiazine-3,5-(4*H*,6*H*)-dione-1,1-dioxide (IV),[2,6] we had hoped that the related reaction of sulfamylacetamide (VI) with a suitable derivative of carbonic acid might provide a more direct route to IV. However, neither refluxing a large excess of ethyl carbonate with VI in the presence of sodium (mol. ratio of VI/Na = 1/2) nor of ethyl chloroformate with VI in the presence of sodium ethoxide (mol. ratio of ethyl chloroformate/sodium ethoxide/VI = 1/2/1) produced any of the desired product. When sulfamylacetamide was fused with urea, only unchanged VI and a higher melting solid, probably biuret, were obtained. These experiments are summarized in equation 4:

$$NH_2COCH_2SO_2NH_2 + \begin{matrix} C_2H_5O_2COC_2H_5 \\ \text{or} \\ C_2H_5O_2CCl \\ \text{or} \\ NH_2CONH_2 \end{matrix} \longrightarrow IV \quad (4)$$

EXPERIMENTAL[9]

Diphenyl sulfoacetate (V). A mixture of 96 g. (0.54 mol.) of chlorosulfonylacetyl chloride[2] and 105 g. (1.13 mol.) of freshly distilled phenol was heated for 10–12 hr. in an oil bath held at a temperature of 125°. After cooling, the mixture crystallized, and the solid material was recrystallized from a mixture of benzene and petroleum ether, yielding 129 g. (82%) of pinkish white crystals, m.p. 77.5–80°. Recrystallization from benzene gave 86 g. (54%) of a white amorphous powder m.p. 80–81° (lit.[10] m.p. 77.5°). (Found: C, 57.90; H, 4.32. Calcd. for $C_{14}H_{10}O_5S$: C, 57.65; H, 4.11.)

Phenylcarbamylmethanesulfonate (VIIIa). To approximately 75 ml. of liquid ammonia in a Dewar flask was added in portions and with stirring 26.3 g. (0.09 mol.) of diphenyl sulfoacetate. The mixture was stirred gently for a period of 24 hr., and then transferred to a flask, rinsing with portions of absolute ethanol. After the excess ammonia had been removed by slight warming of the mixture, the remaining alcoholic solution was heated to boiling, filtered, and then chilled. The white crystals which separated were filtered and washed with several small portions of ether. In this way 13.2 g. (68%) of product m.p. 97.5–99° was obtained. (Found: C, 44.75; H, 4.40. $C_8H_9NO_4S$ requires: C, 44.64; H, 4.22.)

Phenyl N-methylcarbamylmethanesulfonate (VIIIb). This compound was prepared by the reaction of diphenyl sulfoacetate and liquid methylamine in the same manner as the above experiment. It was also synthesized *via* ethyl phenyl sulfoacetate in the following manner. A mixture of 25.2 g. (0.24 mol.) of carbethoxymethanesulfonylchloride,[2] and 14.0 g. (0.15 mol.) of freshly distilled phenol was heated for a period of 9 hr. in an oil bath held at a temperature of 120–130°. After cooling, the mixture was dissolved in 100 ml. of absolute ethanol. The ethanolic solution was heated to boiling, decolorized, filtered, and chilled. Even by the addition of petroleum ether, no crystallization could be induced. The solvents were removed leaving an oil which would not crystallize. The oil, presumably *ethyl phenyl sulfoacetate*, was taken up in a small amount of ethanol and added slowly to approximately 60 ml. of liquid methylamine contained in a tube immersed in a bath of Dry Ice and isopropyl alcohol. The mixture was allowed to stand with occasional stirring for a period of 40 hr. It was then rinsed into a flask and warmed slightly to remove excess methylamine. The residual ethanolic solution was heated to boiling, filtered, and allowed to cool. By filtration, 20.2 g. (66% crude) of a light amorphous solid was obtained. Recrystallization of this material from CCl_4 produced a white crystalline solid, m.p. 82–83°. (Found: C, 46.95; H, 4.94. $C_8H_{11}NO_5S$ requires: C, 47.20; H, 4.84.)

Sulfamylacetamide (VI). A solution of 25.0 g. (0.086 mol.) of diphenyl sulfoacetate in approximately 30 ml. of liquid ammonia contained in a sealed tube was heated at a temperature of 75° for a period of 17 hr. At the end of the heating period the tube was cautiously opened and its contents were transferred to a flask, rinsing with small portions of methanol. After evaporation of excess ammonia by slight warming, the methanol solution was heated to boiling, filtered, and allowed to cool thoroughly. By filtration of the cold mixture, 10.9 g. (92% crude) of a light tan solid, m.p. 132–135°, was obtained. Two recrystallizations from absolute ethanol yielded white granular crystals, m.p. 134–135°. (Found: C, 17.62; H, 4.37; N, 20.33. $C_2H_6N_2O_3S$ requires: C, 17.40; H, 4.35; N, 20.03.)

Carbamylmethanesulfonylurea (VII). A mixture of 6.8 g. (0.05 mol.) of sulfamylacetamide, 4.2 g. (0.05 mol.) of potassium cyanate, and 250 ml. of absolute ethanol was refluxed on a steam bath for 4 hr. After heating for approximately 0.5 hr. a voluminous white precipitate began to separate, causing considerable bumping of the mixture. At the end of the reflux period, the mixture was thoroughly chilled and then filtered. The crystalline white solid was washed with several portions of ether and when completely free of solvents weighed 9.2 g. (83%) in crude form. Recrystallization from 95% ethanol yielded 8.3 g. (74%) of purified potassium carbamylmethanesulfonylureide. (Found: C, 16.38; H, 2.77; N, 19.60. $C_3H_6KN_3O_4$ requires: C, 16.45; H, 2.74; N, 19.20.) A solution of 3.0 g. (0.022 mol.) of potassium car-

(8) (a) J. L. Bowin and P. A. Bowin, *Can. J. Chem.*, **32**, 561 (1954). (b) Methanesulfonylurea was pelleted in potassium bromide. The other compounds were in Nujol mull. Additional peaks appear in the spectra of many of the sulfonylureas when obtained from potassium bromide pellets. We have therefore relied almost entirely on Nujol mulls in this work. The two peaks at 1714 and 1698 cm.$^{-1}$ reported[2] for compound IV were obtained in Nujol. In potassium bromide a single band at 1710 cm.$^{-1}$ was observed. Whether this is due to reactions which take place under the conditions of pelleting, or whether it reflects changes in the per cent enolization of the compound is not known.

(9) Melting points and boiling points are uncorrected. Infrared spectra were obtained with a Model 21 Perkin-Elmer recording spectrophotometer equipped with a sodium chloride prism.

(10) R. Vieillefosse, *Bull. soc. chim. France*, 6, 34 (1939).

bamylmethanesulfonylureide in 20 ml. of distilled water was passed through a column of Dowex-50 resin (acid form), and eluted with water. The strongly acidic portion of the eluant was evaporated under a jet of filtered air to about one fourth its original volume. After thorough chilling of the concentrated solution a white crystalline solid separated. This material, when filtered and washed with an ethanol ether mixture and, finally, with ether, weighed 2.0 g. (80% conversion) and melted with decomposition at 165–170°. Recrystallization from absolute ethanol yielded soft white crystals, m.p. 171–172° (dec.). (Found: C, 19.95; H, 3.66; N, 23.63. $C_3H_7N_3O_4S$ requires: C, 19.91; H, 3.87; N, 23.22.)

Pyridinium 1,2,4,2H-thiadiazine-3,5(4H,6H)-dione-1,1-dioxide. A mixture of 1.0 g. (0.0065 mol.) of carbamylmethanesulfonylurea and 20 ml. of anhydrous, freshly distilled pyridine, protected from atmospheric moisture by means of either a calcium chloride or barium oxide drying tube, was refluxed for a period of 2.5 hr. The solid was completely dissolved after 0.5 hr. refluxing. After the reflux period the mixture was chilled in an ice bath. By the addition of a small amount of absolute ether a granular white solid was made to precipitate. This material, after filtration and washing with several portions of an ethanol ether mixture, weighed 0.91 g. (68% crude) and melted at 172–179° (dec.). Two recrystallizations from absolute ethanol yielded a pure product, m.p. 176–178° (dec.). (Found: C, 39.56; H, 3.93; N, 17.47. $C_8H_9N_3O_4S$ requires: C, 39.55; H, 3.71; N, 17.47.)

1,2,4,2H-Thiadiazine-3,5(4H,6H)-dione-1,1-dioxide (IV). Pyridinium 1,2,4,2*H*-thiadiazine-3,5(4*H*,6*H*)-1,1-dioxide (4.3 g., 0.018 mol.), obtained in the manner described above, was dissolved in approximately 20 ml. of distilled water and eluted from a column of Dowex-50 cationic exchange resin. The portion of the eluant strongly acidic to litmus was evaporated on a steam bath with a gentle jet of filtered air. The light tan material thus obtained was recrystallized from absolute ethanol, whereby a total of 2.6 g. (88% conversion from the pyridinium salt) of white, powdery material m.p. 226–227° (dec.) was obtained. This material was identical in m.p. and infrared spectrum so that previously reported.[2]

Sulfamylacetylurea (IX). Chlorosulfonylacetyl chloride (17.7 g., 0.1 mol.), was added to 6 g. (0.1 mol.) of urea and the mixture was stirred until it became a viscous mass. This salve-like material, which contained chlorosulfonylacetylurea,[6] was allowed to stand in a vacuum desiccator over potassium hydroxide for 3 days and was then dissolved in 100 ml. of dry tetrahydrofuran. To this solution was added 3.4 g. (0.2 mol.) of ammonia in 100 ml. of tetrahydrofuran. After 1 hr. the ammonium chloride formed was removed by filtration. Evaporation of the filtrate yielded about 10 g. (56%) of crude product. Three recrystallizations from ethanol water mixtures gave the pure compound, m.p. 185–186°. (Found: C, 19.97; H, 3.60; N, 23.75. $C_3H_7N_3O_4S$ requires: C, 19.89; H, 3.87; N, 23.21.)

β-Ureidoethanesulfonamide (XI). A solution of 2.8 g (0.035 mol.) of potassium cyanate in 6 ml. of water was added to a solution of 5.5 g. (0.035 mol.) of β-aminoethanesulfonamide[11] hydrochloride in 25 ml. of 80% ethanol, and the resulting solution was allowed to stand for 4 hr. at room temperature. It was then evaporated to dryness under reduced pressure. The residue was extracted thrice with 20-ml. portions of absolute ethanol and twice with 15-ml. portions of 95% ethanol. Evaporation of the combined extracts left a clear paste, which crystallized when cooled on Dry Ice. Two recrystallizations from absolute ethanol and one from 95% ethanol produced 1.5 g. (26%) of white needles, m.p. 144–145°. The product was soluble in water and insoluble in chloroform. (Found: C, 21.83; H, 5.30; N, 25.14. $C_3H_9N_3O_3S$ requires: C, 21.52; H, 5.43; N, 25.14.)

1,2,4,2H-Thiadiazine-3(4H,5H,6H)-one-1,1-dioxide (XII). One g. (0.006 mol.) of β-ureidoethanesulfonamide was subjected to the procedure described for the cyclization of VII, except that the volume of ether added to precipitate the product was equal to the volume of pyridine used for the reaction. In this way 0.6 g. (67%) of white crystals m.p. 272–273° (dec.), was obtained after recrystallization from absolute ethanol. [Found: C, 23.93; H, 4.10; N, 18.49; neut. equiv. (by potentiometric titration) 149. $C_3H_6N_2O_3S$ requires: C, 23.99; H, 4.03; N, 18.66; neut. equiv. 150.]

Methanesulfonylurea. This compound was prepared from methanesulfonamide[12] and potassium cyanate by the method described above for carbamylmethanesulfonylurea (VII). After two recrystallizations from absolute ethanol, the white crystals melted at 153–5°. (Found: C, 17.43; H, 4.53; N, 20.24: S, 23.13. $C_2H_6N_2O_3S$ requires: C, 17.39; H, 4.38; N, 20.28; S, 23.21.)

The infrared spectrum of a sample in potassium bromide showed strong absorption bands at 1710 (C=O), 1331, 1318, and 1157 cm.$^{-1}$ (SO_2 of —SO_2N—).

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(11) Prepared from taurine by the method of R. Winterbottom, J. W. Clapp, W. H. Miller, J. P. English, and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, 69, 1393 (1947). Although either the phthalyl or benzoyl group could be used, as described by these authors, to protect the amino group of taurine, we found that the latter gave better results. We also used a refluxing mixture of phosphorus oxychloride (instead of thionyl chloride) and a suspension of the sodium salt of *N*-benzoyltaurine in benzene to prepare β-benzamidoethanesulfonyl chloride. In this case the yield was low.

(12) L. Field and F. A. Greenwald, *J. Am. Chem. Soc.*, **75**, 934 (1953).

[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Solvolysis of 4,4-Dimethylcholesteryl-*p*-toluenesulfonate. II[1]

ROBERT M. MORIARTY AND EVERETT S. WALLIS

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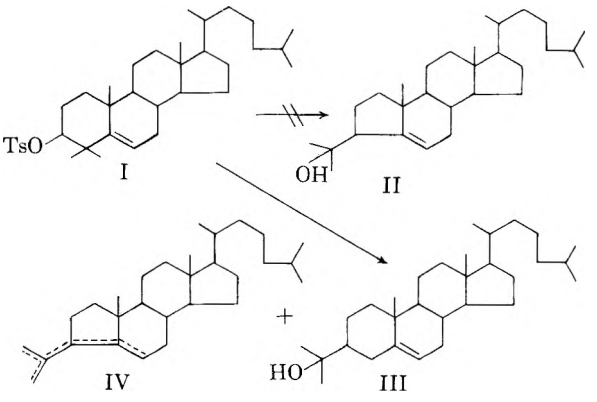
We have studied the solvolysis of 4,4-dimethylcholesteryl-*p*-toluenesulfonate (I) under conditions which favor the formation of a 3,5-cyclosterol ("*i*-sterol"). After completion of our investigation, another group of workers reported results on this problem.[2] These workers reached different conclusions concerning the structures of the products of this solvolysis. Their results are discussed and additional data obtained by us are here presented.

A general reaction which 3β-hydroxy-Δ^5-sterols undergo is solvolysis *via* an intermediary homoallylic-type carbonium ion to yield a 3,5-cyclosterol as the product of kinetic control.[3] If, however, such a system be saturated and possess 3β-hydroxy,4,4-dimethyl substituents, as in the case of certain triterpenes, then rearrangement takes place with ring contraction to yield an A-nor-product.[4]

Therefore, it appeared to be of interest to study the solvolysis of compound I, which contains both a Δ^5 double bond, and 4,4-dimethyl substituents since in such a molecule either or both of these reactions can conceivably take place, namely: formation of 4,4-dimethyl - 3,5 - cyclocholestan-6β-ol (II) or ring contraction to yield 3-(2-hydroxy-2-propyl)-A-norcholest-5-ene (III).

We have previously reported[1] that the solvolysis of 4,4-dimethylcholesteryl-*p*-toluenesulfonate (I) in 60% aqueous acetone in the presence of potassium acetate yielded 70% of a mixture composed of isomeric, conjugated dienes (IV), 20% 3-(2-hydroxy-2-propyl)-A-norcholest-5-ene (III) and 7% 4,4-dimethylcholesterol. No 4,4-dimethyl-3,5-cyclocholestan-6β-ol (II) was found.



(1) Part I, *J. Org. Chem.*, 24, 1274 (1959).

(2) Y. M. Y. Haddad and G. H. R. Summers, *J. Chem. Soc.*, 769 (1959).

(3) E. S. Wallis, E. Fernholz, and F. T. Gephardt, *J. Am. Chem. Soc.*, 59, 137 (1937); H. H. Hafez, G. Halsey, and E. S. Wallis, *Science*, 110, 474 (1949); S. Winstein and R. Adams, *J. Am. Chem. Soc.*, 70, 838 (1948).

(4) W. Klyne, *Progress in Stereochemistry*, Butterworth's, London, 1954, Vol. 1, p. 70.

(5) We wish to thank LeRoy Johnson, Varian Associates, Palo Alto, Calif., for determining and interpreting the n.m.r. curve of this compound.

Recently there has appeared a paper by Y. M. Y. Haddad and G. H. R. Summers which is an account of their investigation of this reaction.[2]

Under the same solvolytic conditions as our experiment these investigators obtained the same products as reported by us. In contrast to our structural assignment, however, they concluded that the isomeric alcohol which we identified as 3-(2-hydroxy-2-propyl)-A-norcholest-5-ene (III) [m.p. 125–126°, $[\alpha]_D$ −24.7 (c, 0.8)] was an *i*-sterol (II).

They based their assignment of structure on the following data: (a) the method of preparation, (b) the hindered nature of the hydroxyl group, and (c) oxidation in a very small yield to a supposed *i*-ketone whose structural assignment was based on infrared absorption and microanalysis.

On the other hand, there are data in their paper which allow a different interpretation and which we believe can best be explained in terms of our structural assignment (III) which postulates a tertiary alcohol; namely (a) failure to acetylate, epimerize, and oxidize under the usual conditions for these reactions; (b) failure to undergo acid-catalyzed rearrangement to the normal alcohol, a property characteristic of 3,5-cyclosteroids; and (c) the sign of the rotatory power of the compound. All these latter observations we also made.

In addition, we reported certain other results on the isomeric laevorotatory alcohol in question: (a) the presence of a double bond as shown by bromine addition, decolorization of potassium permanganate solution, and a positive test with tetranitromethane; (b) oxidation to A-norcholest-5-en-3-one, identical with an authentic sample; and (c) dehydration to the conjugated diene, 3-isopropylidine-A-norcholest-5-ene (V). All these facts in our opinion were best explained on the assignment of a tertiary alcohol structure[1] for the compound of m.p. 125–126°.

In this paper we now wish to report further results obtained in our studies of this alcohol which we believe clearly disprove the 3,5-cyclosterol structure proposed by Haddad and Summers.[2]

The nuclear magnetic resonance spectrum[5] of III, measured at 60 m.c. with deuterochloroform as the solvent and tetramethylsilane as the internal standard, shows a signal at 333 c.p.s., a position characteristic of a proton on a doubly bonded

carbon. This n.m.r. result is incompatible with structure (II). In cholesterol the C_{18} peak is seen at 43 c.p.s. and C_{19} at 63 c.p.s. In the spectrum of III these two signals appear at 41 and 54 c.p.s., respectively. With the five-membered A-ring the two angular methyl groups are more nearly equivalent and so the two peaks are brought closer together.

Ozonolysis of compound III yields an amorphous product which possesses strong absorption in the infrared at 5.75–5.85μ, a fact in agreement only with our proposed structure, since it has been shown that the geminal dimethylcyclopropyl group[6] is unaffected by ozone.

Upon treatment of III with excess perbenzoic acid the compound reacts with an equivalent amount of the peracid as shown by titration to yield the epoxide 3-(2-hydroxy-2-propyl)-A-norcholestan-5.6-oxide (VI) m.p. 119–121°. The stability of the geminal dimethylcyclopropyl group to perbenzoic acid has been amply demonstrated[7] and so again a structure such as II would be unchanged when treated with this reagent.

In conclusion we would like to report a further observation on the work of Haddad and Summers.[2] As stated earlier in this paper, about 70% of the total product from the solvolysis of I is a mixture of dienic material. Haddad and Summers report this as a pure compound, 3-isopropylidene-A-norcholest-5-ene (m.p. 85°) $[\alpha]_D^{22}$ −65.7 (c, 1.4), $\lambda_{max.}$ 241mμ; log ϵ 4.22. This is incorrect; it is a mixture. We have prepared this compound (V) in a pure state by phosphorus oxychloride-pyridine dehydration of III. The compound melts at 102–104° $[\alpha]_D^{22}$ −168.4; λ_{max} 249 mμ, log ϵ 4.14. On the basis of empirical rules for predicting the position of the ultraviolet spectrum it is evident that the value of 241 mμ is too low for V, if one considers the degree of substitution and exocyclic arrangement of the conjugated double bonds.[8,9]

EXPERIMENTAL[10]

Solvolysis of 4,4-dimethylcholesteryl-p-toluenesulfonate (I). A solution of 2.58 g. of ester, 2.83 g. of potassium acetate, and 50 ml. of water in 75 ml. of acetone was kept at reflux for 15 hr. Then most of the acetone was removed under reduced pressure. The remaining aqueous portion was extracted with ether. The combined extracts were dried and concentrated *in vacuo*. The residual oil was dried further under high vacuum, resulting in a thick, clear, semiviscous gum, 1.92 g. This product was dissolved in a small volume of ether and absorbed on a column of 100 g. of neutral alumina. Elution with 200 ml. of pentane yielded 1.37 g. of a clear, viscous oil. Further elution with 8:2 ether chloroform and 1:1 ether chloroform yielded 540 mg. of crystalline material. The 1.37 g. of oil was crystallized from acetone at −78° to yield 1.0 g., m.p. 49–60°. This material was chromatographed on 30 g. neutral alumina, and fractional elution with *n*-pentane gave diene IV, 720 mg., m.p. 78–80°, $[\alpha]_D^{22}$ −126.6° (c, 0.73), $\lambda_{max}^{CCl_4}$6. 02μ, λ_{max}^{EtOH} 242 mμ, ϵ 13,990, sh. 238 mμ, ϵ 13,200, 250 mμ, ϵ 10,560. The analytical sample, prepared by repeated recrystallization from acetone, had m.p. 84–86°.

Anal. Calcd. for $C_{29}H_{48}$: C, 87.80; H, 12.20. Found: C, 87.59; H, 12.50.

The 540 mg. of crystalline material was rechromatographed on 20 g. acid washed alumina. Elution with 1:1 pentane ether gave III, 300 mg., m.p. 120–122°. The analytical sample prepared by recrystallization from acetone had m.p. 125–126°, $[\alpha]_D^{22}$ −21.90° (*c*, 2).

Anal. Calcd. for $C_{29}H_{50}O$: C, 84.00; H, 12.15. Found: C, 84.26; H, 12.45.

Further elution with pure ether gave 100 mg. of material m.p. 142–144° which was identified as 4,4-dimethylcholesterol (IV) by a mixed melting point determination and infrared absorption comparison with authentic IV.

Perbenzoic acid titration of III. The samples were dissolved in chloroform and a solution of perbenzoic acid in chloroform (7.5 mg./ml.) was added. After being stored overnight at 2°, an aqueous solution of sodium iodide and 3 drops of acetic acid were added. The liberated iodine was titrated with 0.1212*N* sodium thiosulfate: (a) 45.5 mg. (0.109 mml.) III requires 15.07 mg. of perbenzoic acid, 30 mg. was added, and 1.83 ml. of 0.1212*N* sodium thiosulfate was required to titrate the excess iodine; (b) 101.5 mg. (0.245 mml.) requires 33.8 mg. of perbenzoic acid, 52.5 mg. was added, and 2.30 ml. of 0.1212*N* sodium thiosulfate was required to titrate the excess; (c) 93.5 mg. (0.226 mml.) III requires 31.4 mg. of perbenzoic acid, 45.0 mg. was added, and 1.66 ml. of 0.1212*N* sodium thiosulfate was needed to titrate the excess; (d) 46.1 mg. (0.119 mml.) of cholesterol requires 16.45 mg. of perbenzoic acid, 30.0 mg. was added, and 1.63 ml. of 0.1212*N* sodium thiosulfate was used to titrate the excess iodine. All these results indicate the presence of *one* double bond in the molecule.

3-(2-Hydroxy-2-propyl)-A-norcholestan-5,6-oxide (VI). To a solution of 200 mg. of III was added 12 ml. of a solution of perbenzoic acid in chloroform which contained 7.5 mg. perbenzoic acid per ml. The solution was stoppered and stored overnight at 2°. Water was added followed by extraction with chloroform. The chloroform solution was washed with a saturated solution of sodium bicarbonate and water, dried, and concentrated *in vacuo*. The crude product crystallized upon trituration with acetone. It was recrystallized from acetone to yield 150 mg. m.p. 119–121°, $[\alpha]_D^{23}$ −14° (c, 2).

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.85; H, 11.79.

Ozonolysis of III. One hundred mg. of III was dissolved in 5 ml. of chloroform. At 0° ozone was passed through the solution for 0.5 hr. Water was added and the mixture was stirred for 0.5 hr. The chloroform layer was separated, dried, and concentrated *in vacuo*, yielding a gum which failed to crystallize from the usual solvents. $\lambda_{max}^{CCl_4}$ broad 5.75–5.85μ.

3-Isopropylidene-A-norcholest-5-ene (V). To a solution of 200 mg. of II dissolved in 2 ml. of pyridine, 2 ml. of phosphorus oxychloride was added. After heating at reflux for

(6) E. P. Kohler and J. B. Conant, *J. Am. Chem. Soc.*, **39**, 1404 (1917).

(7) G. Büchi, M. Schack, V. Wittenau, and D. M. Smith, *J. Am. Chem. Soc.*, **81**, 1968 (1959).

(8) R. B. Woodward, *J. Am. Chem. Soc.*, **64**, 72 (1942).

(9) Compare abietic acid and neoabietic acid, G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 339 (1948).

(10) Melting points were taken on a Kofler block and are uncorrected. Rotations were taken using chloroform as the solvent. The microanalyses were performed by George Robertson, Florham Park, N. J. Tetramethylsilane was used as the internal standard in the n.m.r. spectrum determination and deuterochloroform was the solvent.

1 hr., the reaction mixture was cooled and ice water cautiously added. The reaction mixture was extracted with ether and the ethereal extracts were washed with cold dilute hydrochloric acid and a saturated solution of sodium bicarbonate, dried, and concentrated *in vacuo*. The resulting crystalline product, 180 mg., was recrystallized from acetone to yield 135 mg. of V, m.p. 102–104°, $[\alpha]_D^{22}$ −168 (*c*, 2), λ_{max}^{EtOH} 249 mμ, lcg ε 4.22.

Anal. Calcd. for $C_{29}H_{48}$: C, 87.80; H, 12.20. Found: C, 88.10; H, 12.33.

PRINCETON, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Labor-saving Procedures for Calculating Wave Functions for Molecules with Axes of Symmetry

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Detailed procedures are given for calculating the first approximation LCAO-MO energies and wave functions for the π-electrons of molecules with *n* conjugated atoms and a two- or k-fold axis of rotation.

Organic chemists make increasing use of approximate calculations of resonance energy, charge distribution, bond order, force constant, free valence and localization energy (Dewar reactivity number) in correlating and predicting structures and reactivities of unsaturated systems.[1] General procedures have been described for evaluating these quantities for the π-electrons of any molecule with *n* conjugated atoms using the first-approximation LCAO-MO method.[2] These generally call for solution of an $n \times n$ determinant. When *n* is large, as in triphenylmethyl, the work involved becomes prohibitive unless a digital computer is employed. However, the work can be appreciably reduced whenever the molecule has a two- or *k*-fold axis of rotation by replacing the $n \times n$ determinant by two or more smaller determinants. This can be done by choosing trial wave functions belonging to families of different basic symmetry (Γ-types) so that no two from different families will have any resonance integrals (*i.e.*, off-diagonal elements between them in a secular determinant involving them as trial functions). Then only trial functions of the same family can interact with one another. Rules for choosing trial functions belonging to different families are given below for several kinds of molecular symmetry. Benzene will be used as an illustration in each section because it has each of these kinds of symmetry. Although the derived molecular wave functions may depend on the approach, the energies, charges, bond orders, and free valences do not. These useful procedures may be familiar or obvious to many physical chemists, but the authors know of no single source where one may find them described concisely for the cases of interest to organic chemists.

Two-fold axis. Ethylene, propene, butadiene, benzene, phenanthrene, pentadienyl, and benzyl radicals all have a two-fold axis for their π-electrons. Number all conjugated atoms of the molecule and tabulate them in a vertical column. Beside each in an adjacent column write the number of the atom it becomes after a 180° rotation about the two-fold axis. For minimum size determinants, choose the axis so that as many numbers change as possible. Now use the character table

Determinant	E	C_2^z	Family
D_1	1	1	Γ_1
D_2	1	−1	Γ_2

to generate trial wave functions ψ_1, ψ_2... for use in each determinant D by taking "dot products" of the E, C_2^z characters by the atomic wave functions corresponding to the pairs of numbers thus tabulated (see first example, which illustrates this process). Normalize each of these trial functions by dividing through by the sum of the squares of the coefficients. For each determinant D

(1) R. J. Windgassen, Jr., W. H. Saunders, Jr., and V. Boekelheide, *J. Am. Chem. Soc.*, **81**, 1459 (1959); R. Breslow and C. Yuan, *J. Am. Chem. Soc.*, **80**, 5991 (1958); R. Breslow, R. Haynie, and J. Mirra, *J. Am. Chem. Soc.*, **81**, 247 (1959); F. Sondheimer and R. Wolovsky, *J. Am. Chem. Soc.*, **81**, 1771 (1959); J. H. Richards, Abstracts of Papers, 135th ACS meeting, Boston, Mass., April 5–10, 1959, p. 86-O; A. Streitwieser, Jr., and P. M. Nair, *Tetrahedron*, **5**, 149 (1959); M. M. Kreevoy, *Tetrahedron*, **2**, 354 (1958); M. J. S. Dewar, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **19**, 1 (1958); D. R. Augood and G. H. Williams, *Chem. Revs.*, **57**, 123 (1957); D. Peters, *J. Chem. Soc.*, 2654 (1957); E. Heilbronner, *Helv. Chim. Acta*, **37**, 913 (1954); F. L. J. Sixma, *Rec. trav. chim.*, **72**, 673 (1953); J. D. Roberts and D. A. Semenow, *J. Am. Chem. Soc.*, **77**, 3152 (1955); A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **74**, 5288 (1952); J. D. Roberts, A. Streitwieser, Jr., and C. M. Regan, *J. Am. Chem. Soc.*, **74**, 4579 (1952).

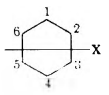
(2) C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc. (London)*, **A191**, 39 (1947); **A192**, 16 (1948); **A193**, 447, 456 (1948); **A195**, 188 (1948); H. C. Longuet-Higgins, *J. Chem. Phys.*, **18**, 265, 275, 283 (1950); R. D. Brown, *Quart. Revs.*, **6**, 63 (1952); M. J. S. Dewar, *Progr. Org. Chem.*, **2**, 1 (1953); H. C. Longuet-Higgins, *Proc. Chem. Soc.*, 157 (1957).

$$\begin{vmatrix} H_{11} - E & H_{12} & \dots \\ H_{21} & H_{22} - E & \dots \\ \dots & \dots & \dots \end{vmatrix} = 0$$

each $H_{mj} = \int \psi_m H \psi_j d\tau$ is evaluated by expanding it in terms of atomic orbitals and setting each $\int \phi_r H \phi_s d\tau$ equal to α when $r = s$, to β when atom r is adjacent to atom s, and to zero when it is not adjacent. Replace $\alpha - E$ by x (standing for $-\epsilon$) and β by 1 and solve each determinant for x to get $-\epsilon$ values in units of β. Substitute each value of x back into the simultaneous linear equations in c_1, c_2... corresponding to the determinant from which it was derived, and solve for c_1, c_2... (the coefficients of the trial functions in that molecular orbital). Expand each molecular orbital wave function in terms of the atomic orbitals and normalize.

In this first approximation overlap integrals are neglected. The coulomb integral α is the energy of a π-electron localized in a p atomic orgital of one atom. The resonance integral β is the change in energy when a π-bond is formed, and is approximately -18 kcal. for a π-bond between adjacent carbons separated by the bond distance in benzene. The binding energy ϵ is a positive multiple of β for bonding orbitals, and therefore also a negative quantity.

Example: benzene



E	C_2^z
1	4
2	3
3	2
4	1
5	6
6	5

The solution involves two 3×3 determinants. D_1, the first of these, is set up and solved as follows:

Unnormalized	Normalized
$\psi_1 = \phi_1 + \phi_4$	$\psi_1 = (1/\sqrt{2})(\phi_1 + \phi_4)$
$\psi_2 = \phi_2 + \phi_3$	$\psi_2 = (1/\sqrt{2})(\phi_2 + \phi_3)$
$\psi_3 = \phi_5 + \phi_6$	$\psi_3 = (1/\sqrt{2})(\phi_5 + \phi_6)$

Other combinations are duplicates of these.

$$H_{11} = \int \psi_1 H \psi_1 d\tau = \tfrac{1}{2}(\int \phi_1 H \phi_1 d\tau + 2\int \phi_1 H \phi_4 d\tau + \int \phi_4 H \phi_4 d\tau)$$
$$= \tfrac{1}{2}(\alpha + 0 + \alpha) = \alpha$$
$$H_{12} = \tfrac{1}{2}(\int \phi_1 H \phi_2 d\tau + \int \phi_1 H \phi_3 d\tau + \int \phi_4 H \phi_2 d\tau + \int \phi_4 H \phi_3 d\tau)$$
$$= \tfrac{1}{2}(\beta + 0 + 0 + \beta) = \beta = H_{21}$$
$$H_{13} = \tfrac{1}{2}(0 + \beta + \beta + 0) = \beta = H_{31}$$
$$H_{22} = \tfrac{1}{2}(\alpha + \beta + \beta + \alpha) = \alpha + \beta = H_{33}$$
$$H_{23} = \tfrac{1}{2}(0 + 0 + 0 + 0) = 0 = H_{32}$$

$$\begin{vmatrix} x & 1 & 1 \\ 1 & x+1 & 0 \\ 1 & 0 & x+1 \end{vmatrix} = 0 \qquad \begin{pmatrix} xc_1 + c_2 + c_3 = 0 \\ c_1 + (x+1)c_2 = 0 \\ c_1 + (x+1)c_3 = 0 \end{pmatrix}$$

$$x(x+1)(x+1) - (x+1) - (x+1) = 0$$
$$x^3 + 2x^2 - x - 2 = 0$$

Plotting shows that $x = +1$ is one root. Long division by $(x - 1)$ gives $x^2 + 3x + 2 = 0$ for the rest, hence $x = \tfrac{1}{2}(-3 \pm \sqrt{9-8}) = +1, -1, -2$. If $x = +1$, $\epsilon = -\beta$; the three equations are $c_1 + c_2 + c_3 = 0$, $c_1 + 2c_2 = 0$, $c_1 + 2c_3 = 0$; therefore $c_2 = c_3 = -\tfrac{1}{2}c_1$; $\psi = c_1(\psi_1 - \tfrac{1}{2}\psi_2 - \tfrac{1}{2}\psi_3) = (1/\sqrt{12})(2\phi_1 - \phi_2 - \phi_3 + 2\phi_4 - \phi_5 - \phi_6)$. Thus three of the roots are

$$x = +1,\ \epsilon = -\beta,\ \Psi = (1/\sqrt{12})(2\phi_1 - \phi_2 - \phi_3 + 2\phi_4 - \phi_5 - \phi_6)$$
$$x = -1,\ \epsilon = \beta,\ \Psi = \tfrac{1}{2}(\phi_2 + \phi_3 - \phi_5 - \phi_6)$$
$$x = -2,\ \epsilon = +2\beta,\ \Psi = (1/\sqrt{6})(\phi_1 + \phi_2 + \phi_3 + \phi_4 + \phi_5 + \phi_6)$$

D_2, the other determinant, supplies the three remaining roots.

$$\psi_1 = (1/\sqrt{2})(\phi_1 - \phi_4)$$
$$\psi_2 = (1/\sqrt{2})(\phi_2 - \phi_3)$$
$$\psi_3 = (1/\sqrt{2})(\phi_5 - \phi_6)$$

Other conditions are equivalent to these.

$$\begin{vmatrix} x & 1 & -1 \\ 1 & x-1 & 0 \\ -1 & 0 & x-1 \end{vmatrix} = 0$$

$$x = +1,\ \epsilon = -\beta,\ \Psi = \tfrac{1}{2}(\phi_2 - \phi_3 + \phi_5 - \phi_6)$$
$$x = -1,\ \epsilon = +\beta,\ \Psi = (1/\sqrt{12})(2\phi_1 + \phi_2 - \phi_3 - 2\phi_4 - \phi_5 + \phi_6)$$
$$x = +2,\ \epsilon = -2\beta,\ \Psi = (1/\sqrt{6})(\phi_1 - \phi_2 + \phi_3 - \phi_4 + \phi_5 - \phi_6)$$

Linear conjugated polyenes $H(CH)_nH$ have roots calculable alternatively from

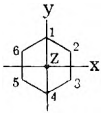
$$\epsilon_j = 2\beta \cos\left(\frac{\pi j}{n+1}\right), j = 1, 2, \dots n$$

$$\Psi_j = \sum_r \left[\sqrt{\frac{2}{n+1}} \sin\left(\frac{\pi j r}{n+1}\right)\right] \phi_r$$

Three two-fold axes at 90°. Cyclobutadiene, benzene, stilbene, and anthracene all have this symmetry. Proceed as for one two-fold axis except consider 180° rotations about all three axes and use the character table

Determinant	E	C_2^x	C_2^y	C_2^z	Family
D_1	1	1	1	1	Γ_1
D_2	1	1	−1	−1	Γ_2
D_3	1	−1	1	−1	Γ_3
D_4	1	−1	−1	1	Γ_4

Example: benzene



E	C_2^x	C_2^y	C_2^z
1	4	1	4
2	3	6	5
3	2	5	6
4	1	4	1
5	6	3	2
6	5	2	3

The solution involves two 2×2 determinants and two 1×1 determinants.

D_1: $\psi_1 = (1/\sqrt{2})(\phi_1 + \phi_4)$ $\quad H_{11} = \alpha$

$\psi_2 = {}^1/_2(\phi_2 + \phi_3 + \phi_5 + \phi_6)$ $\quad H_{12} = \sqrt{2}\beta = H_{21}$

$H_{22} = \alpha + \beta$

$$\begin{vmatrix} x & \sqrt{2} \\ \sqrt{2} & x+1 \end{vmatrix} = 0$$

$x = +1, \quad \epsilon = -\beta, \quad \Psi = (1/\sqrt{12})(2\phi_1 + \phi_2 + \phi_3 + 2\phi_4 + \phi_5 + \phi_6)$

$x = -2, \quad \epsilon = 2\beta, \quad \Psi = (1/\sqrt{6})(\phi_1 + \phi_2 + \phi_3 + \phi_4 + \phi_5 + \phi_6)$

D_2: $\psi_1 = {}^1/_2(\phi_2 + \phi_3 - \phi_5 - \phi_6) = \Psi$

$H_{11} = \alpha + \beta, \ \epsilon = +\beta$

D_3: $\psi_1 = (1/\sqrt{2})(\phi_1 - \phi_4)$

$\psi_2 = {}^1/_2(\phi_2 - \phi_3 - \phi_5 + \phi_6)$

$$\begin{vmatrix} x & \sqrt{2} \\ \sqrt{2} & x-1 \end{vmatrix} = 0$$

$x = +2, \quad \epsilon = -2\beta, \quad \Psi = (1/\sqrt{6})(\phi_1 - \phi_2 + \phi_3 - \phi_4 + \phi_5 - \phi_6)$

$x = -1, \quad \epsilon = \beta, \quad \Psi = (1/\sqrt{12})(2\phi_1 + \phi_2 - \phi_3 - 2\phi_4 - \phi_5 + \phi_6)$

D_4: $\psi_1 = {}^1/_2(\phi_2 - \phi_3 + \phi_5 - \phi_6) = \Psi$

$H_{11} = \alpha - \beta, \quad \epsilon = -\beta$

A k-fold axis. Benzene, 1,3,5-trivinylbenzene, cyclopropenyl, and triphenylmethyl radicals all have a three-fold axis for their π-electrons. Benzene and toluene have six-fold axes for their π-electrons. Tropilium ion has a seven-fold axis. Number all conjugated atoms. Generate as many trial functions as atoms (n). For each atom e on the axis (e.g., the central carbon of triphenylmethyl), use one trial function of the form

$$\psi = \phi_e$$

When there is a k-fold axis, for each group of k equivalent atoms $f, g, h, \ldots$ (*e.g.*, the 3 p-carbons of triphenylmethyl or the 6 of benzene), use k trial functions of the form

$\psi = (1/\sqrt{k})(\phi_f + \phi_g + \phi_h + \ldots)$ $\quad \Gamma_1$

$\psi = (1/\sqrt{k})(\omega^1\phi_f + \omega^2\phi_g + \omega^3\phi_h + \ldots)$ $\quad \Gamma_3$

$\psi = (1/\sqrt{k})(\omega^{-1}\phi_f + \omega^{-2}\phi_g + \omega^{-3}\phi_h + \ldots)$ $\quad \Gamma_3$

$\psi = (1/\sqrt{k})(\omega^2\phi_f + \omega^4\phi_g + \omega^6\phi_h + \ldots)$ $\quad \Gamma_3$

$\psi = (1/\sqrt{k})(\omega^{-2}\phi_f + \omega^{-4}\phi_g + \omega^{-6}\phi_h + \ldots)$ $\quad \Gamma_3$

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$\psi = (1/\sqrt{k})(\phi_f - \phi_g + \phi_h - \ldots)$ $\quad \Gamma_2$

where $\omega = e^{2\pi i/k}$ and $i = \sqrt{-1}$. Note that the Γ_3 trial functions occur always as degenerate pairs (complex and complex conjugate). The Γ_2 orbital is missing if k is odd. Only the first 3 apply if k is 3.

When k is 3 but cannot be 6, for each group of 6 equivalent atoms o, p, q, r, s, t (e.g., the 6 o-carbons of triphenylmethyl), use the 6 trial functions

$\psi = (1/\sqrt{6})(\phi_o + \phi_p + \phi_q + \phi_r + \phi_s + \phi_t)$ $\quad \Gamma_1$

$\psi = (1/\sqrt{6})[\omega^1(\phi_o + \phi_p) + \omega^2(\phi_q + \phi_r) + \omega^3(\phi_s + \phi_t)]$ $\quad \Gamma_3$

$\psi = (1/\sqrt{6})[\omega^{-1}(\phi_o + \phi_p) + \omega^{-2}(\phi_q + \phi_r) + \omega^{-3}(\phi_s + \phi_t)]$ $\quad \Gamma_3$

$\psi = (1/\sqrt{6})[\omega^1(\phi_o - \phi_p) + \omega^2(\phi_q - \phi_r) + \omega^3(\phi_s - \phi_t)]$ $\quad \Gamma_3$

$\psi = (1/\sqrt{6})[\omega^{-1}(\phi_o - \phi_p) + \omega^{-2}(\phi_q - \phi_r) + \omega^{-3}(\phi_s - \phi_t)]$ $\quad \Gamma_3$

$\psi = (1/\sqrt{6})(\phi_o - \phi_p + \phi_q - \phi_r + \phi_s - \phi_t)$ $\quad \Gamma_2$

All trial functions of a given family are combined in one determinant and solved for energies and molecular orbital wave functions by expanding each H_{mj} in terms of atomic orbitals using the rules given before. If trial functions of all three families (Γ_1, Γ_2, and Γ_3) have been generated, there will therefore be three determinants. The family designations used in this section (k-fold axis) have nothing in common with the same designations in other sections.

Monocyclic polyenes $(CH)_n$ (*e.g.*, benzene, cyclopropenyl radical, or tropilium ion) have all conjugated atoms equivalent. For monocyclic polyenes, the trial wave functions are the final molecular orbital wave functions directly.

$$\epsilon_j = 2\beta \cos\left(\frac{2\pi j}{n}\right), j = 0, 1, \ldots n-1$$

$$\Psi_j = \sum_r \left[\frac{1}{\sqrt{n}} e^{i2\pi jr/n}\right] \phi_r$$

Because the Γ_3 trial functions are chosen as complex conjugate pairs ψ, ψ^*, it happens that their determinant reduces to two noninteracting determinants with the same roots, so that only one needs to be solved. Let $H_{11} = \int \psi_1^* H \psi_1 dv$, $H_{12} = \int \psi_1^* H \psi_2 dv$, $H_{21} = \int \psi_2^* H \psi_1 dv$, ... Whenever the off-diagonal elements are complex (involve i), $H_{jm} = H_{mj}^*$, where * means complex conjugate (i replaced by $-i$). The ϵ values obtained are then each doubly degenerate, with corresponding complex conjugate molecular orbital wave functions for the other roots (from the other determinant). For triphenylmethyl a 19×19 determinant is thus replaced by one 5×5 (Γ_1), one 2×2 (Γ_2), and one 6×6 (Γ_3) determinant (since the other 6×6 (Γ_3) determinant need not be solved).

The rules for evaluating imaginary exponentials are as follows: $e^{ix} = \cos x + i \sin x$; $e^{-ix} = \cos x - i \sin x$; $e^{i(2\pi + x)} = e^{ix}$; $e^{i(2\pi - x)} = e^{-ix}$; $e^{ix} + e^{-ix} = 2 \cos x$. For example, $e^{2\pi i/3} + e^{4\pi i/3} = e^{2\pi i/3} + e^{-2\pi i/3} = 2 \cos(2\pi/3) = -1$. Imaginary parts will all vanish when energies or charges are computed.

Example: benzene

The highest symmetry axis is 6-fold. There are 6 equivalent atoms. Hence the molecular orbital wave functions are

$$\Psi = (1/\sqrt{6})(\phi_1 + \phi_2 + \phi_3 + \phi_4 + \phi_5 + \psi_6) \quad \epsilon = 2\beta$$
$$\Psi = (1/\sqrt{6})(e^{\pi i/3}\phi_1 + e^{2\pi i/3}\phi_2 + e^{\pi i}\phi_3 + e^{-2\pi i/3}\phi_4 + e^{-\pi i/3}\phi_5 + \phi_6) \quad \epsilon = \beta$$
$$\Psi = (1/\sqrt{6})(e^{-\pi i/3}\phi_1 + e^{-2\pi i/3}\phi_2 + e^{-\pi i}\phi_3 + e^{2\pi i/3}\phi_4 + e^{\pi i/3}\phi_5 + \phi_6) \quad \epsilon = \beta$$
$$\Psi = (1/\sqrt{6})[e^{2\pi i/3}(\phi_1 + \phi_4) + e^{-2\pi i/3}(\phi_2 + \phi_5) + (\phi_3 + \phi_6)] \quad \epsilon = -\beta$$
$$\Psi = (1/\sqrt{6})[e^{-2\pi i/3}(\phi_1 + \phi_4) + e^{2\pi i/3}(\phi_2 + \phi_5) + (\phi_3 + \phi_6)] \quad \epsilon = -\beta$$
$$\Psi = (1/\sqrt{6})(\phi_1 - \phi_2 + \phi_3 - \phi_4 + \phi_5 - \phi_6) \quad \epsilon = -2\beta$$

Quantities derivable from wave functions. From the normalized molecular orbital wave functions

$$\Psi_j = a_1\phi_1 + a_2\phi_2 + \ldots a_n\phi_n, j = 1, 2, \ldots n$$

and the number of electrons ν_j in each molecular orbital j, one may calculate in the usual way the total energy of the π-electrons:

$$E = \sum \nu_j(\epsilon_j + \alpha) = \sum_j \nu_j \int (\Psi_j H \Psi_j d\tau)$$

the resonance (delocalization) energy relative to a localized structure with d double bonds:

$$\text{R.E.} = \sum_j \nu_j\epsilon_j - d(2\beta)$$

the π-electron density q_r or the net positive charge Q_r or any atom r:

$$q_r = \sum_j \nu_j a_{jr}^2 = 1 - Q_r$$

the π-bond order p_{rs} or the total bond order N_{rs} of the bond between atoms r and s:

$$p_{rs} = \sum_j \nu_j a_{jr} a_{js} = N_{rs} - (\text{No. of } \sigma\text{-bonds})$$

and the free valence on any atom:

$$F_r = 4.732 - \sum_s N_{rs}$$

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Isomerization of *N*-Substituted Glycidyl Carbamates

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Received July 19, 1959

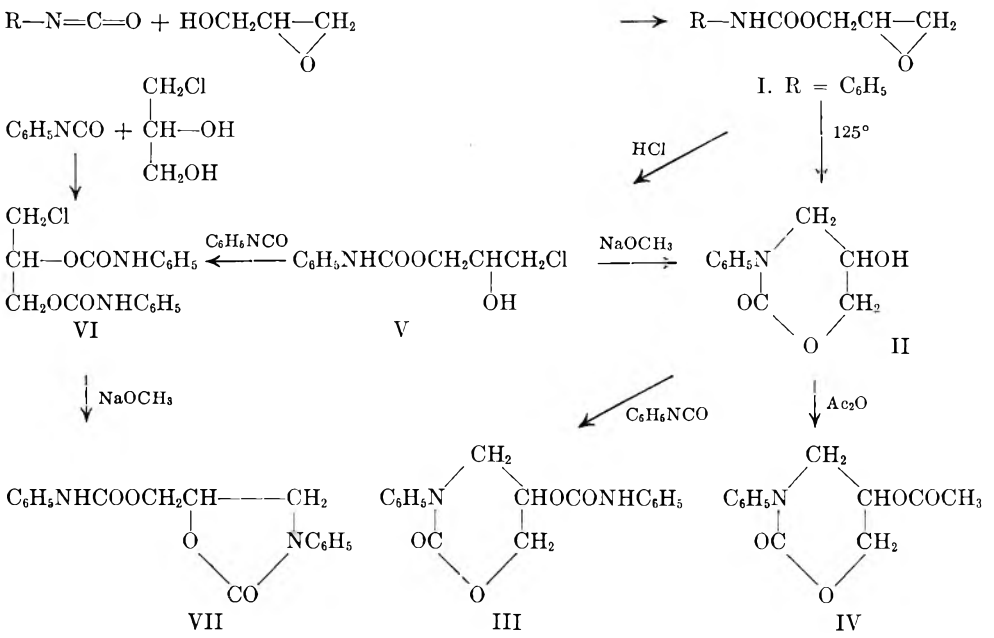
Glycidyl aryl- or alkylcarbamate undergoes a pyrolytic rearrangement to give 3-aryl- or alkyl-5-hydroxytetrahydro-1,3-oxazine-2-one in good yields.

In connection with a research on the addition reaction of glycidyl *N*-aryl- or alkylcarbamates, it happened that they thermally isomerized to give *N*-substituted 5-hydroxytetrahydro-1,3-oxazine-2-one (*N*-substituted 5-hydroxy-2-pentoxazolidone). On the isomerization of three- membered ring compounds, it was reported that *N*-acyl-[1,2] or *N*-phenylthiocarbamyl ethyleneimine[3] and their derivatives[4] underwent a rearrangement to give 2-substituted oxazoline-2 or thiazoline-2. No literature was found, however, on the ring expansion of *N*-substituted glycidyl carbamates. In the first place from the reactivity of epoxy ring to imino group, it is considered that the isomerization of glycidyl carbamate to substituted tetrahydro-1,3-oxazine-2-one will be caused by intramolecular addition reaction of epoxy ring to urethane linkage.

To confirm the structure of isomers, isomerization of glycidyl phenylcarbamate and some of the alkylcarbamates prepared from phenyl or alkyl isocyanate and glycidol were studied in detail.

When glycidyl phenylcarbamate (I) was heated without solvent in a test tube at 125° for 1 hr., crystalline II was obtained in 95% yield, the molecular weight and microanalysis of which were found to be similar to those of I. Phenyl isocyanate or acetic anhydride reacts with II to give phenylcarbamate (III) or acetate (IV) of II. II was also obtained from 1-chloro-2-hydroxy-3-phenylcarbamyloxypropane (V), prepared from I and hydrogen chloride.[5] This confirms II to be 3-phenyl-5-hydroxytetrahydro - 1,3 - oxazine - 2 - one. From 1-chloro - 2,3 - bis(phenylcarbamyloxy)propane (VI), 3 - phenyl - 5 - phenylcarbamyloxymethyl-2 - oxazolidone (VII) was obtained without forming III. This might be because of the fact that five-membered cyclic urethane was more stable and easier to form than six membered one.[6-8] An attempt to obtain IV from 1-chloro-2-acetoxy-3-phenylcarbamyloxypropane by ring closure with sodium methoxide, gave unexpectedly 10% yield of II and 90% yield of oily polymeric substance.

(1) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).
(2) H. W. Heine and Z. Proctor, *J. Org. Chem.*, **23**, 1554 (1958).
(3) A. S. Deutsch and P. E. Fanta, *J. Org. Chem.*, **21**, 892 (1956).
(4) A. S. Deutsch and P. E. Fanta, *J. Org. Chem.*, **23**, 72 (1958).
(5) L. Smith and S. Skyle, *Acta Chem. Scand.*, **5**, 1415 (1951).
(6) G. Y. Lesher and A. R. Surrey, *J. Am. Chem. Soc.*, **77**, 636 (1955).
(7) E. Dyer and H. Scot, *J. Am. Chem. Soc.*, **79**, 672 (1957).
(8) H. K. Hall and A. K. Schneider, *J. Am. Chem. Soc.*, **80**, 6409 (1958).



Structures of isomer (II) and its derivatives were also confirmed by the comparison of the infrared spectra of I, II, and IV.

Glycidyl alkylcarbamates were easily converted to 3 - alkyl - 5 - hydroxytetrahydro - 1,3 - oxazine-2-one at 80–100° for 1 hr., and methylcarbamate happened to isomerize during distillation at 80–82°/1 mm. Physical properties and analytical data of glydyl alkylcarbamates and substituted tetrahydro-1,3-oxazine-2-ones are listed in Tables I and II.

EXPERIMENTAL[9]

Glycidyl phenylcarbamate (I). To a boiling solution of 11.9 g. (0.1 mol.) of phenyl isocyanate in 200 ml. of benzene, was added dropwise with stirring during 1 hr. 7.2 g. (0.1 mol.) of newly distilled glycidol in 50 ml. of benzene, and the mixture was heated under reflux for an additional 3 hr. After removal of benzene at reduced pressure, the residue was recrystallized from ether–petroleum ether (2:1) to give 17.5 g. (92%) of glycidyl phenylcarbamate, m.p. 59.8–60.0° (lit.[10] m.p. 60°, lit.[11] m.p. 60–61°).

In the infrared spectra are found strong absorption bands arising from N–H vibrations at 1449, 1555, and 3370 cm.$^{-1}$, and from epoxy group at 865, 910, and 1260 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_{11}O_3N$: N, 7.25. Found: N, 7.25.

3-Phenyl-5-hydroxytetrahydro-1,3-oxazine-2-one (II). Five g. of I was heated in an oil bath kept at 125° for 1 hr. Oily viscous substance was crystallized from benzene in 95% yield. Pure sample melted at 109.5–110.5°. A mixed melting point with authentic sample showed no depression.

In the infrared spectra are found strong O—H absorption bands at 1090, 1350, and 3420 cm.$^{-1}$, and no absorption band arising from N—H and epoxy group was recognized.

Anal. Calcd. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25; mol. wt. 193. Found: C, 62.35; H, 5.75; N, 7.54; mol. wt. 198.

3-Phenyl-5-phenylcarbamyloxytetrahydro-1,3-oxazine-2-one (III). II, 1.93 g. (0.01 mol.), and 1.19 g. (0.01 mol.) of phenyl isocyanate in 30 ml. of benzene were heated under reflux for 1 hr. After cooling, the adduct was precipitated and recrystallized from ethanol to give 3.0 g. (96%) of 3-phenyl-5-phenylcarbamyloxytetrahydro-1,3-oxazine-2-one, m.p. 175–175.5°.

Anal. Calcd. for $C_{17}H_{16}O_4N_2$: N, 8.97. Found: N, 9.29.

3-Phenyl-5-acetoxytetrahydro-1,3-oxazine-2-one (IV). II, 1.93 g. (0.01 mol.), 13.5 g. of pyridine, and 10.0 g. of acetic anhydride were allowed to stand overnight. After removal of pyridine and excess of acetic anhydride, the crystalline solid was obtained and recrystallized from ether to give 1.74 g. (90%) of 3-phenyl-5-acetoxytetrahydro-1,3-oxazine-2-one, m.p. 70.8–71.6°.

The infrared spectra had neither N—H, O—H nor epoxy group absorption.

Anal. Calcd. for $C_{12}H_{13}O_4N$: C, 62.27; H, 5.57; N, 5.96. Found: C, 61.49; H, 5.54; N, 6.33.

1-Chloro-2-hydroxy-3-phenylcarbamyloxypropane (V). Into 50 ml. of ether containing 9.7 g. (0.05 mol.) of I was bubbled gradually dry hydrogen chloride at 10° for 30 min. After removal of the solvent, the liquid residue (11.5 g.) was distilled at 155–157°/0.05 mm. or 180–183°/1 mm. to give 9.0 g. (79%) of 1-chloro-2-hydroxy-3-phenylcarbamyloxypropane, which was solidified by cooling and melted at 55–59°.

Anal. Calcd. for $C_{10}H_{12}O_3NCl$: N, 6.10. Found: N, 5.95.

1-Chloro-2,3-bis(phenylcarbamyloxy)propane (VI). A mixture of 2.29 g. (0.01 mol.) of V and 1.19 g. (0.01 mol.) of phenyl isocyanate in 50 ml. of benzene was heated under reflux for 1 hr. After cooling, the precipitate was collected and recrystallized from ethanol to give 2.4 g. (69%) of 1-chloro-2,3-bis(phenylcarbamyloxy)propane, m.p. 128–130°. A mixed melting point with authentic sample prepared from α-chloroglycerin and phenyl isocyanate showed no depression.

Anal. Calcd. for $C_{17}H_{17}O_4N_2Cl$: N, 8.03. Found: N, 7.74.

Authentic 2-phenyl-5-hydroxytetrahydro-1,3-oxazine-2-one (II). To 1.15 g. (0.05 mol.) of V in 30 ml. of methanol was added dropwise 0.27 g. of sodium methoxide in 5 ml. of methanol, the solution being kept at 20° for 3 hr. After removal of the solvent, the residue was washed with water

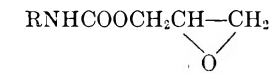
(9) Melting points and boiling points are uncorrected. Microanalyses were performed by A. Kondo in Laboratory of Organic Chemistry, Tokyo Institute of Technology. Infrared measurements were made by Government Chemical Industrial Research Institute, Tokyo.

(10) T. H. Rider and A. J. Hill, *J. Am. Chem. Soc.*, **52**, 1521 (1930).

(11) A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **74**, 2100 (1952).

TABLE I

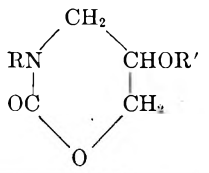
GLYDIDYL ALKYLCARBAMATES.



R	B.P.	Refractive Index, n_D^{25}	Formula	N, % Calcd.	N, % Found
Ethyl	112–116 (4 mm.)	1.4502	$C_6H_{11}O_3N$	9.65	9.85
n-Propyl	103–108 (1.6 mm.)	1.4516	$C_7H_{13}O_3N$	8.80	8.89
n-Hexyl	126–128 (2 mm.)	1.4537	$C_{10}H_{19}O_3N$	6.96	7.20

TABLE II

3,5-DISUBSTITUTED TETRAHYDRO-1,3-OXAZINE-2-ONES



R	R′	M.P.	Refractive Index, n_D^{25}	Formula	N, % Calcd.	N, % Found
Me	H		1.4880	$C_6H_9O_3N$	10.68	10.87
	PhNHCO	214–216		$C_{12}H_{14}O_4N_2$	11.20	11.27
Et	H		1.4743	$C_6H_{11}O_3N$	9.65	
	PhNHCO	172.0–172.5		$C_{13}H_{16}O_4N_2$	10.60	10.60
n-Pr	H		1.4680	$C_7H_{13}O_3N$	8.80	
	PhNHCO	161–162		$C_{14}H_{18}O_4N_2$	10.07	9.98
n-Hex	H	72–75		$C_{10}H_{19}O_3N$	6.96	
	PhNHCO	137–139		$C_{17}H_{24}O_4N_2$	8.84	8.70

and recrystallized from benzene. Yield of the product was 0.7 g. (72%).

3-Phenyl-5-phenylcarbamyloxymethyl-2-oxazolidone (VII). Into 1.74 g. (0.05 mol.) of VI in 30 ml. of methanol was added dropwise 0.27 g. of sodium methoxide in 5 ml. of methanol, the mixture being kept at 20° for 3 hr. After removal of the solvent, the residue was washed with water and recrystallized from methanol to give 1.22 g. (78%) of 3-phenyl-5-phenylcarbamyloxymethyl-2-oxazolidone, m.p. 156.2–157.5°. A mixed melting point with III was 140–148°.

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.12; H, 5.50; N, 9.19.

1-Chloro-2-acetoxy-3-phenylcarbamyloxypropane. V, 2.3 g. (0.01 mol.), in 10 g. of acetic anhydride containing a small amount of *p*-toluenesulfonic acid as a catalyst was heated under reflux for 1 hr. After removal of excess of acetic anhydride, the residue was distilled at 160–164°/0.07 mm. to give 1.85 g. (88%) of 1-chloro-2-acetoxy-3-phenylcarbamyloxypropane. The index of refraction was n_D^{25} 1.4990.

Anal. Calcd. for $C_{12}H_{14}O_4NCl$: N, 5.16. Found: N, 5.00.

Glycidyl alkylcarbamates. A mixture of equimolecular amount of glycidol and alkyl isocyanate was allowed to stand for 3 days and distilled under reduced pressure to obtain glycidyl alkylcarbamates. Glycidyl methylcarbamate was not isolated, however, which underwent the rearrangement during distillation to give 3-methyl-5-hydroxytetrahydro-1,3-oxazine-2-one, b.p. 80–82°/1 mm.

3-Alkyl-5-hydroxytetrahydro-1,3-oxazine-2-ones. Isomerization proceeded while glycidyl alkylcarbamates were heated at 100° for 1 hr. to yield 3-alkyl-5-hydroxytetrahydro-1,3-oxazine-2-ones. They were confirmed by their phenylcarbamates.

3-Alkyl-5-phenylcarbamyloxytetrahydro-1,3-oxazine-2-ones. A mixture of 3-alkyl-5-hydroxytetrahydro-1,3-oxazine-2-one and equimolecular amount of phenyl isocyanate was heated with 30 ml. of benzene for 3 hr. After cooling, the crystalline precipitate was collected and recrystallized from ethanol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WELLESLEY COLLEGE]

The Flavonoid Constituents of Barley (*Hordeum vulgare*). II. Lutonarin[1]

MARGARET K. SEIKEL AND ANNE J. BUSHNELL

Received July 16, 1959

A glycoside which on hydrolysis yields luteolin derivatives that resemble the unusual flavones vitexin and saponaretin (apigenin derivatives) has been isolated from barley.

Previous work[2] on many genotypes of barley (*Hordeum vulgare*) has shown that the principal flavonoid constituent of the leaves is saponarin, a 7-glucoside which on hydrolysis yields an equilibrium mixture of saponaretin and vitexin. In addition, barley was shown to contain two other relatively important flavonoid compounds, the behavior of which on paper chromatography and on hydrolysis suggested similarity to but not identity with saponarin and its two aglycons. Vitexin and saponaretin have hydroxylated hexyl groups attached to the 8-position of apigenin. The structure of the side chain in vitexin has been recently postulated by two groups[3,4] to take the form of a hydroxylated tetrahydrofuran ring, but that of saponaretin is still a matter of speculation.[2,5]

Continued investigation by paper chromatographic and spectrographic methods of the compound originally designated as spot 0[2] has shown it to be a glycoside of a flavone related to luteolin. It has been named lutonarin. Unlike saponarin and the substance called spot 1, lutonarin is not present in all samples of developing barley. It has been obtained only from plants grown outdoors in soil and only at certain stages of growth. Like saponarin lutonarin yields two aglycons on hydrolysis, first lutonaretin and later lutexin, both of which are convertible to an equilibrium mixture of the two in hot acid solution. Lutonarin and particularly its aglycons are much less stable than saponarin and its aglycons, at least in the dilute solutions used in this work, for they often disappeared completely or produced on chromatography a vivid yellow band as yet unidentified. The compounds are relatively strong acids as they grew yellow on paper or in solution at a characteristically low *p*H. Spots on paper viewed in ultraviolet light in the presence of ammonia show a characteristic orange tint in comparison with the other flavonoids in barley and with luteolin.

That lutonarin and its two aglycons have luteolin-like nuclei is shown by the similarity of their ultraviolet absorption spectra with that of luteolin and the shifts in the spectra obtained with various diagnostic reagents (Table I). Evidence for the ortho dihydroxyl groups on the flavone nuclei include the shifts in the spectra, similar to those of luteolin, with aluminum chloride plus sodium acetate[6] and with boric acid plus sodium acetate[7,8] as well as the green coloration with ferric chloride obtained with a relatively concentrated solution of lutonarin. The unreliable behavior of the spectrum of lutonarin in the presence of sodium acetate resembles that of saponarin[2] and suggests that lutonarin is also a 7-glycoside.[9]

That the compounds possess hydroxylated side chains is postulated from the behavior of the aglycons on paper chromatography coupled with the co-occurrence of lutonarin with saponarin in barley. They run considerably slower than luteolin in organic solvents and much faster in aqueous solvents, facts suggesting greater polarity and possibility for hydrogen bonding. Since the spectra do not suggest further hydroxylation of the aromatic rings and since continued hydrolysis did not lead to the removal of another sugar group by cleavage of a glycosidic link, it seems logical to assume that the extra hydroxyl groups are on a side chain attached by a C—C bond as in vitexin and related compounds. Whether the side chains in the lutonarin series of compounds are the same as in the saponarin series cannot be postulated yet except on biogenetic grounds, but work has been commenced on this problem.

Comparison of lutonaretin and lutexin with orientin, isolated by Hörhammer *et al.* from *Polygonum orientale* and *Spartium junceum L.* and tentatively identified by them as a difficulty hydrolyzable glycoside of luteolin[7] leads to the interesting speculation that one of them is identical with orientin. The spectra, with the exception of the relatively unreliable sodium acetate shift,[2] are very similar, particularly in the case of lutexin (orientin, $\lambda_{max.}$

(1) This investigation was supported in part by a research grant (G-1830) from the National Science Foundation to which grateful acknowledgment is made.

(2) M. K. Seikel and T. A. Geissman, *Arch. Biochem. Biophys.*, **71**, 17 (1957).

(3) W. H. Evans, A. McGookin, L. Jurd, A. Robertson, and W. R. N. Williamson, *J. Chem. Soc.*, 3510 (1957).

(4) L. H. Briggs and R. C. Cambie, *Tetrahedron*, **3**, 269 (1958).

(5) R. C. Cambie, *Chem. & Ind. (London)*, **87** (1959).

(6) L. Jurd and T. A. Geissman, *J. Org. Chem.*, **21**, 1395 (1956).

(7) L. Hörhammer, H. Wagner, and F. Gloggengiesser, *Arch. Pharm.*, **291/63**, 126 (1958); L. Hörhammer, H. Wagner, and H. S. Dhingra, *Arch. Pharm.*, **292/64**, 83 (1959).

(8) L. Jurd, *Arch. Biochem. Biophys.*, **63**, 376 (1956).

(9) T. A. Geissman and U. Kranen-Fiedler, *Naturwissenschaften*, **43**, 226 (1956).

in alcohol 351, 257, with sodium acetate 381, 274, and with boric acid and sodium acetate, 377, 263 mμ).[10a]

Hörhammer mentions the possibility of a C—C bond for his compounds. That it would be possible to break such a bond to some extent under the conditions he used is in part substantiated by the ease with which vitexin was converted to apigenin by Briggs and Cambie.[4,10b]

Lutonarin represents the third type of flavonoid nucleus believed to possess a hydroxylated side chain. Vitexin and related compounds have been discovered lately in an increasing number of plants,[2] but the only other compound reported is the anthocyanin in *Spirodela oligorrhiza*.[11] Recently evidence has been obtained that *Oxalis cernua* contains the luteolin analog.[12]

EXPERIMENTAL

Paper chromatography. In general the methods of chromatography described in the first paper were used.[2] For assay of the relative amounts of the different flavonoids in different samples of plant material one dimensional chromatography of the standard aqueous extracts with BAW (equal volumes of butanol and 27% acetic acid, v/v) as the developing solvent was employed. For following the hydrolysis of the glycoside, 5, 15, and 30% aqueous acetic acid solutions were preferred as the developing solvents, the second giving the best separation of spots. Because the glycoside and its aglycons were extremely unstable in air at room temperature in anything but acid environments, the following precautions were found desirable in obtaining solutions of them by the method of paper chromatographic banding: (a) extracts were banded at once, (b) elutions were done in the presence of minute traces of hydrochloric acid vapor and generally in an atmosphere of nitrogen or carbon dioxide, and (c) extracts and eluates were stored in a refrigerator below 0°.

Ultraviolet absorption spectra. Methods described in the first paper were employed,[2,13] all elutions for spectra being done with 95% alcohol. In addition, the aluminum chloride–sodium acetate shift[6] was determined by adding excess solid sodium acetate to the solution on which the aluminum chloride shift had been determined, and the boric acid–sodium acetate shift[8] by adding to 3 ml. of alcoholic eluate in the spectrophotometer cell 0.75 ml. of saturated boric acid in 95% alcohol and excess solid sodium acetate and by checking the readings until the shift was complete.

Plant material. Barley was grown from commercial seed[2] and from the genotype Atlas 46.[2,14] Plant material containing lutonarin could be obtained only under certain cultural conditions which have not yet been completely worked out so each crop must be assayed as it grows. Only field grown crops contained it. It was obtained in a concentration equal to 70–100% of that of the saponarin in the following crops listed by place, month and age: Los Angeles, May, 2–3 weeks; Wellesley, June–July, 5.5 and 7 weeks; Wellesley, September 4–7 weeks. Younger material grown in Wellesley showed no lutonarin as follows: June–July, 4 and 5 weeks, August, 4–5.5 weeks. Highest concentrations were generally found just before the plants went to seed, but lutonarin disappeared after seeding. It can be developed in the plants after harvesting, but only in a concentration equal to 10–50% of the saponarin concentration, by drying at room temperature, at elevated temperatures or under ultraviolet light, or by standing in water in a refrigerator, the highest concentrations being obtained if the roots are still attached to the leaves.

Isolation and purification of lutonarin. Aqueous extractions of barley followed essentially the method described earlier.[2] For isolation work 10 g. of dried barley (from commercial seed) was extracted five times with 200 ml. of ether. The first two aqueous extracts (200 and 150 ml.), which removed

TABLE I

DATA ON LUTONARIN AND ITS AGLYCONS

	Luton-arin	Luton-aretin	Lutexin	Lute-olin
A. Color tests[a,b]				
NaOH	1Y			Y
H_2SO_4	1Y			Y
$FeCl_3$	G			G
$Pb(OAc)_2$	Y			Y
Alc. Mg-HCl	OPk			PkO
B. R_f values				
BAW[c]	0.39	0.66	0.54	0.86
5% HOAc	0.33	0.19	0.10	0.02
15% HOAc	0.59	0.40	0.19	0.07
30% HOAc	0.70	0.56	0.39	0.24
C. Colors on paper[b]				
Vis. light	1Y	C	C	C
Vis. + NH_3	Y	1Y	1Y	Y
U.V. light	P	P	P	P
U.V. + NH_3	bOY	BYO	YO	GY
D. Absorption spectra, λ_{max} mμ[d]				
95% alc.	353	354	352	352
			Tr. 295	Tr. 295
	270	270	269	Sh. 267
	260	259	258	259
+$AlCl_3$	390	388	388	389[e]
	Sh. 365	363	358	361
	Sh. 295	Sh. 295	297	
	278	279	276	275
		Sh. 266	Sh. 266	
+$AlCl_3$ + NaOAc	422	419	419	418[e]
	Tr. 329	Tr. 330	Tr. 332	329
	277	277	275	274
+H_3BO_3+ NaOAc	380	384	381	373.5[e]
	264	264	264	261
+NaOAc	[f]	410	400	382[e]
		Tr. 320		
		275	270	264.5
+$NaOC_2H_5$	413	415	414	413
		283	276	271

[a] On solutions. [b] C = colorless (perhaps due to low concentration), Y = yellow, P = purple, O = orange, G = green, Pk = pink, B = brown, l = light, p = pale, b = bright. [c] See text. [d] Tr. = barely discernible maximum in a minimum; Sh. = shoulder. [e] These spectra are in the literature, footnotes 6 and 8. [f] Once no change was observed in the spectrum except for a slight increase in absorption at long wave lengths; once the original peak plus one of equal intensity at 418 mμ were observed.

(10a) Footnote added in proof: Recent comparison of orientin (kindly furnished by Dr. Hörhammer) and lutexin by paper chromatography in ten solvent systems showed no separation of spots and hence offers further evidence that the two are identical.

(10b) This work cannot be repeated in this laboratory.

(11) T. A. Geissman and L. Jurd, *Arch. Biochem. Biophys.*, 56, 259 (1955).

(12) T. A. Geissman, private communication.

(13) T. A. Geissman, J. B. Harborne, and M. K. Seikel, *J. Am. Chem. Soc.*, 78, 825 (1956).

(14) Supplied by Dr. C. W. Schaller, Department of Agronomy, University of California, Davis, Calif.

most of the flavonoid material, were finally evaporated *in vacuo* to 25 ml. giving a solution approximately ten times as concentrated as the standard solution.[2] From this solution crude lutonarin was isolated by banding on Whatman #3 filter paper with BAW (see earlier) as the developing solvent and, after elution, was purified from traces of the other flavonoids by rebanding with 30% acetic acid, once for hydrolysis work, twice for spectral work. The color tests, chromatographic data and ultraviolet absorption spectral data obtained from the purified eluate are given in Table I.

Isolation and purification of lutonaretin and lutexin. Lutonarin was hydrolyzed by 1*N* hydrochloric acid as previously described,[2] the reaction being complete in 20–30 hr. At that time the ratio of lutonaretin (the aglycon which formed first) to lutexin was approximately 2:1, but refluxing for 4 days gave a 1:1 ratio. After the methanol had been volatilized, the reaction mixture was neutralized to *p*H 5 with solid sodium acetate. The two aglycons were separated by banding with 15% acetic acid and were eluted with 50% methanol. Each was purified by rebanding with BAW. Chromatographic and spectral data obtained on solutions of these compounds are given in Table I, and the results are compared with results on luteolin obtained simultaneously or recorded in the literature. Co-chromatography with luteolin showed separation of spots in all four solvents.

Interconversion of the aglycons. Solutions of both purified aglycons were subjected to the usual hydrolytic conditions[2] for approximately one day. Paper chromatographic studies of the resulting solutions with four solvents (Table I) showed that each aglycon had been converted in part into the other; the ratio of lutonaretin to lutexin was 1:1 from lutonaretin, 1:2 from lutexin.

WELLESLEY 81, MASS.

[CONTRIBUTION FROM ORGANIC CHEMICALS DIVISION, MONSANTO CHEMICAL CO.]

Alcoholysis of Alkyl Benzyl Esters of Phthalic Acid[1]

LOUIS O. RAETHER AND HARRY R. GAMRATH

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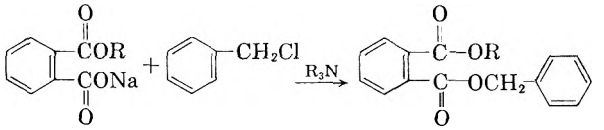
Alkyl benzyl phthalate esters of high purity are not readily prepared by simple conventional methods, especially when the alkyl group contains eight or more carbon atoms. However, a smooth procedure for the preparation of these unsymmetrical esters has been found, involving alcoholysis of the more easily prepared lower alkyl benzyl phthalates with higher molecular weight alcohols. In this alcoholysis reaction the benzyl group exhibits a surprising immobility toward displacement, even if the displacing alcohol has a boiling point higher than that of benzyl alcohol. A mechanistic theory is advanced to explain this immobility.

Methods of preparation of esters date back to the early days of organic chemistry, and one would anticipate little novelty in the reactions of alcohols and acids or in esterification techniques involving alcoholysis or acidolysis. Yet, in our study of the alcoholysis of alkyl benzyl *o*-phthalates, we have observed a behavior anomalous to classical description in that alcoholysis of unsymmetrical diesters does not unequivocally lead to displacement of the lower boiling alcohol by a higher boiling alcohol.

For some time we have been interested in the synthesis of unsymmetrical esters of phthalic acid, particularly those containing a benzyl moiety. These materials have utility in the plasticization of poly(vinyl chloride); this being particularly true of the higher alkyl benzyl phthalates. Preparation of some of these esters by conventional means can be extremely cumbersome. An obvious method of preparation for such esters would involve reaction between the sodium salt of the selected alkyl acid phthalate with benzyl chloride, in the presence of an amine catalyst.[2]



(1) Presented in part before the Division of Organic Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958.

(2) Reid, U. S. Patent 1,554,032 (September 15, 1925).

This method is not entirely feasible, however, with the higher alkyl benzyl phthalates, due to the gross insolubility of the sodium alkyl phthalate in many of the common organic solvents. Nonetheless, it is possible to obtain a small (30–40%) yield of the desired unsymmetrical ester if one utilizes the potassium salt of the acid ester and a several-fold excess of the alcohol used in preparation of the alkyl acid phthalate. Preparation of the lower alkyl benzyl phthalates does not result in this low yield, however. Thus, methyl, ethyl, or butyl benzyl phthalates can be prepared smoothly and in excellent yield from the sodium or potassium salt of the acid ester and benzyl chloride. The preparation of the unsymmetrical esters by use of benzyl alcohol and the aliphatic alcohol is also contraindicated, since, assuming equal rates of reaction of the two alcohols, one obtains a statistical mixture of the three possible esters (25% dialkyl phthalate, 50% alkyl benzyl phthalate, and 25% dibenzyl phthalate). Separation of the pure unsymmetrical ester from the other two components is often difficult.

It occurred to us that it should be possible to take advantage of the relative ease of preparation of the lower alkyl benzyl phthalates and utilize these materials as a starting point in the synthesis of the higher alkyl benzyl phthalates. It remained, therefore, only to displace the lower alkyl group, which should be easily carried out by the base-catalyzed alcoholysis with the desired alcohol. In the case of

TABLE I

ALCOHOLYSIS USING ALCOHOLS BOILING LOWER THAN BENZYL ALCOHOL

Exchange Alcohol	Catalyst % Conc. on Ester	Resulting Ester d_{25}^{25}	Resulting Ester Theory yield	% of Theory ROH Removed[c]	ROH Removed d_{25}^{25}	ROH Removed Boiling range
2-Ethylhexanol[a]	NaOH 1.6	1.0066	90%	89	0.8104	115–119
Isooctanol[a]	NaOH 1.2	1.0056	88%	90	0.8111	115–118
p-Methylcyclohexanol[a]	$NaOCH_3$ 0.7	1.1116	85%	94	0.8108	115–117
2(2-Ethylhexoxy) ethanol[a]	$NaOCH_3$ 0.65	1.0630	90%	92	0.8101	112–117
2-Ethylhexanol[b]	$NaOCH_3$ 0.60	1.0055	92%	95	0.776	77–81
2-Octanol[b]	$NaOCH_3$ 0.65	1.0365	93%	94	0.778	77–81

[a] The starting ester in these experiments was benzyl *n*-butyl phthalate. [b] The starting ester in these experiments was benzyl ethyl phthalate. [c] Reaction time in all cases was 3–4 hr., reaction conditions at end of alcoholysis were 160°/25 mm.

TABLE II

ALCOHOLYSIS WITH ALCOHOLS BOILING HIGHER THAN BENZYL ALCOHOL

Exchange Alcohol[c]	Catalyst % Conc. on Ester	Resulting Ester d_{25}^{25}	Resulting Ester Theory yield	% of Theory ROH Removed[d]	ROH Removed d_{25}^{25}	ROH Removed Boiling range
Isodecanol (oxo),[a] b.p. 216–220°	$NaOCH_3$ 0.7	1.0402	93.2%	93	0.8124	115–118
Tridecyl alcohol[a] (oxo), b.p. 262°	NaOH 1.2	1.0238	92%	93	0.8103	115–118
n-Decanol,[a] b.p. 233°	$NaOCH_3$ 0.7	1.0306	94%	93.5	0.8103	115–118
Br. Octadecanol,[a,e] b.p. 200°/15 mm.	$NaOCH_3$ 0.65	0.9940	92%	94	0.8110	115–118
Oleyl alcohol,[b] b.p. 210°/15 mm.	$NaOCH_3$ 0.65	0.9839	85%	91	0.8105	115–111
Isodecanol (oxo)[b]	$NaOCH_3$ 0.8	1.0410	91%	95	0.8100	115–118
Tridecyl alcohol[b] (oxo)	$NaOCH_3$ 0.8	1.0241	89%	93	0.8106	115–188

[a] Concentration of exchange alcohol in these experiments was 1.2 mol./mol. of starting ester. [b] Concentration of exchange alcohol in these experiments was 1.5 mol./mol. of starting ester. [c] Starting ester in all cases was benzyl *n*-butyl phthalate. [d] Reaction time in all cases was 3–4 hr., conditions at end of alcoholysis were 160°/25 mm. Hg in all cases. [e] 2,2,-4,9,11,11-Hexamethyl-1-dodecanol.

benzyl *n*-butyl phthalate it was assumed that the butyl group would be replaced preferentially, if the displacing alcohol had a boiling point suitably higher than that of the displaced alcohol, but lower than that of benzyl alcohol, to form little or no symmetrical ester. Consequently, benzyl *n*-butyl phthalate was treated with various commercially available alcohols from C_8 through C_{10} in the presence of a variety of alkaline catalysts. In all cases, the desired alkyl benzyl phthalates were produced smoothly and in good yields (87–95%). The results of these alcoholysis reactions are shown in Table I. During the course of this work certain alcohols with boiling ranges near or higher than the boiling point of benzyl alcohol were utilized. In none of these experiments was there any evidence of even a small portion of the benzyl alcohol having been displaced by alcoholysis. It appeared at this point that the benzyl group exhibited a definite immobility in the reaction. An attempt was made, therefore, to replace both the lower alkyl and benzyl groups in the benzyl alkyl phthalates, by using an exchange alcohol with a boiling point higher than that of benzyl alcohol (b.p. 205°). Five such alcohols were readily available, namely isodecanol (oxo), b.p. 216°, tridecanol (oxo), b.p. 264°, octadecenol (oleyl), b.p. 210°/15 mm., *n*-decanol, b.p. 233°, and a branched octadecanol, b.p. 200°/15 mm. In none of these cases was benzyl alcohol recovered, either with the displaced alcohol or from the reaction mass, as shown in Table II. This immobility of the benzyl group toward displacement by the displacing alcohol persisted despite increased catalyst concentration, higher reaction temperature, or an increase in the molar concentration of the displacing alcohol. The absence of benzyl alcohol in the displaced alcohols was determined by means of the ultraviolet spectra of these materials.

EXPERIMENTAL

The reaction vessel consisted of a 1-l., 3 necked flask fitted with a stirrer, 6-in. Vigreux column, with variable take-off still head, thermometer well, and a Glas-Col mantle for heating. In experiments in which the two alcohols had less than 20° difference in boiling points, a 500 mm. long, 20-mm. diameter glass-helices packed column was used to remove the displaced alcohol. In all cases the alcoholysis of the lower alkyl benzyl phthalates followed a standard reaction scheme, with only minor variations, as dictated by the boiling point and molecular weight of the displacing alcohol. A typical reaction sequence will be described here, involving the alcoholysis of benzyl *n*-butyl phthalate with isodecanol (oxo).

To the reaction vessel, as described above, were charged 312.4 g. (1 mol.) of benzyl *n*-butyl phthalate,[3] 165.9 g. (1.05 mol.) isodecanol, and 2.5 g. (.046 mol.) of sodium methylate. Heat was then applied to the reaction vessel at such a rate that the temperature of the reaction mass was raised to 135–145°, over a period of 30 min. When this temperature was attained, the system was slowly evacuated by means of a water aspirator, until the displaced alcohol began to distill forward at a steady rate (usually 100–200 mm. Hg). As the displaced alcohol removal began to slow, pressure was further reduced so that forward distillation began again. The vapor temperature was controlled by regulation of the reflux ratio, if it became apparent that some exchange alcohol was distilling with the lower molecular weight displaced alcohol. The pressure was gradually reduced, so that the final conditions of 160°/25 mm. were usually obtained about 3 hr. following initial removal of the displaced alcohol. When removal of the displaced alcohol was completed, the reaction mass was cooled under vacuum to room temperature. The system was vented to the atmosphere and 250 cc. water was added. The displaced alcohol was analyzed by examination of its physical properties and ultraviolet spectrum, and found to be pure *n*-butyl alcohol.

The water-oil mixture was heated to 70–75°, with agitation and stirred at this temperature for 15 min. The heterogeneous mixture was allowed to settle into two phases, and the heavier, aqueous, layer was removed from the oil layer. Another 250 cc. portion of water was then added to the oil, and washing as described above was carried out. The aqueous layer from the first wash was acidified to *p*H 2 with 75% sulfuric acid to neutralize the catalyst and recover any acid constituents present in the wash as sodium salt. By this neutralization there was recovered 3.3 g. of *o*-phthalic acid (m.p. 190–193° d., neut. equiv. 82), indicating a small amount of ester hydrolysis had taken place during the removal of the alkaline catalyst.

Following the two washes described above, the oil layer was heated to 135–140° under 75 mm. Hg vacuum, and live steam passed into the mass *via* a subsurface entrance tube. This operation was continued, until the volume of distillate collected equaled the volume of the crude reaction mass. The (upper) organic layer from the steam distillate weighed 11.1 g. after drying over Drierite. Analysis of the ultraviolet spectrum of this material showed it to contain 18.4% benzyl alcohol and 81.6% decyl alcohol. The quantity of benzyl alcohol obtained here corresponds to the quantity of phthalic acid recovered from the acidification of the first water wash. The source of benzyl alcohol here, therefore, is due to hydrolysis rather than alcoholysis. The alcohol-free ester was then further washed first with alkali, then with water, and dried. By this procedure, there was obtained 368.1 g. of neutral ester, specific gravity at 25/25° 1.037, refractive index 1.5135.

Identification of the product of the alcoholysis of benzyl *n*-butyl phthalate was carried out by (1) determination of boiling range to ascertain whether a mixture of esters was present or if a relatively pure benzyl isodecyl phthalate had been prepared and (2) hydrolysis of the finished ester with subsequent qualitative and quantitative identification of the alcohols thus separated.

Distillation was carried out under 0.1-mm. Hg with a short punched column to prevent entrainment. Under these conditions 95% of the material charged boiled between 198° and 203° at 0.1 mm. From these data we conclude that the neutral ester obtained by alcoholysis is not a mixture of a lower with a higher boiling ester.

Hydrolysis of benzyl isodecyl phthalate involved heating the ester at 140–150° at atmospheric pressure with a 200% excess of 50% (aq.) sodium hydroxide. Steam was passed through this mixture until no more alcohol was distilled with the steam distillate, this operation required 12 hr. under these conditions. The steam distillate was saturated with sodium carbonate and the supernatant organic layer separated and dried over Drierite. The remainder of the steam distillate was saturated with sodium carbonate and extracted with ether to remove any alcohol in solution. The ether was evaporated and the residual alcohol added to that separated from the steam distillate. The aqueous solution of the sodium salt of phthalic acid remaining after the hydrolysis was acidified with sulfuric acid to *p*H 2 and the precipitated phthalic acid filtered and dried to constant weight.

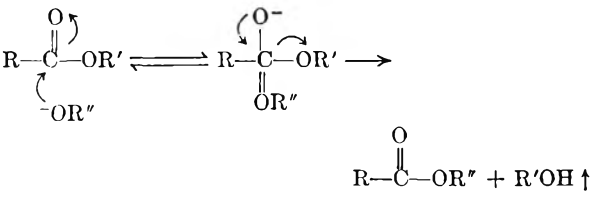
The alcohols were analyzed by ultraviolet spectrophotometry and the spectra compared to synthetic mixtures of benzyl and isodecyl alcohol. The characteristic absorption of benzyl alcohol at 285 mμ was used in this analysis. From these data, the ester before hydrolysis could be shown to contain 51 mol. % isodecyl alcohol and 49 mol. % benzyl alcohol, indicating a relatively pure unsymmetrical ester was formed by the alcoholysis.

In the majority of the experiments, lower alkyl benzyl phthalates were used as the starting esters. It remained to be shown, however, that the immobility of the benzyl group persisted despite an increase in the size of the alkyl chain in the unsymmetrical ester. This was shown to be the case by alcoholysis of benzyl 2-octyl phthalate and benzyl isodecyl phthalate, which were subjected to alcoholysis with tridecyl alcohol (Table III). The displaced alcohol was again identified by its physical properties and found to be free of benzyl alcohol. In the case of alcoholysis of benzyl isodecyl phthalate with tridecyl alcohol, both the alcohol to be displaced and the displacing alcohol had boiling points higher than that of benzyl alcohol. Even under these conditions the alcohol displaced showed no benzyl alcohol to be present, indicating the preferential removal of an aliphatic alcohol although its boiling point is higher than benzyl alcohol.

In experiments in which an attempt was made to remove benzyl alcohol, the charge of the exchange alcohol was increased to 1.5 moles per mole of neutral ester. With this increased charge of alcohol, benzyl n-butyl phthalate was treated with three such alcohols, namely isodecyl (oxo) alcohol, tridecyl (oxo) alcohol, and oleyl alcohol. As shown in Table II the benzyl group exhibited the same immobility despite these more favorable conditions for displacement.

DISCUSSION

The resistance of the benzyl moiety toward displacement by the exchange alcohol is somewhat unexpected and may be due to several factors. Base-catalyzed alcoholyses are considered to proceed through the following sequence[4]:



The driving force in the reaction is, of course, removal of the more volatile alcohol, thereby displacing the equilibrium toward the desired ester.

Several reasons for the lack of activity of the benzyl group in this reaction may be postulated. This lack of activity, for instance, may be due to formation of a stable anion, as follows:

(3) Trade-name Santicizer 160, Monsanto Chemical Co.

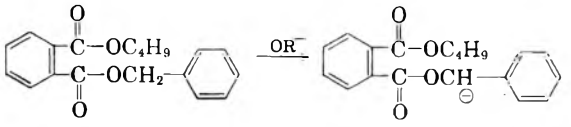
(4) Alexander, *Ionic Organic Reactions*, John Wiley and Sons, New York, 1950, p. 231.

TABLE III

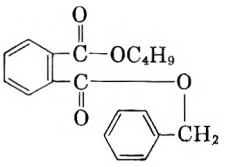
ALCOHOLYSIS OF HIGHER MOLECULAR WEIGHT ALKYL BENZYL PHTHALATES

Starting Ester	Exchange Alcohol[a]	Catalyst % Conc. on Ester	Resulting Ester D_{25}^{25}	Resulting Ester Theory yield	% of Theory ROH Removed[b]	ROH Removed n_D^{25}
Benzyl 2-octyl phthalate	Tridecyl (oxo) alcohol	$NaOCH_3$, 0.8	1.0240	87	88.2	1.4292[c]
Benzyl isodecyl phthalate	Tridecyl (oxo) alcohol	$NaOCH_3$, 0.9	1.0232	81.6	82.8	1.378[d]

[a] Exchange alcohol present in 1.2 mol. concentration per mol. of starting ester. [b] Reaction time in both cases was 4 hr., reaction conditions at end of alcoholysis was 185°/25 mm. in both cases. [c] n_D^{25} pure 2-octanol, 1.4245. [d] n_D^{25} commercial isodecyl(oxo)alcohol, 1.374.



It is entirely conceivable that the contribution of species like the anion shown above is pronounced in the reaction medium. Attack on this species by the alkoxide ion of the exchange alcohol should not result in attack at the carbonyl group of the benzyl ester because the required polarization would be inhibited by the already strong nucleophilic center about the benzyl anion. In addition, this anion derives resonance stabilization from the neighboring phenyl nucleus. This same inhibition to polarization of the carbonyl carbon of the benzyl ester may also be due to an inductive steric effect of the ring:



Thus, in this case the presence of the highly negative aromatic ring may, in part, negate the necessary polarization of the benzyl ester carbonyl carbon. Since this polarization is inhibited by either of the two factors already mentioned, the necessary attack by the alkoxide ion at the carbonyl carbon of the benzyl ester, which is a prerequisite of alcoholysis under these conditions, is inhibited, thereby resulting in the removal of the alkyl group only.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

Compounds Related to Isopimpinellin

W. J. HORTON AND E. G. PAUL[1]

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1,2,3,5-Tetramethoxybenzene (III) has been converted to 2,3-dihydroisopimpinellin in a number of steps, two of which employ selective cleavage of a methoxyl group. Acetylation of 4,6,7-trimethoxy-2,3-dihydrocoumarone (VIII) to dihydrokhellinone constitutes an improved method for this compound, an intermediate in the synthesis of khellin. The expected dehydrogenation of 2,3-dihydroisopimpinellin with a number of reagents failed to produce more than spectroscopic amounts of isopimpinellin (I).

The synthesis of furanocoumarins may employ either the appropriate coumarin or a benzofuran. Most of the published work has chosen the coumarin approach[2] due to the activity of the furan ring or the difficulty in dehydrogenation where 2,3-dihydrofuran is used. This latter problem was solved in a synthesis of khellin,[3] a furanochromone, by *N*-bromosuccinimide (NBS) dehydrogenation of an intermediate. Psoralene and related compounds have been produced by dehydrogenation over a palladium-carbon catalyst.[4]

Due to the advantages involved in benzenoid substitution in 2,3-dihydrobenzofuran, we have attempted this approach to isopimpinellin (I).[5] The synthesis was terminated when 2,3-dihydro-I failed to dehydrogenate by any of the variety of methods tried.

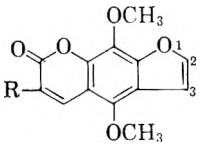
(1) From the Doctoral dissertation of E. G. Paul, National Science Foundation Cooperative Research Fellow, 1959–60.

(2) F. M. Dean, *Progr. in Chem. Org. Nat. Prod.*, 9, 225 (1952).

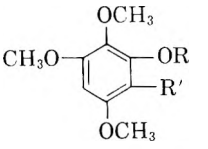
(3) T. A. Geissman and T. G. Halsall, *J. Am. Chem. Soc.*, 73, 1281 (1951).

(4) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, 72, 1514 (1950).

(5) (a) Isopimpinellin has been obtained recently from xanthotoxin, M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, 24, 523 (1959), and earlier (b) from bergapten, F. Wessely and F. Kallab, *Monatsh. Chem.*, 59, 161 (1932).



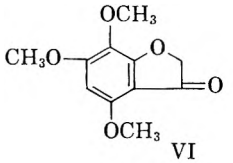
I. R = H
II. R = CO_2H



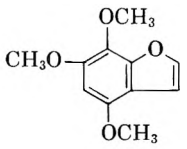
III. R = CH_3; R′ = H
IV. R = CH_3; R′ = CCH_2Cl (=O)

V. R = H; R′ = CCH_2Cl (=O)

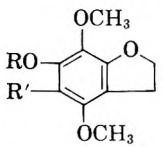
In the preparation of VI from III, the use of 1,3-bisbenzyloxy-2,5-dimethoxybenzene[3] was circumvented by the chloroacetylation of III, selective cleavage of IV by means of hydrogen bromide in acetic acid[6] to yield V and cyclization of V with sodium acetate.[7] Treatment of the coumaranone VI with lithium aluminum hydride gave the coumarone VII (77%) which was reduced over a palladium-carbon catalyst (96%) to give VIII. Reduction of the acetate of VI over platinum also gave VIII. The most convenient process was found to be the direct hydrogenation of VI over Raney nickel to VIII (89%).



VI



VII



VIII. R = CH_3; R′ = H
IX. R = CH_3; R′ = CHO
X. R = H; R′ = CHO
XI. R = H; R′ = CCH_3 (=O)

The dihydrobenzofuran, VIII, reacted with *N*-methylformanilide to yield IX which was selectively cleaved to X by aluminum chloride. Condensation of X with cyanoacetic acid and hydrolysis of the nitrogenous product gave 2,3-dihydro-II. Decarboxylation[8] using sodium bisulfite with pyridine gave dihydro-I.

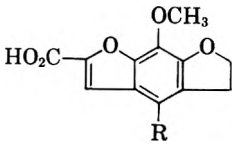
The conversion of VIII to 2,3-dihydrokhellinone in one step by acylation using boron trifluoride with simultaneous cleavage of the methoxyl at position 6 supports the proposed structure of VIII. This also constitutes a modification of Geissman's total synthesis of khellin in that dihydrokhellinone has previously been converted to khellin.[3]

(6) W. J. Horton and J. T. Spence, *J. Am. Chem. Soc.*, **77**, 2894 (1955).

(7) R. L. Shriner, E. J. Matson, and R. E. Damschroder, *J. Am. Chem. Soc.*, **61**, 2322 (1939).

(8) R. Adams and J. Mathieu, *J. Am. Chem. Soc.*, **70**, 2120 (1948).

Although dihydrokhellinone (as acetate) yields khellinone when treated with NBS,[3] the reagent on attempted dehydrogenation of dihydro-I gave 6-bromo-2,3-dihydro-I (52%), as did bromine in chloroform. The nature of the bromo compound was shown by conversion by base to a dihydrofuranocoumaric acid, XII.[9]



XII. R = OCH_3
XIII. R = H

Experiments with chloranil, lead tetraacetate, selenium dioxide, or palladium-carbon on dihydro-I gave only unreacted starting material with the last giving a minute amount of product having the ultraviolet spectra of isopimpinellin (I).[10] Similarly, 6-bromo- or 6-carboxy-2,3-dihydro-I failed to dehydrogenate with NBS. Financial support from the University Research Fund is gratefully acknowledged.

EXPERIMENTAL[11]

2,3,4,6-Tetramethoxy-α-chloroacetophenone (IV). To a suspension of 70 g. of freshly fused zinc chloride in 250 ml. of anhydrous ether was added slowly with stirring 98 g. (0.494 mol.) of 1,2,3,5-tetramethoxybenzene (III) and 30.3 g. (0.401 mol.) of chloroacetonitrile. Dry hydrogen chloride was passed slowly through the suspension while stirring, causing refluxing of the ether. Within 1 hr. all material in the flask had solidified to a yellow mass. Hydrogen chloride addition was continued for an additional 5 hr. and the mixture was allowed to stand overnight.

The ether was decanted from the solids and the solids were washed with dry ether. The solids were then taken up in 1 l. of water and the aqueous solution was extracted three times with ether. The aqueous solution was warmed on the water bath for 1 hr. and the oil which separated was taken up in ether and benzene, dried, and the solvents were distilled. The residual oil IV was used directly in the subsequent step.

For analysis the material from a subsequent run was distilled, b.p. 162–165° (1 mm.) and then recrystallized from petroleum ether (b.p. 65–110°). Colorless clusters of rods, m.p. 55.6–56.4° were obtained.

Anal. Calcd. for $C_{12}H_{15}O_6Cl$: C, 52.46; H, 5.50. Found: C, 52.90; H, 5.66.

The ether extracts, combined with the ether decanted from the solids above, were distilled, and 20 g. of starting material was recovered. The residue from the distillation of III solidified and on recrystallization from ethanol, 0.89 g. of large colorless needles m.p. 152–153° was obtained.

(9) A bromo compound was similarly obtained from 2,3-dihydroxanthotoxin. M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **23**, 589 (1958). It seems likely that this compound is 6-bromo-2,3-dihydroxanthotoxin in that these authors converted the compound by means of base to a compound, $C_{12}H_{10}O_5$, for which we suggest the structure XIII.

(10) F. Wessely and J. Kotlan, *Monatsh. Chem.*, **86**, 430 (1955).

(11) Melting points of analytically pure materials are corrected.

Further crystallization from ethanol gave material melting at 152.1–152.9°. The compound contained chlorine but no nitrogen. It melted with depression when mixed with V or VI.

Anal. Calcd. for $C_{11}H_{13}O_5Cl$: C, 50.68; H, 5.03. Found: C, 51.03; H, 5.11.

This material proved to be identical to *2,4,6-trimethoxyphenyl chloroacetate*. *2,4,6-Trimethoxyphenol*,[12] warmed with chloroacetyl chloride, gave after crystallization from alcohol, long colorless needles m.p. 152.0–153.1°.

Anal. Calcd. for $C_{11}H_{13}O_5Cl$: C, 50.68; H, 5.03. Found: C, 50.63; H, 4.99.

Mixed with the above Hoesch by-product, the sample melted at 151–153°.

2-Hydroxy-3,4,6-trimethoxy-α-chloroacetophenone (V). The crude IV above was allowed to stand in a solution of 1.4 l. of acetic acid and 285 ml. of 30% hydrogen bromide–acetic acid at room temperature for 4.5 hr.[6] Short thick yellow rods separated after 1 hr. The solution was poured into 4 l. of ice and water, filtered, and used directly in the next step.

Recrystallization of a sample from benzene produced yellow rods m.p. 165.8–167.2°. It gave a brown color in alcohol with ferric chloride.

Anal. Calcd. for $C_{11}H_{13}O_5Cl$: C, 50.68; H, 5.03. Found: C, 50.20; H, 4.87.

4,6,7-Trimethoxycoumaranone (VI). The unpurified V was refluxed on the steam bath for 2 hr. in 300 ml. of ethanol containing 33 g. of anhydrous sodium acetate. The solution was poured into 2 l. of ice and water and allowed to stand overnight at 5°. On filtration, 42.4 g. (37% from III; 48% from unrecovered III) m.p. 142–149° was obtained. Recrystallization from ethanol gave 36.3 g. of pale tan needles, m.p. 153–155°; reported[7] m.p. 153.5–154.5°.

The *acetate* of VI was prepared by heating 4.5 g. with 8.2 g. of acetic anhydride and 1.6 g. of pyridine on the water bath for 2 hr. After standing overnight, the solids were dissolved by warming on the steam bath. The solution, poured into 150 ml. of ice and water gave 2.4 g. (45%; crystallized from 1:2 ethanol water) of orange-red crystals, m.p. 93–96°. Further recrystallization from ethanol water gave long amber needles, m.p. 97.4–98.0°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.85; H, 5.36.

4,6,7-Trimethoxybenzofuran (VII). Five g. of VI was added in portions to a stirred suspension of 2 g. of lithium aluminum hydride in 200 ml. of anhydrous tetrahydrofuran. The reaction mixture was stirred for an additional 15 min., refluxed with stirring for 30 min., cooled, and treated with wet ether and water. After acidification with dilute hydrochloric acid, the solution was saturated with salt and the aqueous layer was extracted with ether and with benzene. The combined ether, benzene, and THF solution was washed with saturated salt and dried over sodium sulfate. The residual oil after distillation of the solvent, was sublimed at 95° (0.5 mm.) for 19 hr. yielding 3.58 g. (77%), m.p. 45–49°. Continued sublimation gave only starting material. Recrystallization from aqueous methanol and sublimation gave colorless rods, m.p. 49.0–50.2°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.59; H, 5.74.

4,6,7-Trimethoxy-2,3-dihydrobenzofuran (VIII). (a) Hydrogenation of 3.45 g. of VII over 1 g. of 5% palladium carbon in 50 ml. of ethanol at slightly above atmospheric pressure gave, after crystallization from 1:1 aqueous methanol, 3.35 g. (96%) of colorless rods, m.p. 64–65°. Further crystallization from this solvent and sublimation gave rods, m.p. 64.5–65.1°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.13; H, 6.66.

(b) A solution of 11.2 g. of VI in 150 ml. of absolute ethanol with 5 g. of W-2 Raney nickel hydrogenated for 6 hr. at 95° under 400 lb. initial pressure gave 9.38 g. (89%) of VIII m.p. 64–65°. (c) The acetate of VI (0.67 g.) in 50 ml. of acetic acid containing 250 mg. of platinum oxide consumed 2 mol. of hydrogen when shaken at room temperature and slightly above atmospheric pressure. The product (0.25 g.) from 1:1 aqueous methanol melted at 62–65°, unchanged when mixed with material from (a).

4,6,7-Trimethoxy-5-formyl-2,3-dihydrobenzofuran (IX). The reagent was prepared by combining 9.1 g. of phosphorus oxychloride and 8.1 g. of *N*-methylformanilide and allowing it to stand at room temperature for 30 min. Ten g. of VIII was then added in portions with swirling after each addition. Occasional swirling in water was required to keep the solution cool. It was then stirred for 3 hr. at room temperature, allowed to stand overnight, and poured into 150 ml. of water. After stirring for 30 min., the solution was extracted with ether and with benzene, the ether benzene was washed with aqueous sodium bicarbonate, dried over sodium sulfate, and the solvents were removed by distillation. The residual amber oil was used below without further purification.

The *semicarbazone* of IX formed colorless needles from ethanol m.p. 194.5–196.0°.

Anal. Calcd. for $C_{13}H_{17}O_5N_3$: C, 52.87; H, 5.80. Found: C, 53.14; H, 5.91.

4,7-Dimethoxy-6-hydroxy-5-formyl-2,3-dihydrobenzofuran (X). The crude oil IX in 125 ml. of anhydrous ether was treated with a solution of 6 g. of anhydrous aluminum chloride in 125 ml. of dry ether and refluxed on the water bath for 9 hr. After standing overnight at room temperature the green complex was decomposed with dilute hydrochloric acid. The product was collected by extraction with benzene and with ether, the benzene ether was washed with saturated salt solution, and the solvents were removed by distillation. The solution of the residue in hot ethanol (carbon) gave on cooling 6.83 g. (64% from VIII), m.p. 115–120°. Further crystallization from ethanol water and benzene–petroleum ether (90–120°) gave yellow needles, m.p. 118.3–118.9°. A deep red-brown color was obtained with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 58.92; H, 5.40. Found: C, 59.25; H, 5.53.

2,3-Dihydro-6-carboxyisopimpinellin. A suspension which contained 40 ml. of ethanol, 75 ml. of 20% aqueous sodium hydroxide, 6.8 g. of X, and 9.7 g. of cyanoacetic acid was warmed on the steam bath for 30 min. during which time the solids dissolved. After standing overnight at room temperature, the solution was poured into 200 ml. of 6*N* hydrochloric acid and diluted to 750 ml. This was refluxed with stirring for 40 min., cooled, and filtered. The yellow solid obtained weighed 7.60 g. (91%), m.p. 278–287°. Crystallization from ethanol produced microscopic yellow needles, m.p. 292–293.5°.[13]

Anal. Calcd. for $C_{14}H_{12}O_7$: C, 57.54; H, 4.14. Found: C, 57.35; H, 4.37.

2,3-Dihydroisopimpinellin (*dihydro-I*). A suspension of 2.2 g. of the above carboxylic acid in 20 ml. of 25% sodium bisulfite, 1 ml. of pyridine, and a trace of copper powder[8] was warmed on the water bath with occasional stirring until the solids dissolved and the yellow color had disappeared. After stirring for an additional 5 min. and boiling over a burner for 30 sec., 17 ml. of 50% potassium hydroxide was added dropwise causing the solution to boil. The solution was then boiled for 10 sec., cooled in an ice bath, and acidi-

(12) *2,4,6-Trimethoxyphenol* was prepared in 48.4% yield from III according to the method of C. D. Hurd and H. E. Winberg, *J. Am. Chem. Soc.*, 64, 2085 (1942). It formed colorless long thin prisms from cyclohexane-benzene, m.p. 61.9–63.5°. Alcoholic ferric chloride gave a brown color. *Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 59.14; H, 6.62. The *benzoate* formed colorless plates from methanol m.p. 97.0–98.4°. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.65; H, 5.60. Found: C, 66.78; H, 5.69.

(13) Taken on a Fisher-Johns Melting Point Block.

fied with concentrated hydrochloric acid. After cooling at −5° for 2 hr., filtration gave material which was crystallized from 250 ml. of 25% aqueous ethanol by concentration of the solution until the solid appeared. In this manner 1.48 g. (79%) of nearly colorless long needles m.p. 145–153° was obtained. Recrystallization from ethanol water gave long colorless needles, m.p. 156.6–157.4°; λ_{max}^{alc} 253, 262, 326 mμ (log ε, 3.82, 3.83, 4.17).

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.88. Found: C, 63.19; H, 4.86.

6-Bromo-2,3-dihydroisopimpinellin. (a) A solution of 1.0 g. of dihydro-I and 2.1 g. of bromine in 35 ml. of chloroform was evaporated to dryness on the steam bath. The residual solid in 500 ml. of ethanol was concentrated to the crystallization point. On cooling, 1.15 g. (87%) of light tan needles, m.p. 223–230°, was obtained. Crystallization from ethanol and again from benzene gave small light yellow needles, m.p. 231.2–233.0°.

Anal. Calcd. for $C_{13}H_{11}O_5Br$: C, 47.73; H, 3.39; Br, 24.43. Found: C, 47.73; H, 3.66; Br, 25.0.

The bromo compound was not effected by stirring with potassium iodide in acetone, by refluxing in ethanolic sodium acetate nor by refluxing in dimethylaniline. (b) After 90 min. refluxing of a solution of 250 mg. of dihydro-I in 10 ml. of dry carbon tetrachloride containing 0.09 ml. of pyridine, 200 mg. of NBS, and a trace of benzoyl peroxide, the cooled solution was filtered and the solid product was recrystallized to produce 130 mg. (52%), m.p. 227–232°, undepressed when mixed with material in (a).

6-Carboxy-4,8-dimethoxy-2,3-dihydro[1,2-b,5,4-b']difuran (XII). Heating a mixture of 350 mg. of 6-bromo-2,3-dihydro-I and 20 ml. of sodium hydroxide for 90 min. on the steam bath gave, after cooling and acidification with hydrochloric acid, a yellow solid. This was redissolved in 5% aqueous sodium bicarbonate, reprecipitated with dilute sulfuric acid, and crystallized from aqueous ethanol to give 220 mg. (77%) of long yellow needles, m.p. 251–253°. Further crystallization from ethanol water gave light yellow needles, m.p. 247.0–247.2° (sealed cap).

Anal. Calcd. for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.31; H, 4.90.

Attempted dehydrogenations. (a) A solution of 100 mg. of dihydro-I and 110 mg. of chloranil in 10 ml. of xylene was refluxed on a sand bath for 12 hr. On cooling, the crystals which appeared melted, after purification with 25% ethanol water, at 157–159°, undepressed with the original material. From the xylene filtrate only dihydro-I could be found. The total recovery was 47 mg. (b) Dihydro-I (100 mg.) with 200 mg. of lead tetraacetate in 10 ml. of dry benzene at the reflux point for 30 hr. gave a yellow solid which was purified with difficulty. Crystallization from ethyl acetate gave an orange colored material, m.p. 125–145°, which was brought to m.p. 145–150° by crystallization from ethanol water and did not depress the melting point of the original compound. (c) Heating 148 mg. of dihydro-I with 150 mg. of 30% palladium carbon under nitrogen at 250° for 10 min. and at 320° for 5 min. gave material which melted at 141–145° after three crystallizations from ethanol and melted at 130–133° when mixed with 2,3-dihydroisopimpinellin. This material in ethanol gave maxima at 223, 240, 248, 266–271, and 311 mμ and nearly identical values in dioxan; reported for isopimpinellin[10] in dioxan, 242, 250, 268, and 308 mμ. Larger amounts of catalyst, temperatures above 250°, and extended time resulted in noncrystallizable material. Repeated chromatography on alumina with removal by means of 0.5–3% *tert*-butyl alcohol in benzene did not change the melting point of material melting at 138–142°. (d) The action of 45 mg. of selenium dioxide with 94.5 mg. of dihydro-I in 10 ml. of acetic anhydride refluxed for 2 hr. lead to the recovery of 63 mg. of material, m.p. 155–158°, with an ultraviolet spectra identical to dihydro-I.

2,3-Dihydrokhellinone. A stream of boron trifluoride was passed into a solution of 2.63 g. of VIII in 50 ml. of acetic acid and 3 ml. of acetic anhydride. The temperature was held to 35° and after 45 min., 38.5 g. of the gas had been absorbed. After standing at room temperature overnight, the solution was poured into 500 ml. of ice and water. The precipitated solid was crystallized from methanol water whereupon 1.9 g. (64%) was obtained as yellow plates m.p. 103–106°. Additional crystallizations from aqueous methanol gave large yellow plates, m.p. 103.5–104.5°; reported[3] m.p. 102–103°. A mixture with authentic material melted undepressed.[14]

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.00; H, 5.85.

The *acetate* formed colorless plates from methanol-water, melting partially at 86° and completely at 96–97°. Sublimation produced colorless material m.p. 95.2–95.6°, not changed when mixed with an authentic sample.[14]

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.76. Found: C, 60.20; H, 5.71.

The *benzoate* formed colorless diamond shaped crystals from methanol m.p. 139.9–140.9°.

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.88; H, 5.43.

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(14) Samples of 2,3-dihydrokhellinone (m.p. 102–103°) and its acetate (m.p. 95–96°) were very generously supplied by Prof. T. A. Geissman.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Some New Reactions of Methanesulfenyl Chloride[1]

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Methanesulfenyl chloride (I) has been found to react with methyl thiolacetate to form acetyl chloride and methyl disulfide (II). I also reacts with methyl methanethiolsulfonate (III) in an analogous manner to form II and methanesulfonyl chloride (IV). With ethyl ethanesulfinate (V), I reacts to form ethyl chloride, ethanesulfonyl chloride, and II. With methanol the reaction products are hydrogen chloride, methyl chloride, II, and III. Toward water, I reacts more slowly to form hydrogen chloride, II, and III. These reactions are readily explained if one assumes that I behaves as an electrophilic reagent.

Sulfenyl chlorides have been found to attack a wide variety of reagents. Most of these reactions have appeared to involve simple addition to double bonds, replacement of active hydrogens, or rupture of strained rings. More recently reactions have been found which require a less simple explanation. Sulfenyl chlorides, for example, have been found to react with trialkyl phosphites to form monothiophosphate esters and alkyl chlorides.[2]

$$RSCl + R'OP(OR')_2 \longrightarrow R'Cl + RSP(OR')_2 \quad (1)$$

Morrison[3] has described this reaction as one involving nucleophilic displacement of chloride accompanied by elimination of alkyl chloride. Considered from the standpoint of the sulfenyl chloride as the attacking reagent, this reaction can also be described as an electrophilic attack on phosphorus accompanied by elimination of alkyl chloride.

Indeed, if one examines most of the well known reactions of the sulfenyl chlorides the concept of electrophilic attack is useful in explaining reaction mechanisms. The concept also helps to explain the results observed when methanesulfenyl chloride (I) reacts with methyl thiolacetate, methyl methanethiolsulfonate, ethyl ethanesulfinate, methanol, and water.

Methanesulfenyl chloride (I) reacts readily with methyl thiolacetate with the formation of methyl disulfide (II) and acetyl chloride. The reaction can be explained as an electrophilic attack on sulfur with elimination of acetyl chloride.

$$\underset{}{CH_3COSCH_3} + \underset{\text{I}}{CH_3SCl} \longrightarrow CH_3COCl + \underset{\text{II}}{CH_3SSCH_3} \quad (2)$$

When I reacts with methyl methanethiolsulfonate (III) an analogous but much slower reaction takes place forming methanesulfonyl chloride (IV) and II.

$$\underset{\text{I}}{CH_3SCl} + \underset{\text{III}}{CH_3SO_2SCH_3} \longrightarrow \underset{\text{IV}}{CH_3SO_2Cl} + \underset{\text{II}}{CH_3SSCH_3} \quad (3)$$

With ethyl ethanesulfinate (V), I reacts to form ethyl chloride, ethanesulfonyl chloride (VI), and II. Before attempting this reaction, compound V was considered to be analogous to the dialkyl phosphonous esters, which have an unshared electron pair on the phosphorus atom and which react with sulfenyl chlorides to form thiophosphonate esters.[4] By analogy it was expected that compounds I and V would react to form methyl ethanethiolsulfonate, $C_2H_5SO_2SCH_3$ (VII). Instead, however, the reaction took place as indicated in Equation 4 with no trace of thiolsulfonate ester being found among the products.

$$2\underset{\text{I}}{CH_3SCl} + \underset{\text{V}}{C_2H_5SOC_2H_5} \longrightarrow \underset{\text{VI}}{C_2H_5SO_2Cl} + C_2H_5Cl + \underset{\text{II}}{CH_3SSCH_3} \quad (4)$$

The absence of thiolsulfonate ester and the presence of VI and II among the products first suggested that the expected methyl ethanethiolsulfonate (VII) had reacted with excess I as soon as it had been formed. On further thought, however, this view did not seem tenable in consideration of the fact that Equation 3 is slow, being only 10% complete in one hour, 26% in 6 hours, and only 45% in 24 hours. Likewise, there was evidence for the formation of only a 40% yield of VI when VII and I stood in contact for 2 weeks.

The following alternative mechanism is tentatively advanced to explain the results observed (Equations 5a and 5b). The electrophilic sulfenyl chloride (I) first attacks the oxygen of the alkoxy group in V with elimination of ethyl chloride and the formation of an unstable sulfinic - sulfenic anhydride (VIII) with which additional I reacts by electrophilic attack on sulfur followed by elimination of ethanesulfonyl chloride (VI).

(1) Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) E. E. Gilbert and C. J. McGough, U. S. Patents 2,690,450 and 2,690,451, issued Sept. 28, 1954.

(3) D. C. Morrison, *J. Am. Chem. Soc.*, **77**, 181 (1955).

(4) D. C. Morrison, *J. Org. Chem.*, **21**, 705 (1956).

$$\underset{\text{I}}{CH_3SCl} + \underset{\text{V}}{C_2H_5S(O)OC_2H_5} \longrightarrow \left[C_2H_5S(O)OSCH_3\right] + C_2H_5Cl \quad (5a)$$

(VIII)

$$\underset{\text{VIII}}{C_2H_5S(O)OSCH_3} + \underset{\text{I}}{CH_3SCl} \longrightarrow \underset{\text{VI}}{C_2H_5S(O)Cl} + \underset{\text{II}}{CH_3SSCH_3} \quad (5b)$$

The reaction between methanol and I is rapid, forming methyl chloride, methyl methanethiolsulfonate (III), methyl disulfide (II), and hydrogen chloride. The sequence of reactions would appear to involve first the formation of methyl methanesulfenate (IX) with which I then reacts by electrophilic attack on sulfur with elimination of methyl chloride and the formation of methyl methanethiolsulfinate (X). This latter compound then disproportionates to III and II.

$$\underset{\text{I}}{CH_3SCl} + CH_3OH \longrightarrow \underset{\text{IX}}{CH_3SOCH_3} + HCl \quad (6a)$$

$$\text{I} + \text{IX} \longrightarrow \underset{\text{X}}{CH_3S(O)SCH_3} + CH_3Cl \quad (6b)$$

$$2\text{X} \xrightarrow{\text{Disproportionation}} \underset{\text{III}}{CH_3SO_2SCH_3} + \underset{\text{II}}{CH_3SSCH_3} \quad (6c)$$

Sulfenate esters are stable derivatives of 2,4-dinitrobenzenesulfenyl chloride,[5] but alkyl esters derived from alkanesulfenyl chlorides have not been reported. The aliphatic thiolsulfinate esters have been prepared by the oxidation of disulfides but they are reported to be unstable.[6] Likewise, the addition of a mercaptan to an aliphatic sulfinyl chloride, a reaction which might be expected to produce a thiolsulfinate ester, produces instead a thiolsulfonate ester and a disulfide.[7]

Additional work on the reaction between methanol and I, now in progress, suggests that other products are formed, in addition to those indicated, but the results are consistent with the chemical behavior of I described in this paper.

The reaction of I with water is slower than that with methanol but it follows a somewhat similar course. The products formed are II, III, and hydrogen chloride. The proposed mechanism involves the electrophilic attack of I on water to form methanesulfenic acid (XI) which then reacts with additional I to form methyl methanethiolsulfinate (X) which undergoes disproportionation as already described.

$$\underset{\text{I}}{CH_3SCl} + HOH \longrightarrow \underset{\text{XI}}{CH_3SOH} + HCl \quad (7a)$$

$$\text{I} + \text{XI} \longrightarrow \underset{\text{X}}{CH_3S(O)SCH_3} + HCl \quad (7b)$$

$$2\text{X} \xrightarrow{\text{Disproportionation}} \underset{\text{III}}{CH_3SO_2SCH_3} + \underset{\text{II}}{CH_3SSCH_3} \quad (7c)$$

The first part of this proposed mechanism is supported by the recent findings of Vinkler and Klevényi that the "sulfenic anhydrides" formed by the reaction of aromatic sulfenyl chlorides with water actually have the thiolsulfinate structure.[8]

EXPERIMENTAL

Preparation of methanesulfenyl chloride (I). A weighed quantity of liquid chlorine was allowed to evaporate into slightly more than the calculated quantity of pure methyl disulfide maintained at −10° to −20° during the reaction. When the last of the chlorine had been added, the reaction mixture was shaken to bring unchanged methyl disulfide in contact with the solid methylsulfur trichloride which had been formed to convert both to the desired sulfenyl chloride. The product was considered ready for use when the solid had disappeared. Best results were obtained when the desired quantity was prepared immediately before use.

Reaction of I with methyl thiolacetate. Methyl thiolacetate (0.2 mol.) was added slowly to well stirred methanesulfenyl chloride (0.2 mol.) in a flask cooled to −10°. Reaction occurred readily to give a colorless reaction mixture. Distillation gave an 85% yield of acetyl chloride and 75% yield of methyl disulfide. Both products were identified by boiling point and density determinations.

Reaction of I with methyl methanethiolsulfonate (III). Methyl methanethiolsulfonate (III) (0.8 mol.) and methanesulfenyl chloride (I) (0.4 mol.) were mixed at room temperature and stirred for 1 hr. but there was no evidence of reaction. The mixture was heated to 75° for 2 hr. but there was still no apparent change in color. Finally, the mixture was allowed to stand two weeks. During this period hydrogen chloride was evolved but the color did not change appreciably. On distilling the mixture, 15.0 g. of purified methyl disulfide (40% yield) and 10 g. of methanesulfonyl chloride (21.8%) were obtained. The methyl disulfide recovered had the same boiling point and refractive index as an authentic sample. The methanesulfonyl chloride was identified by conversion to the *p*-toluidide which melted at 103–104° and unchanged when mixed with an authentic sample.

In a second experiment, 0.1 mol. of methyl methanethiolsulfonate (III) and 0.087 mol. of methanesulfenyl chloride (I) were added to each of three tubes and allowed to stand at room temperature. At different times each tube in turn was treated as follows: Acetone was added to react with excess I, then the reaction mixture was diluted with ether, treated with *p*-toluidine in presence of sodium bicarbonate and, after standing several hours, was extracted with 10% sodium hydroxide. On acidifying, the alkaline extract, methanesulfon-*p*-toluidide, separated.

Tube	Time of Standing, Hr.	Wt. Methanesulfon-*p*-toluidide	Corresponding Yield of Methanesulfonyl Chloride
1	1	1.61 g.	10%
2	6	4.29	26.5%
3	24	7.17	45%

(5) N. Kharasch, D. P. McQuarrie, and C. M. Buess, *J. Am. Chem. Soc.*, **75**, 2658 (1953).

(6) V. D. Small, N. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, 69, 1710 (1947).

(7) J. v. Braun and K. Weisbach, *Ber.*, 63B, 2836 (1930) and unpublished work in this laboratory.

(8) E. Vinkler and F. Klevényi, *Acta, Chim. Acad. Sci. Hung.*, **11**, 15 (1957).

Reaction of I with methyl ethanethiolsulfonate (VII). To 0.2 mol. of I, 0.2 mol. of VII was added, and the mixture was allowed to stand at room temperature for two weeks. There was no change in color. The mixture was then distilled yielding 5.27 g. of methyl disulfide (58% recovery) and 1.39 g. of a fraction boiling 57–63° (12 mm.). The latter was diluted with ether and caused to react with *p*-toluidine and yielded 15.7 g. of ethanesulfon-*p*-toluidide, corresponding to a 40% yield of ethanesulfonyl chloride.

Reaction of I with ethyl ethanesulfinate (V). Ethyl ethanesulfinate, $C_2H_5SOC_2H_5$ (V) (0.2 mol.), was added dropwise to 0.2 mol. of I at −20°. The mixture gradually faded in color and was nearly colorless by the time it had warmed to room temperature. It was heated to 90° to drive off volatile matter and was then cooled to await distillation.

The volatile portion after purification consisted of ethyl chloride (3.0 g., 23%). Molecular wt.: Calcd., 64.52; found, 66. Boiling pt.: Reported, 12.3°; found, 12–13°.

Distillation of the residual reaction mixture yielded 8.5 g. of methyl disulfide, identified by boiling point and refractive index and 12.4 g. of ethanesulfonyl chloride (VI). The latter was identified by conversion to the *p*-toluidide which melted at 81° and unchanged when mixed with an authentic sample.

More than 20% of the original V was recovered unchanged.

Reaction of I with methanol. In an attempt to prepare methyl methanesulfenate, $CH_3S—O—CH_3$ (IX), 0.6 mol. of I was added slowly to 1.2 mol. of well stirred methanol at −20°. The resulting colorless reaction mixture was then distilled but no product with the properties expected of IX was found. There was obtained, however, 12.5 g. of III or 66% yield on the basis of the postulated reactions described above.

The reaction was repeated using 1.6 mol. I and 0.8 mol. of methanol under conditions which would insure the recovery of any methyl chloride and methyl disulfide formed. A 55% yield of methyl chloride, identified by boiling point and molecular weight, was obtained. Methyl disulfide, having properties identical to an authentic sample, was recovered in 70% yield.

Reaction of I with water. Water (0.25 mol.) was added dropwise to well stirred I (0.25 mol.) at −20°. At first there was little evidence of reaction but gradually the evolution of hydrogen chloride became apparent and when the last of the water had been added the mixture was only faintly yellow. After warming slowly to room temperature, the reaction mixture was distilled and yielded 8.0 g. of methyl disulfide and 12.0 g. of III. The yields were 64% and 72%, respectively, based on the reactions outlined above. Both products proved identical to authentic samples.

ORONO, ME.

[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE UNIVERSITY OF PENNSYLVANIA]

Investigations on Steroids. XXX. New Transformation Products of Strophanthidin: 19-Hydroxytestosterone, 19-Hydroxy-1-dehydrotestosterone Diacetate and Estradiol-17β[1-3]

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Improvements in the synthesis from strophanthidin of 19-hydroxy-Δ^4-androstene-3,17-dione (II) are presented. The role of II as a possible key intermediate in the metabolic transformation of androgens into estrogens is pointed out. Under specific conditions, reduction of II with sodium borohydride gave mainly 19-hydroxytestosterone (IV) and, as a by-product, Δ^4-androstene-3β,17β,19-triol (VI). By treatment with selenium dioxide, 19-hydroxytestosterone diacetate (V) was converted into 19-hydroxy-1-dehydrotestosterone diacetate (IX). Even under mild alkaline conditions, it was not possible to saponify IX to the free 19-hydroxy-1-dehydrotestosterone (VIII). By the action of mild alkali, IX is rapidly transformed into the 17-monoacetate of estradiol-17β (XI), whereas with stronger alkali, free estradiol-17β (X) is obtained. The physiological activities of IV and IX are discussed.

The synthesis from strophanthidin of analogs of steroid hormones oxygenated in the 19- position was reported from this laboratory some time ago.[6-10] A number of such products were subsequently isolated from various biological systems. Thus, several 19-hydroxy steroids have been isolated from adrenocortical extracts.[11] Hydroxyl groups have been introduced into the 19- position either by incubation with beef adrenal homogenates

(1) This paper is dedicated to the memory of Lyndon F. Small, former editor of this journal.

(2) This investigation was supported by research grants (CY757-C5 and CY757-C6) from the National Cancer Institute of the National Institutes of Health, Public Health Service. A part of the K-Strophanthin used in this investigation was kindly donated by S. B. Penick & Co., New York, N. Y.

(3) The essential findings of this paper were presented on September 5, 1958, at the 4th International Congress of Biochemistry in Vienna (*cf.* Maximilian Ehrenstein: Biochemistry of the Corticoids, Proceedings of the Fourth International Congress of Biochemistry, Vol. 4 (Symposium: Biochemistry of Steroids), Pergamon Press, p. 259 (1959).

(4) Dr. Klaus Otto was the recipient of a Fulbright Travel Grant and was on leave of absence from the Physiologisch-chemisches Institut der Universität Bonn, West Germany.

(5) In collaboration with G. Winston Barber.

(6) G. W. Barber and M. Ehrenstein, *J. Am. Chem. Soc.*, 76, 2026 (1954).

(7) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, 19, 1758 (1954).

(8) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, 20, 1253 (1955).

(9) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, 21, 774 (1956).

(10) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, 21, 783 (1956).

(11) *Cf. e.g.*, Albert Wettstein: Biochemie der Corticoide, Proceedings of the Fourth International Congress of Biochemistry, Vol. 4 (Symposium: Biochemistry of Steroids), Pergamon Press, p. 233 (1959).

or by perfusion through bovine adrenal glands.[12] Recently a microorganism was described which is capable of producing the same effect.[13]

Of particular interest is 19-hydroxy-Δ^4-androstene-3,17-dione (II).[9,14] It is considered to be a metabolic intermediate in the transformation of Δ^4-androstene-3,17-dione into estrone.[15–18] In this connection it appears interesting that Δ^4-androstene-3,17-dione and its metabolic precursor 17α-hydroxyprogesterone have been identified in human follicles and corpora lutea.[19]

In view of the role of 19-hydroxy-Δ^4-androstene-3,17-dione (II) as a potential key intermediate in steroid metabolism, it was indicated to extend the chemical investigations on this compound. As was reported earlier,[9] II was prepared from 5β-androstane-3β,5,17β,19-tetrol (I) by oxidizing with 2.4 equivalents of *N*-bromoacetamide and subjecting the reaction product to dehydration with Girard's reagent T. On repeating this work, it was found that reproducible and satisfactory yields of II are obtained by increasing the amount of *N*-bromoacetamide to 3 equivalents. The rotatory dispersion curve of II[20] is in good agreement with that of a standard Δ^4-3-ketone.

In incubation experiments with human ovarian slices, testosterone-3-C^{14} has been converted into C^{14}-labeled estradiol-17β.[16] The question arises whether 19-hydroxytestosterone (IV) is an intermediate in such a conversion. With the intention of preparing IV, we had previously[9] subjected I to selective oxidation with 1.2 equivalents of *N*-bromoacetamide. However, the resulting product was not the desired 3-keto compound but rather 3β,5,19-trihydroxy-5β-androstan-17-one. Although the selective catalytic dehydrogenation of 3-hydroxyl groups with platinum has been achieved in several instances,[21–23] in the case of strophanthidol[23] rather poor yields are reported, because to some extent also the primary alcohol group was attacked.[23a] Therefore, it was decided not to apply this procedure to the rather scarce tetrol I.

We were able to prepare 19-hydroxytestosterone (IV) by a different approach. Norymberski found[24] that, under specific conditions, the reduction of Δ^4-androstene-3,17-dione with sodium borohydride gives testosterone in 60–70% yield. This method of selective reduction was applied to 19-hydroxy-Δ^4-androstene-3,17-dione (II). With a 1:1 molecular ratio of the steroid and the reducing agent a satisfactory yield (71.9%; 84.5%) of 19-hydroxytestosterone (IV) resulted. Reasoning by analogy, the hydroxyl group at carbon atom 17 was considered to possess the β-configuration. The correctness of this assumption was proved by the ultimate transformation of IV into estradiol-17β (*v. infra*). To a second reduction product was assigned the structure of Δ^4-androstene-3β,17β,19-triol (VI). Although the formation of a 3β-hydroxyl group (equatorial) appears favored on the basis of conformational considerations, mixtures of epimers, with the β-form prevailing, have been obtained in analogous instances.[22,25] Consequently, the configuration of the 3-hydroxyl group of VI is not claimed to be proved. By treatment with manganese dioxide,[26] VI could be converted into 19-hydroxytestosterone (IV). IV was characterized by the crystalline diacetate (V). The acetylation product of VI, probably representing the triacetate (VII), resisted all attempts at crystallization, even after chromatography.

Recent investigations performed with human placental tissue[18] indicate that 19-nortestosterone and $\Delta^{1,4}$-androstadiene-3,17-dione are not likely intermediates in the biosynthesis of estrogens. Since the role of 19-hydroxy-Δ^4-androstene-3,17-dione (II) as a possible intermediate has been demonstrated, one may assume[17] that the hydroxylation of the C-19 angular methyl group is probably the primary reaction in the conversion of 19-carbon steroids to estrogens. Subsequently a 1-2 dehydrogenation may occur leading to another intermediate, *viz.*, a 19-hydroxy-$\Delta^{1,4}$-dien-3-one. Such a compound should be very easily convertible into a compound of estrogen type even by ordinary organic chemical means.[17] In order to make compounds of this type available for the study of intermediary metabolism, it was decided to convert the diacetate of 19-hydroxytestosterone (V) into the corresponding 1-dehydro compound (IX) with the aim of hydrolyzing the latter to 19-hydroxy-1-dehydrotestosterone (VIII).

(12) Lit. *cf.* ref. 9.

(13) M. Nishikawa and H. Hagiwara, *Chemical and Pharmaceutical Bulletin*, 6, 226 (1958).

(14) A. S. Meyer, *Experientia*, 11, 99 (1955).

(15) A. S. Meyer, *Biochim. et Bioph. Acta*, 17, 441 (1955).

(16) B. Baggett, L. L. Engel, K. Savard, and R. I. Dorfman, *J. Biol. Chem.*, 221, 931 (1956).

(17) P. Talalay, *Physiol. Reviews*, 37, 362, *v.p.* 374 (1957).

(18) K. J. Ryan, *J. Biol. Chem.*, 234, 268 (1959).

(19) J. Zander, *J. Biol. Chem.*, 232, 117 (1958).

(20) Determined through the courtesy of Professor Carl Djerassi at Wayne State University, Detroit 2, Mich. *Cf.* the chapter on Rotatory Dispersion, pp. 180–185 in "Steroids" by Louis F. Fieser and Mary Fieser, Reinhold Publishing Corp., New York, 1959.

(21) R. P. A. Sneeden and R. B. Turner, *J. Am. Chem. Soc.*, 77, 130 (1955).

(22) A. Katz, *Helv. Chim. Acta*, 40, 831 (1957).

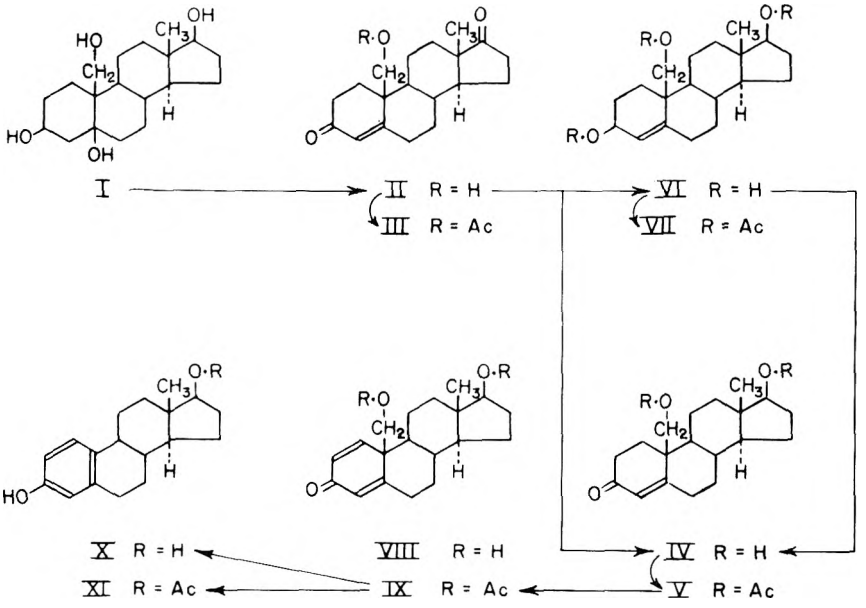
(23) Ch. Tamm and A. Gubler, *Helv. Chim. Acta*, 42, 239 (1959).

(23a) Addition (September 15, 1959): In contrast, treatment of methyl 3β,5,12β(?),14,19-pentahydroxy-5β,14β-etianate with platinum has been reported to give a good yield of 3-oxo-5,12β(?),14,19-tetrahydroxy-5β,14β-etianate. *Cf.* R. P. Martin and Ch. Tamm, *Helv. Chim. Acta*, 42, 696 (1959).

(24) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

(25) P. Th. Herzig and M. Ehrenstein, *J. Org. Chem.*, 17, 713 (1952).

(26) F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Am. Chem. Soc.*, 75, 5930 (1953).



Treatment of V with selenium dioxide[27] provided 19-hydroxy-1-dehydrotestosterone diacetate [17β,-19-diacetoxy-$\Delta^{1,4}$-androstadien-3-one] (IX) in good yield. As has been demonstrated in the case of 19,21-diacetoxy-17-hydroxy-$\Delta^{1,4}$-pregnadiene-3,20-dione,[13] compounds of this type aromatize easily when treated with ethanolic potassium hydroxide or with ethanolic hydrochloric acid. Therefore, in attempting the conversion of IX into the free 19-hydroxy-1-dehydrotestosterone (VIII), it was essential to select the mildest possible conditions.

In previous work from this laboratory, the saponification of 19-acetoxy groups has been achieved in some instances with potassium bicarbonate,[7] but more generally with potassium carbonate.[7,9,10] Therefore, in an orienting experiment, IX was subjected to treatment with potassium carbonate at room temperature.[28] As indicated by the ultraviolet absorption curve, extensive aromatization took place within a period of 1 hr. On the basis of this observation, the behavior of IX in various concentrations of alkali was studied on a microscale, using as criteria paper chromatographic and ultraviolet absorption data.[5] In these studies under mild conditions the formation of only the 17-monoacetate of estradiol-17β (XI)[29,30] was demonstrated, whereas under slightly more vigorous conditions, estradiol-17β (X) itself was obtained.

In 0.01*N* sodium carbonate solution containing 10% ethanol, conversion of IX to XI was essentially complete in 30 min., and in 0.1*N* sodium hydroxide containing 10% ethanol, conversion of IX to X was nearly instantaneous. Even in 0.01*N* sodium bicarbonate containing 10% ethanol, on standing overnight, partial conversion of IX to XI was indicated by paper chromatography, although here the ultraviolet studies were inconclusive. The possibility of confusing XI with a compound such as the 17-monoacetate of VIII having the same mobility in the paper chromatographic system is not very likely (*cf.* Experimental). It follows, therefore, that the preparation of VIII from the diacetate IX is probably not possible.[30a]

After these orienting studies, IX was converted on a preparative scale with aqueous methanolic potassium carbonate into XI, and with ethanolic sodium hydroxide into X.

Physiological activity. According to preliminary bioassays, conducted by Dr. Ralph I. Dorfman at the Worcester Foundation for Experimental Biology, 19-hydroxytestosterone (IV) possesses little, if any, androgenic activity (chick inunction test). Similar findings had been obtained with 19-hydroxy-Δ^4-androstene-3,17-dione (II).[14] The estrogenic activity (20-day-old female mice; uterine weight) of 19-hydroxy-1-dehydrotestosterone diacetate (IX) is about 1% that of estradiol-17β (X) and less than 1% that of the 17-monoacetate of estradiol-17β (XI). The details of the bioassay and a series of biochemical studies on compound IX will be published later. Furthermore, in particular, compounds IV and IX will be tested for androgen and estrogen inhibitory activity.

(27) For method, *cf.* Ch. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(28) For method, *cf.* J. Schmidlin, G. Anner, J.-R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **40**, 2291, *v.p.* 2319 (1957).

(29) K. Miescher and C. Scholz, *Helv. Chim. Acta*, **20**, 263, *v.p.* 270 (1937).

(30) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534, *v.p.* 4539 (1950).

(30a) Addition (September 15, 1959): A 19-hydroxy-$\Delta^{1,4}$-dien-3-one (methyl 3,11-dioxo-14,19-dihydroxy-$\Delta^{1,4}$,14β-etiadienate) has recently been obtained in very small amounts as a by-product of a chemical reaction. It obviously undergoes facile aromatization. *Cf.* G. Volpp and Ch. Tamm, *Helv. Chim. Acta*, **42**, 1408 (1959).

EXPERIMENTAL

Melting points. The m.p.'s were determined with the Fisher-Johns melting point apparatus and are uncorrected.

Absorption spectra. Ultraviolet spectra were determined in 95% ethanol with a Beckmann Model DU spectrophotometer. The infrared studies pertaining to this paper were carried out on a Perkin-Elmer Model 21 double beam spectrometer in the Division of Steroid Metabolism of the Sloan-Kettering Institute for Cancer Research through the courtesy of Dr. Thomas F. Gallagher. The interpretation was done by Dr. David Fleischer and Mrs. Beatrice S. Gallagher. The correlations are based upon those summarized in the publication of Jones and Herling.[31] Only those bands are mentioned which appear to have a direct bearing upon the structure of the particular compound. Details of other correlations between spectrum and structure will be summarized at a later time by the group at the Sloan-Kettering Institute.

Analyses. Unless stated otherwise, the microanalyses were performed by Dr. E. W. D. Huffman, Wheatridge, Colo., on samples which were dried to constant weight in vacuo (P_2O_5; 80°) according to Milner and Sherman.[32] The percentage loss of weight on drying is recorded; there was in no instance a gain of weight on exposure of the sample to the atmosphere.

Optical rotations. No corrections for crystal solvent have been made. Unless stated otherwise, the sample was dissolved in chloroform to make 2 cc. of solution and the rotation was determined in a 2-dm. semimicro tube.

Chromatography. The alumina (activity II) used as adsorbent for chromatography has been described.[7]

Remarks concerning the preparation of the starting material: Δ^4-androstene-3,17-dione (II). Generally the procedures used and the yields obtained in the preparation of the various intermediates were in agreement with the data published earlier.[9] This applies in particular to the conversion of strophanthidin by way of strophanthidol into ethyl 3β,5,19-trihydroxy-Δ^{14}-etienate. Pertinent observations concerning some of the subsequent steps are recorded as follows:

Hydrogenation of ethyl 3β,5,19-trihydroxy-Δ^{14}-etienate. Average yield (15 expts.) of pure ethyl 3β,5,19-trihydroxyetianate, 88%. Recryst. from ethanol water; double m.p. 186° and 195–196°.

Saponification of ethyl 3β,5,19-trihydroxyetianate. Average yield (7 expts.) of pure 3β,5,19-trihydroxyetianic acid, 94%.

3β,19-Diacetoxy-5-hydroxyetianic acid. Recryst. from acetone-hexane; double m.p. 167–170° and 182–184°.

3β,19-Diacetoxy-5-hydroxy-21-diazo-5β-pregnan-20-one from 3β,19-diacetoxy-5-hydroxyetianic acid. Average yield (10 expts.) of crude crystalline diazoketone, as obtained after chromatography, 73%. Occasionally, without discernible reason, the reaction did not proceed according to schedule.

3β,19-Diacetoxy-5-hydroxy-5β-pregnan-20-one from 3β,19-diacetoxy-5-hydroxy-21-diazo-5β-pregnan-20-one. Relative to the previously reported data, the volume of the 48% hydriodic acid used in this reaction was reduced to two fifths and the shaking with this reagent to 45 sec. Average yield (8 expts.) of crude crystalline methyl ketone, as obtained after chromatography, 85%.

3β,5,19-Triacetoxy-5β-pregnan-20-one from 3β,19-diacetoxy-5-hydroxy-5β-pregnan-20-one. One part (g.) of the diacetate was refluxed with 200 parts (cc.) of acetic anhydride for 15 hr. Uniform, satisfactory yields of the pure triacetate resulted, average 78% (7 expts., range 0.100–1.0 g. of diacetate).

3β,5,17β,19-Tetraacetoxy-5β-androstane from 3β,5,19-triacetoxy-5β-pregnan-20-one. Average yield (4 expts.) of the pure crystalline product, 89%.

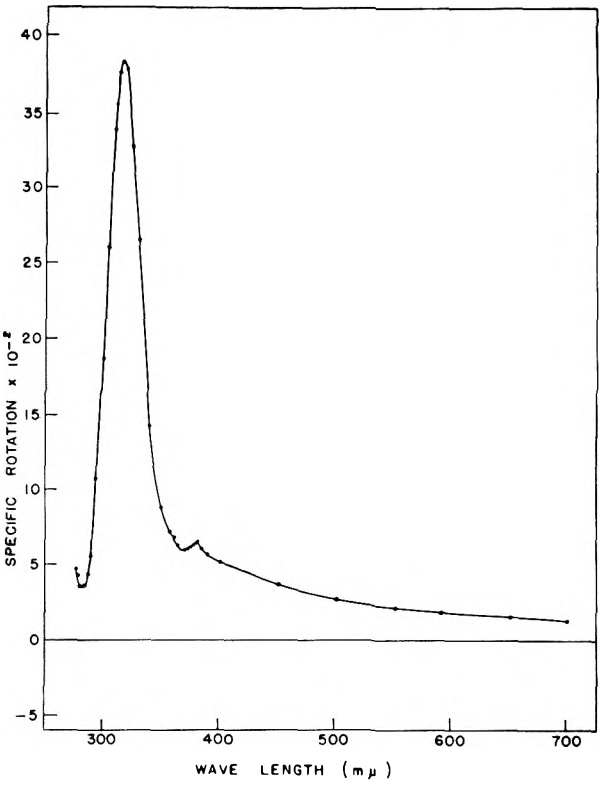


Fig. 1. Rotatory dispersion curve of 19-hydroxy-Δ^4-androstene-3,17-dione (II) (double m.p. 169–172° and 180–182°) in dioxane (c = 0.078, 700 ~ 305 mμ; c = 0.015, 300 ~ 277.5 mμ).

Saponification of 3β,5,17β,19-tetraacetoxy-5β-androstane. Average yield (4 expts.) of pure 5β-androstane-3β,5,17β,19-tetrol (I), 88%.

Conversion of 5β-androstane-3β,5,17β,19-tetrol (I) *into 19-hydroxy-Δ^4-androstene-3,17-dione* (II). Reproducible, satisfactory yields were obtained by using for the oxidation 3 rather than 2.4 equivalents of *N*-bromoacetamide. A revised and simplified procedure is given as follows: To 263.1 mg. of I, m.p. 205–207°, in 7 cc. of redistilled *tert*-butanol were added 336 mg. of *N*-bromoacetamide and 1.2 cc. of water. After keeping the solution at room temperature for 16 hr., 80 cc. of water was added and a sufficient amount of *N* sodium thiosulfate to destroy the bromine. Following extraction with ethyl acetate, drying, and evaporating the solvent, a partly crystalline reaction product resulted. This was dissolved in 12 cc. of ethanol and, after the addition of 800 mg. of Girard's reagent T and 0.27 cc. of glacial acetic acid, the solution was refluxed for 1 hr. and was subsequently concentrated *in vacuo* at room temperature to a volume of approximately 6 cc. Following the addition of 210 mg. of sodium carbonate, ice, and some water, the mixture was extracted with ethyl acetate, yielding only 2.4 mg. of nonketonic material. The aqueous phase was then acidified to Congo Red with 50% sulfuric acid and, after standing overnight, the ketonic material was isolated by extracting with ethyl acetate; yield, 181 mg. of yellowish, mostly crystalline material. Chromatography over 8 g. of alumina (diameter of column, 1.3 cm.) and elution with benzene ether gave 147.8 mg. (yield, 60%) of crude crystalline II. Recrystallization from acetone hexane furnished 135.9 mg. (yield, 55.5%) of pure II; double m.p. 169–172° and 180–182°. Elution with methanol gave 9 mg. of crystalline material, probably representing 3β,5,19-trihydroxy-5β-androstan-17-one.

19-Hydroxytestosterone [*17β,19-dihydroxy-Δ^4-androsten-3-one*] (IV) *and Δ^4-androstene-3β,17β,19-triol* (VI) *from 19*

(31) R. N. Jones and F. Herling, *J. Org. Chem.*, 19, 1252 (1954).

(32) R. T. Milner and M. S. Sherman, *Ind. Eng. Chem., Anal. Ed.*, 8, 427 (1936).

hydroxy-Δ⁴-androstene-3,17-dione (II). A solution of 30.2 mg. (0.1 mmol.) of II, m.p. 169–171°, in 6 cc. of redistilled methanol was treated with 5.7 mg. (0.15 mmol.) of sodium borohydride for 1 hr. at 0°. After the addition of 5 drops of glacial acetic acid, the solution was brought to dryness *in vacuo*. The crystalline residue was extracted with two 10-cc. portions of hot benzene and of ethyl acetate. After evaporation of the solvents, the resulting material (43.8 mg.) was taken up in 50 cc. of benzene (8.0 mg. remained undissolved) and chromatographed over 3 g. of alumina (diam. of column, 0.8 cm.). The following eluates were collected: (a) benzene (50 cc.), 0.2 mg. of resin; (b) benzene ether, range 9:1 to 3:2 (total 120 cc.), 0.5 mg. of resin; (c) benzene ether, range 3:7 to 1:9 (total 60 cc.), ether (20 cc.) and ether methanol, 99:1 (20 cc.), 14.3 mg. of crystalline material; (d) ether methanol, 39:1 (20 cc.), 1.3 mg. of resin; (e) ether methanol, 19:1 and 17:3 (20 cc. each), 12.1 mg. of crystalline product; (f) ether methanol, 3:1 and 1:1 (20 cc. each); 0.6 cc. of resin.

The fractions (c) (14.3 mg., m.p. range 200–204°, yield 47%) consisted essentially of 19-hydroxytestosterone (IV). Repeated recrystallization from acetone hexane gave pure IV, m.p. 201–203°, $[\alpha]_D^{20}$ +109.7° (23.41 mg. in 2 cc. of chloroform containing 5 drops of ethanol, α + 2.57°),[33] λ_{max}^{alc} 243 mμ, ε 14900.[33]

Infrared spectrum of IV ($CHCl_3$ suspension): 3613 cm.$^{-1}$, hydroxyl absorption (Note: comparing IV and II which have the same amount of CH_2 and CH_3 absorption, the ratio of the O—H stretching absorption to this C—H stretching absorption is approximately twice as large in IV. This is in agreement with the presence of two hydroxyl groups); 1710 cm.$^{-1}$, small unexplained absorption; 1665 cm.$^{-1}$, C=O absorption of the Δ⁴-3-ketone; 1617 cm.$^{-1}$, C=C absorption of the Δ⁴-3-ketone.

Anal. Calcd. for $C_{19}H_{28}O_3$(304.41): C, 74.96; H, 9.27. Found: C, 74.82; H, 9.26. Weight loss, 0.29.

The fractions (e) (12.1 mg., m.p. range 180–187°, yield 39.5%) represented crude Δ⁴-androstene-3β,17β,19-triol (VI) which is markedly less soluble in acetone than IV. Repeated recrystallization from acetone hexane gave 6.3 mg. of VI, m.p. 202–205°. The product gave no color with tetranitromethane. No ultraviolet absorption in the range 220–300 mμ. $[\alpha]_D^{21}$ +44.5° (11.25 mg. in 2 cc. of ethanol, α + 0.50°).[34]

Infrared spectrum of VI (KBr pellet): hydroxyl absorption present (very broad band); 1656 cm.$^{-1}$, C=C absorption of the Δ⁴-group. (Note: No conclusions can be drawn from the infrared spectrum regarding the configuration of the OH— group at C-3.)

Anal. Calcd. for $C_{19}H_{30}O_3$(306.43): C, 74.47; H, 9.87. Found: C, 74.30; H, 9.88. Weight loss, 0.1.

Orienting experiments were carried out to determine to what extent the yields of IV and VI could be influenced by varying the molecular ratio of II and sodium borohydride. Summary of experiments; the yields apply to the pertinent chromatographic fractions, as weighed before recrystallization. (A) Ratio 1:1; 2 experiments: (a) 54.6 mg. of II in 10 cc. of methanol, 7 mg. of $NaBH_4$, yield of IV 39.4 mg. = 71.9% (eluted with ether methanol); (b) 60.0 mg. of II in 12 cc. of methanol, 8 mg. of $NaBH_4$, yield of IV 51 mg. = 84.5% (eluted with ether methanol). In both experiments the estimated yield of VI (eluted with ether methanol) was less than 5%. (B) Ratio 2:3, 1 experiment, in addition to the example described in detail above: 55.1 mg. of II in 10 cc. of methanol, 10.3 mg. of $NaBH_4$; yield of IV, 31.2 mg. = 56.3% (eluted with benzene ether); yield of VI, 9.4 mg. = 16.9% (eluted with ether methanol). (C) Ratio 1:2; 1 experiment: 45.4 mg. of II in 9 cc. of methanol, 11.5 mg. of $NaBH_4$; yield of IV, 17.3 mg. = 37.9% (eluted with benzene ether); yield of VI, 20.2 mg. = 43.9% (eluted with ether methanol). (D) Ratio 1:3; 1 experiment: 30.2 mg. of II in 6 cc. of methanol, 11.5 mg. of $NaBH_4$; yield of IV, 7.0 mg. = 23.0% (eluted with benzene ether); yield of VI, 12.1 mg. = 39.5% (eluted with ether methanol).

19-Hydroxytestosterone [*17β,19-dihydroxy-Δ⁴-androsten-3-one*] (IV) *from Δ⁴-androstene-3β,17β,19-triol* (VI). A solution of 4.7 mg. of VI, m.p. 199–201°, in 5 cc. of chloroform, containing 50 mg. of freshly prepared manganese dioxide,[35] was allowed to stand at room temperature for 3 days with occasional shaking. The oxide was then removed by filtration and washed with chloroform. Evaporation of the solvent gave 4.2 mg. of crude material which was chromatographed over 1 g. of alumina. The eluates obtained with ether yielded a crystalline product which was recrystallized from acetone-hexane; yield 2.1 mg., m.p. 201–205°. There was no depression of the m.p. when mixed with the analytical sample of IV. The determination of the ultraviolet absorption spectrum (λ_{max}^{alc} 244 mμ; ε 12,750) indicated that the reaction product was approximately 85% pure.

19-Hydroxytestosterone diacetate [*17β,19-diacetoxy-Δ⁴-androsten-3-one*] (V). To 30.4 mg. of 19-hydroxytestosterone (IV) in 1 cc. of pyridine was added 1 cc. of acetic anhydride. The solution was kept at room temperature for 16 hr. and was then evaporated to dryness *in vacuo* (30°). After the addition and evaporation of absolute ethanol and then of benzene, 36.7 mg. of a colorless resinous product resulted which did not crystallize. Chromatography over 4 g. of alumina yielded, by elution with petroleum ether benzene, a total of 32.1 mg. of crystalline residues. By treating this material with acetone hexane and seeding, crystals separated; 2 crops: 25.2 mg. (65%), m.p. 126–128°, 4.2 mg. (10.8%), m.p. 124–126°. By repeated crystallization from methylene chloride–hexane the m.p. was raised to 128.5–130° (analytical sample). In a repeat experiment, the crude acetylation product crystallized directly from acetone water after seeding; very minute colorless rods; m.p. 128.5° (sharp); $[\alpha]_D^{21}$ +133.6° (10.30 mg., α + 1.38°); λ_{max}^{alc} 239 mμ, ε 18,800.

Infrared spectrum of V (CS_2 and CCl_4 solutions): Hydroxyl absorption absent; 1745 cm.$^{-1}$, possibly C=O absorption of the 19-acetate; 1735 cm.$^{-1}$ (shoulder), C=O absorption of the 17-acetate; 1678 cm.$^{-1}$, C=O absorption of the Δ⁴-3-ketone; 1623 cm.$^{-1}$, C=C stretching vibrations of the Δ⁴-3-ketone; 1419 cm.$^{-1}$, due to CH_2 adjacent to the Δ⁴-3-ketone; 1246 cm.$^{-1}$ (shoulder), 1236 cm.$^{-1}$, and 1226 cm.$^{-1}$ (shoulder), combined absorption of the C—O stretching vibrations of the acetate groups.

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.11; H, 8.30. Found: C, 70.83; H, 8.43.

19-Hydroxy-1-dehydrotestosterone diacetate [*17β,19-diacetoxy-Δ¹,⁴-androstadien-3-one*] (IX) *from 19-hydroxytestosterone diacetate* (V).[27] A mixture consisting of 38.5 mg. of V, 4 cc. of *tert*-butanol, 0.04 cc. of glacial acetic acid and 12 mg. of freshly sublimed selenium dioxide was refluxed under nitrogen for 20 hr. Another 12 mg. of selenium dioxide was then added and the refluxing continued for 9 hr. After subsequent standing at room temperature for 15 hr. and the addition of ethyl acetate, the solution was filtered and evaporated to dryness *in vacuo*. The crystalline residue was taken up in 20 cc. of ethyl acetate and the solution was washed successively with the following: 3 cc. of a solution of potassium bicarbonate (5%), 3 cc. of water, two 3-cc. portions of a freshly prepared solution of ammonium sulfide, 3 cc. of ammonia (1%), 3 cc. of water, 3 cc. of *N* hydrochloric acid, three 3-cc. portions of water. After drying over sodium sulfate and evaporating the solvent, 37 mg. (theoretical yield: 38.3 mg.) of an almost colorless crystalline product resulted which was chromatographed over 5 g. of alumina.

(33) Derived from a sample of another experiment, m.p. 204.5–206.5°.

(34) Derived from a sample of another experiment, m.p. 206–209°.

(35) O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

Elution with benzene ether gave a total of 33.8 mg. of uniform crystalline material which, after two recrystallizations from acetone-hexane gave 23.9 mg. (yield 77.5%) of IX with constant m.p. 169–171°. In a repeat experiment,[15] IX was obtained, without chromatography, by direct recrystallization of the crude reaction product; colorless needles (from acetone water), m.p. 170–171°; $[\alpha]_D^{20}$ +59.2° (15.39 mg., α + 0.91°); λ_{max}^{alc} 243 mμ; ϵ 13,700.

Infrared spectrum of IX (CS_2 and CCl_4 solutions): hydroxyl absorption absent; 1746 cm.$^{-1}$, possibly C=O absorption of the 19-acetate; 1735 cm.$^{-1}$ (shoulder), C=O absorption of the 17-acetate; 1671 cm.$^{-1}$, C=O absorption of the $\Delta^{1,4}$-3-ketone; 1650 cm.$^{-1}$, unexplained band; 1635 cm.$^{-1}$ and 1608 cm.$^{-1}$, C=C stretching vibrations of the $\Delta^{1,4}$-3-ketone; 1404 cm.$^{-1}$, usually found with a $\Delta^{1,4}$-3-ketone; 1245 cm.$^{-1}$ (shoulder), 1236 cm.$^{-1}$, and 1220 cm.$^{-1}$ (shoulder), combined absorption of the C—O stretching vibrations of the acetate groups. (Note: While all the necessary absorptions are present, the 1650 cm.$^{-1}$ band indicates the presence of some impurity.)

Anal.[36] Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.03; H, 7.54. Weight loss, 0.83.

Treatment of 19-hydroxy-1-dehydrotestosterone diacetate (IX) *with alkaline reagents.*[5] *A. Treatment with 0.1N sodium hydroxide.* A solution of 0.15 mg. of IX in 1 cc. of 95% ethanol was diluted to 10 cc. with 0.1*N* aqueous sodium hydroxide. Measurement of the development of ultraviolet absorption at 298 mμ was attempted, but the value E = 0.103, obtained 2 min. after mixing, did not change during the following 24 hr., and the absorption curve was essentially the same as that determined for estradiol-17β (X)[37] in the same solvent medium[38]: λ_{min} 226 mμ, ϵ 8300; λ_{max} 238 mμ, ϵ 10,300; λ_{min} 270 mμ, ϵ 1200; λ_{max} 298 mμ, ϵ 3200.

One fourth of the above reaction mixture was made acid to litmus and extracted with ether, and the material so obtained was compared with authentic samples of estradiol-17β (X)[37] and estradiol-17α[37] by paper chromatography in the system, toluene–propylene glycol. After development for 48 hr., the air-dried chromatogram was sprayed with a mixture of equal parts of 1% solutions of ferric chloride and potassium ferricyanide.[39] Under these conditions, 25γ of estradiol-17β[37] moved 13.8 cm., 25γ of estradiol-17α[37] moved 18.2 cm., and the product of treatment of IX with 0.1*N* sodium hydroxide gave a single spot at 13.3 cm.

B. *Treatment with 0.01N sodium carbonate.* A solution of 0.10 mg. of IX in 1 cc. of 95% ethanol was diluted to 10 cc. with 0.01*N* aqueous sodium carbonate and the development of absorption at 298 mμ was followed. The value, E = 0.023, obtained 2 min. after mixing, increased to E = 0.064 after 60 min., and increased only to E = 0.065 after 3 hr. After 24 hr., the absorption curve was measured and was nearly the same as that obtained with authentic 17-monoacetate of estradiol-17β (XI)[40] in the same solvent medium: λ_{min} 230 mμ, ϵ 7000; λ_{max} 238 mμ, ϵ 7400; λ_{min} 265 mμ, ϵ 1200; λ_{max} 298 mμ, ϵ 2200.

One third of the reaction mixture was now extracted with ether and the product was compared with authentic samples of IX, XI,[40] and X[37] by paper chromatography in the system, methyl cyclohexane–propylene glycol. After development for 18 hr., the air-dried chromatogram was sprayed with a mixture of equal parts of 1% ferric chloride, 1% potassium ferricyanide, and 6*N* *hydrochloric acid.*[41] Under these conditions, the reaction product gave two spots, at 0 cm. (small), and 7.8 cm. (large), and 25γ samples of IX, XI, and X gave spots at 16.5 cm., 7.5 cm., and 0 cm., respectively.

C. *Treatment with 0.01N sodium bicarbonate.* A solution of 0.10 mg. of IX in 1 cc. of 95% ethanol was diluted to 10 cc. with 0.01*N* aqueous sodium bicarbonate. The ultraviolet absorption at 298 mμ 2 min. after mixing was E = 0.014, and did not change during 24 hr. The absorption curve then determined (λ_{max} 246 mμ, ϵ 13,000) did not differ greatly from that of IX in alcohol solution (λ_{max} 244 mμ, ϵ 14,000).

After 24 hr., one third of the reaction mixture was extracted with ether, and the product was compared with authentic samples of IX, XI,[40] and X[37] by paper chromatography in the system, methyl cyclohexane–propylene glycol. After development for 18 hr., the air-dried chromatogram was sprayed with the *acidified*[41] ferric chloride–ferricyanide reagent. The reaction product gave three spots, at 0 cm. (minute), 7.7 cm. (large), and 16.3 cm. (large) from the starting line, and 25γ samples of IX, XI, and X gave spots at 16.5 cm., 7.5 cm., and 0 cm. The latter experiment was repeated in identical fashion, except that the air-dried chromatogram, obtained from approximately 50γ of reaction product, was sprayed with *neutral* ferric chloride–potassium ferricyanide reagent. The reaction product gave two spots at 0 cm. (minute) and 12.1 cm. (large) from the starting line. A 12γ sample of XI gave a single spot at 12.4 cm.

Conversion of 19-hydroxy-1-dehydrotestosterone diacetate (IX) *into the 17-monoacetate of estradiol-17β* (XI).[5] To 3.4 mg. of IX, m.p. 172–174°, in 1 cc. of methylene chloride was added 2.5 cc. of 75% methanolic 0.1*N* potassium carbonate.[28] After standing at room temperature for 1 hr., the slightly yellow solution was evaporated to dryness *in vacuo*, and the residue was then taken up in chloroform and water. Drying of the organic layer over sodium sulfate and subsequent evaporation to dryness *in vacuo* gave 3.0 mg. of material which was chromatographed over a small column of alumina (diam., 0.5 cm.; height, 4.0 cm.). Elution with benzene ether gave approx. 3 mg. of crystalline product which on recrystallization from acetone hexane gave 1.8 mg. of XI, m.p. 222–223.5°.

The substance was compared by paper chromatography in the system methyl cyclohexane–propylene glycol with two authentic samples of the 17-monoacetate of estradiol-17β: Sample A,[30] m.p. 225–226°, obtained from Dr. Carl Djerassi (Syntex, Mexico City) and sample B,[29] m.p. 221–222°, supplied by Dr. Emil Schlittler (Ciba Laboratories, Summit, N. J.). After development for 19 hr., the air-dried chromatogram was sprayed with the ferric chloride–potassium ferricyanide reagent. The above reaction product (25γ) gave a single spot at 13.2 cm. from the starting line, and sample A gave a single spot at 13.2 cm. Sample B gave two spots, at 13.1 cm. (large) and 5.1 cm. (small).

Comparison of infrared spectra (CS_2 and CCl_4 solutions): In the same solvent, the spectrum of our compound XI is identical with that of an authentic sample of the 17-monoacetate of estradiol-17β.[30] (Note: Although the material is not too soluble and the spectra were weak, there were more bands to compare than by using a more concentrated $CHCl_3$ solution which limits the regions of absorption.)

Conversion of 19-hydroxy-1-dehydrotestosterone diacetate (IX) *into estradiol-17β* (X).[5] To 5.0 mg. of IX, m.p. 170–171°, in 2 cc. of 95% ethanol was added 8 cc. of 0.1*N* sodium hydroxide. The solution was kept at room temperature for 18 hr. and was then barely acidified by the addition of hydrochloric acid. After extracting with three 20-cc. portions of ether, washing of the solvent with a saturated solution of sodium chloride, drying over sodium sulfate, and evaporating, 5.1 mg. of a colorless resin was obtained. From acetone–petroleum ether microcrystalline material separated which, on recrystallization from acetone water yielded

(36) Dried at room temperature. Drying at 80° *in vacuo* is apparently connected with partial volatilization.

(37) Reference sample kindly supplied by Dr. Albert Wettstein, CIBA-A.G.-Laboratories, Basel, Switzerland.

(38) For comparison, *v.e.g.* the curves recorded by R. P. A. Sneeden R. B. and Turner, *J. Am. Chem. Soc.*, **77**, 130 (1955).

(39) *Cf.* L. R. Axelrod, *Recent Progress in Hormone Research*, 9, Academic Press Inc., New York, 1954, p. 69.

(40) Reference sample kindly supplied by Dr. Carl Djerassi, Syntex S.A., Mexico City. *Cf.* ref. 30.

(41) IX does not react with the neutral reagent.

2.2 mg. of colorless needles, m.p. 177–180°. Mixture m.p. with an authentic sample of estradiol-17β (m.p. 184–187°),[37] 184–188°.

Infrared spectrum of X (KBr pellet): hydroxyl absorption present (very broad band); 1733 cm.$^{-1}$ (relatively small) and 1638 cm.$^{-1}$, both unexplained absorptions, indicating the presence of some impurity. Frequency-wise the region from 1400–650 cm.$^{-1}$ agrees in general with a reference standard of estradiol-17β with two exceptions, *i.e.*, a small missing band at about 1300 cm.$^{-1}$ and a small added band at about 885 cm.$^{-1}$ Intensity-wise differences exist which are possibly due to the variability of the KBr technique.

PHILADELPHIA 4, PA.

Notes

A department for short papers of immediate interest.

Phosphine Oxides. VI. Formation of Disubstituted Phosphine Oxides by Hydrolysis of Disubstituted Phosphinous Halides

ROBERT CLAY MILLER[1]

Received January 5, 1959

Disubstituted phosphine oxides (I), $R_2P(O)H$, have been prepared by the reaction of Grignard reagents[2,3] or organolithium compounds[4] with disubstituted phosphonates. Recently, two methods utilizing trivalent phosphorus reagents have been reported: the air oxidation of disubstituted phosphines in isopropyl alcohol solution[5] and the reaction under Friedel-Crafts conditions of highly methylated benzenes with phosphorus trichloride and aluminum chloride followed by hydrolysis.[6] This work reports the preparation of two examples of I by the hydrolysis of disubstituted phosphinous halides in the absence of air.

Since it has been shown that low molecular weight disubstituted phosphine oxides are unstable,[7] the previously unknown di-*n*-octylphosphinous bromide (II) was synthesized as the starting reagent. The treatment of phosphorus trichloride with two moles of *n*-octylmagnesium bromide followed by dry distillation of the solid product gave II in poor yield. Rather surprisingly, the use of

$$2n\text{-}C_8H_{17}MgBr + PCl_3 \longrightarrow \xrightarrow{\Delta\Delta} (n\text{-}C_8H_{17})_2PBr$$

phosphorus tribromide instead of phosphorus trichloride gave much smaller amounts of II. Treatment of I in refluxing benzene with water and triethylamine gave a 73% yield of the pure di-*n*-octylphosphine oxide (IA).

A similar treatment of diphenylphosphinous chloride (III) with water gave diphenylphosphine oxide, $(C_6H_5)_2P(O)H$, in fair yield. The crude deliquescent product was characterized by its known benzaldehyde addition product, $(C_6H_5)_2P(O)CH(OH)C_6H_5$.[8]

A possible path of the hydrolysis reaction would involve displacement of the halogen from the trivalent phosphorus atom by water followed by a rapid tautomerization of the phosphinous acid formed.

$$R_2P\text{—}X + H_2O \longrightarrow R_2P\text{—}O\text{—}H \rightleftharpoons R_2P(O)H$$

The nature of this reaction appears to be similar to that observed by Sallmann[9] and Michalski[10] when diethyl chlorophosphite was treated with hydrogen sulfide to yield *O,O*-diethyl thiophosphonate.

$$(C_2H_5O)_2PCl + H_2S \xrightarrow[\text{amine}]{\text{tertiary}} (C_2H_5O)_2P\text{—}S\text{—}H \rightleftharpoons (C_2H_5O)_2P(S)H$$

Certain partially oxygenated phosphorus compounds have shown themselves prone to disproportionation upon heating with or without base. Phenylphosphinic acid, $C_6H_5P(O)(H)OH$, has been reported easily converted to phenylphosphine and benzenephosphonic acid at temperatures of 100° and higher.[11] Previous workers have treated III with aqueous strong base to obtain the salt of diphenylphosphinic acid and diphenylphosphine. It was presumed that a disproportionation reaction had taken place[12] which is now proposed as involving the then unknown diphenylphosphine oxide as an intermediate.

$$2(C_6H_5)_2PCl + 2H_2O \longrightarrow [2(C_6H_5)_2P\text{—}O\text{—}H \rightleftharpoons 2(C_6H_5)_2P(O)H]$$

$$[\ldots] \xrightarrow{NaOH} (C_6H_5)_2P(O)ONa \quad (C_6H_5)_2PH$$

To ascertain if such a reaction could involve $R_2P(O)H$ as an intermediate, IA was refluxed with sodium hydroxide under nitrogen to give a 68% yield of di-*n*-octylphosphine (IV) and, after acidification, 110% of di-*n*-octylphosphinic acid. The separation of the distillable liquid phosphine from small amounts of sublimed unreacted IA was made more difficult by the great reactivity of IV with the oxygen in air. This oxidation probably accounts for

(1) (a) Present address: Department of Chemistry, De Paul University, Chicago 14, Ill. (b) For previous paper on this subject by the author, see C. D. Miller, R. C. Miller, and W. Rogers, *J. Am. Chem. Soc.*, **80**, 1562 (1958).

(2) R. H. Williams and L. A. Hamilton, *J. Am. Chem. Soc.*, **74**, 5418 (1952); **77**, 3411 (1955).

(3) B. B. Hunt and B. C. Saunders, *J. Chem. Soc.*, 2413 (1957).

(4) J. L. Willians, *Chem. and Ind. (London)*, 235 (1957).

(5) M. M. Rauhut, I. Hechenbleikner, H. A. Currier, and V. P. Wystrach, *J. Am. Chem. Soc.*, **80**, 6690 (1958).

(6) A. W. Frank, *J. Org. Chem.*, **24**, 966 (1959).

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(8) R. C. Miller, C. D. Miller, W. Rogers, and L. A. Hamilton, *J. Am. Chem. Soc.*, **79**, 424 (1957).

(9) R. Sallmann (Ciba Ltd.), U. S. Patent 2,805,241 (1957).

(10) J. Michalski and Cz. Krawiecki, *Chem. & Ind. (London)*, 1323 (1957).

(11) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley & Sons, 1950, p. 12.

(12) G. M. Kosolapoff, *Organophosphorus Compounds*, p. 52.

the discrepancy in the product balance from that expected from the following equation:

$$2R_2P(O)H + NaOH \longrightarrow R_2PH + R_2P(O)ONa$$

In the absence of base, IA can be heated to 200–250° for several hours with only a negligible loss of starting material. On the other hand, sodium di-*n*-octylphosphinate is stable under similar thermal conditions in the presence or absence of sodium hydroxide. The identity of the di-*n*-octylphosphine was ascertained by an independent two-step synthesis from IA by (1) chlorination with *N*-chlorosuccinimide and (2) reduction of the crude phosphinyl chloride in refluxing ether with lithium aluminum hydride. These two reactions have been previously used to yield IA from di-*n*-octylphosphinic acid when the reduction is carried out at lower temperatures,[2] but at higher temperatures, greater reduction to the substituted phosphine occurs. Both the disproportionation reaction and the reduction method represent reasonable route of synthesis of disubstituted phosphines.

EXPERIMENTAL

Preparation of di-n-octylphosphinous bromide from n-octylmagnesium bromide and phosphorus trichloride. A solution of *n*-octylmagnesium bromide from 164.2 g. (0.851 mol.) of *n*-octyl bromide and 21.3 g. (0.877 g.-atom) of magnesium powder in 640 ml. of anhydrous diethyl ether was added over a 2-hr. period to a mixture of 68.5 g. (0.50 mol.) of phosphorus trichloride and 200 ml. of ether at 0°. A heavy white solid which was sufficiently immobile to stop the electric stirrer was formed. This mixture was heated for 1 hr. on a steam bath, stripped of ether, and the remaining solid was heated at 1 mm. by an oil bath (maximum temperature 278°). A moderate quantity (64.7 g.) of an opaque orange oil was collected through a condenser. Two redistillations through a Vigreux column gave a 24.8 g. cut, boiling at 138.5–140.0° at 0.15–0.19 mm. The colorless liquid reacted immediately with moist air to form a white solid and was therefore always handled under nitrogen. The refractive index at 25.0° was 1.4856.

Anal. Calcd. for $C_{16}H_{34}BrP$: C, 56.97; H, 10.16; P, 9.18; Br, 23.69. Found: C, 57.30; H, 10.34; P, 9.33; Br, 23.36.

The over-all yield from the *n*-octyl bromide run was 17.2%. Most of the solid product did not decompose at the oil bath temperature. Since the crude orange product upon distillation left an easily ignited yellow-orange residue upon the condenser walls, it was found advisable to allow the column to cool to room temperature and to flush the apparatus with nitrogen before exposing the Vigreux column to the air. A similar reaction utilizing phosphorus tribromide yielded only 4.6% of the pure desired product, as the solid complex failed to markedly decompose even at oil bath temperatures of 290–300°.

Conversion of di-n-octylphosphinous bromide to di-n-octylphosphine oxide. A mixture of 4.50 g. (0.0133 mol.) of di-*n*-octylphosphinous bromide, 5.0 g. (0.27 mol.) of water, and 4.0 g. (0.040 mol.) of triethylamine in 100 ml. of benzene was refluxed under nitrogen for 2 hr. After the excess water was removed from the system by distilling it with benzene (as a benzene water azeotrope), 1.90 g. of triethylamine hydrobromide was filtered from the mixture. Upon evaporation of the filtrate, 3.45 g. of white product, melting at 81.5–83.5° was obtained.[13] A benzene solution of the crude product was washed with several portions of cold 25% aqueous potassium carbonate solution and, after evaporation of solvent and recrystallization from *n*-hexane, 2.65 g. (72.5% yield) of di-*n*-octylphosphine oxide, melting at 85.0–86.0°, was obtained. The melting point of a sample mixed with an authentic sample of IA[2] was not depressed, and the infrared spectra were identical.

Anal. Calcd. for $C_{16}H_{35}OP$: C, 70.02; H, 12.86; P, 11.29. Found: C, 69.82; H, 12.80; P, 11.62.

Hydrolysis of diphenylphosphinous chloride. A mixture of 17.0 g. (0.077 mol.) of diphenylphosphinous chloride prepared from diphenylphosphinodithioic acid,[14,15] 6.0 g. (0.33 mol.) of water, and 75 ml. of benzene was refluxed for 16 hr. under nitrogen. After removal of the excess water by azeotropic distillation and evaporation of the benzene, the remaining oil was stored under nitrogen at 0° for 4 days. A 16.5 g. crop of deliquescent needles, melting at 45–53°, was obtained which contained some halide impurity. Recrystallization from ether gave 3.0 g. of colorless needles, melting at 51–54°. The melting point was not depressed when this compound was mixed with an authentic sample of $(C_6H_5)_2P(O)H$,[3] and the infrared spectra, showing a strong P—H peak at 4.25μ, were also in agreement. A 2.50-g. quantity of the product in 5 ml. of ethanol and 2.00 g. of benzaldehyde was treated with a trace of sodium ethoxide in ethanol to yield, after standing overnight, an initial crop of 1.52 g. of white needles. After recrystallization from 2:1 aqueous ethanol, the product melted at 182.5–183.7° and was shown by mixed melting point and infrared spectrum to be identical to an authentic sample of $(C_6H_5)_2P(O)CH(OH)C_6H_5$.[8]

Disproportionation of di-n-octylphosphine oxide. A mixture of 54.8 g. (0.200 mol.) of di-*n*-octylphosphine oxide was heated with 6.0 g. (0.15 mol.) of sodium hydroxide in sealed tubes at 245° for 24 hr. On cooling, the semisolidified white mixture was transferred to a distillation flask in a nitrogen atmosphere and distilled under vacuum. The first distillation yielded a main cut of 23.1 g. of a colorless liquid, boiling at 138–145° at 0.80 mm. This product contained some solid which had initially sublimed into the condenser and was washed down into the receiver. A redistillation gave a 17.6 g. main cut boiling at 140–142° at 1.1 mm. This material had a refractive index of 1.4629 at 25.1°. The rather sweet smelling colorless liquid reacted with air and solidified immediately; it could be maintained only under nitrogen. The infrared spectrum of a sample in chloroform showed a strong P—H band at 4.43μ.

Anal. Calcd. for $C_{16}H_{35}P$: C, 74.36; H, 13.66; P, 11.99. Found: C, 74.42; H, 13.71; P, 12.05.

The pot residue of the initial distillation was acidified with dilute hydrochloric acid and the white solid obtained after evaporation of the aqueous layer was crystallized from *n*-hexane. The 31.9 g. of white solid melted at 83.5–84.7° and failed to depress the melting point of an authentic sample of di-*n*-octylphosphinic acid.[2]

Anal. Calcd. for $C_{16}H_{35}O_2P$: neut. equiv., 290. Found: neut. equiv., 288, 289.

These yields represent 68.2% and 110% of di-*n*-octylphosphine and di-*n*-octylphosphinic acid, respectively. Failure to completely separate the phosphine by distillation and oxidation of the residue by air during the work-up of the acid could account for the high yield of the phosphinic acid obtained.

Two-step reduction of di-n-octylphosphine oxide. A stirred solution of 87.4 g. (0.319 mol.) of di-*n*-octylphosphine oxide in 400 ml. of chloroform was treated with 43.5 g. (0.327 mol.) of *N*-chlorosuccinimide during 1 hr. After standing for 2 hr., the solvent was evaporated and 29.2 g. of succinimide was removed by filtration. The crude di-*n*-octylphosphinyl chloride, a yellow oil, was taken up in 200 ml.

(13) All melting points uncorrected.

(14) W. A. Higgins, P. W. Vogel, and W. G. Craig, *J. Am. Chem. Soc.*, **77**, 1864 (1955).

(15) C. Steube, W. M. LeSeur, and W. G. Craig, *J. Am. Chem. Soc.*, **77**, 3526 (1955).

of anhydrous ether and added to a slurry of 27.5 g. (0.725 mol.) of lithium aluminum hydride in 200 ml. of ether. After the mixture was refluxed for 1 hr., the excess hydride was hydrolyzed by adding an ethanol ether mixture followed by 100 ml. of water. The voluminous precipitate was filtered under nitrogen and washed with 300 ml. of ether. The combined filtrate and washings were distilled under nitrogen to obtain a 43.5 g. main cut (53% yield), boiling at 143–146° at 1.3 mm. The refractive index was 1.4626 at 26.2°, and the infrared spectrum was in complete agreement with the product previously obtained by disproportionation of IA.

Anal. Found: C, 74.64%; H, 13.88%; P, 11.85%.

EXPLOSIVES DEPARTMENT
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The Basicity of 4,4′-Bis(dimethylamino)-Azobenzene

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Although the *p*Ka of a host of 4-aminoazobenzene derivatives has been measured,[1–3] there are no data on the basicity of 4,4′-bis(dimethylamino)-azobenzene [4′-$N(CH_3)_2$-DAB]. This dye shows an unusual behavior in dilute acids inasmuch as it gives a green color[4] and only on increasing the acidity presents the red color shown by 4-dimethylaminoazobenzene (DAB) derivatives in acid media.

The *p*Ka of this dye in 50% aqueous ethanol corresponding to the first proton addition has now been determined spectrophotometrically and found to be 3.2. This value merely represents the over-all basicity because a mixture of conjugate acids is formed on protonation.[2,3,5–7]

The observed *p*Ka value makes 4′-$N(CH_3)_2$-DAB one of the most basic 4-aminoazobenzene derivatives.

This relatively high basicity is in part due to the presence in this dye, but not in monodimethylaminoazobenzenes, of a centre of symmetry; the positions of proton capture are doubled and this statistical factor, log 2, rises the *p*Ka of 0.30 *p*H units. Yet it is possible that these positions of proton capture are more than four—*i.e.*, a third monoprotonated dye coexists besides the dimethylammonium (I) and azonium (II) cations.

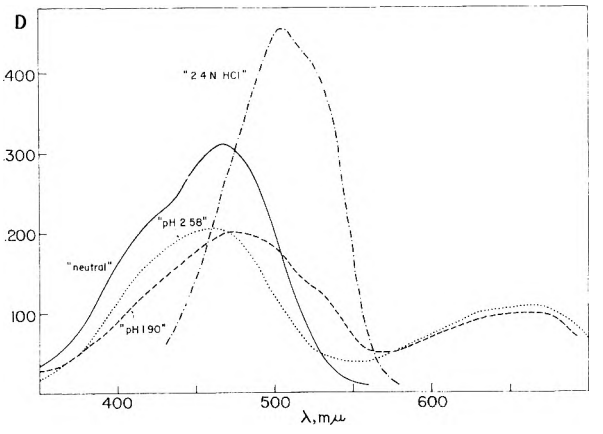
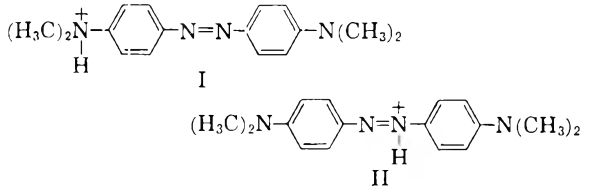


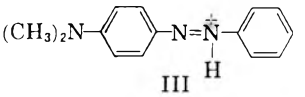
Fig. 1. Visible spectrum of 4′-$N(CH_3)_2$-DAB at different acidities. (Only a few curves are shown: ——— neutral; ····· *p*H = 2.58; - - - - *p*H = 1.90; - · - · - 2.4*N* HCl.)



I

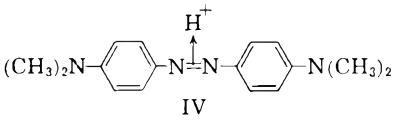
II

The evidence is mainly spectral. In the acid spectrum, λ_{max} of the longer transition is at 670 mμ (Fig. 1). This band cannot of course be due to the cation I. Sawicki[8] ascribed it to the cation II and interpreted the enormous shift with respect to the β-azonium cation of DAB (III) (λ_{max} 516 mμ) to extrachromophoric resonance.



III

This explanation is by no means convincing.[9] We propose that the 670 mμ transition is due to the cation IV, a π-complex resulting from incorporation of the π-electrons of the azo group in the vacant 1s orbital of the proton. In such a cation the positive charge can be efficiently distributed over the



IV

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(2) G. M. Badger, R. G. Buttery, and G. E. Lewis, *J. Chem. Soc.*, 1888 (1954).
(3) E. Sawicki, *J. Org. Chem.*, **22**, 621 (1957).
(4) F. Kehrmann and St. Hempel, *Ber.*, **50**, 856 (1917).
(5) G. Cilento, E. C. Miller, and J. A. Miller, *J. Am. Chem. Soc.*, **78**, 1718 (1956).
(6) A. Hantzsch and A. Burawoy, *Ber.*, **63**, 1760 (1930).
(7) E. Sawicki, (a) *J. Org. Chem.*, **21**, 605 (1956); (b) *J. Org. Chem.*, **22**, 365 (1957).
(8) E. Sawicki, *J. Org. Chem.*, **22**, 1084 (1957).
(9) This point has also been stressed by a referee who reports that "structure IIIa-IIIb in reference (8) for the monocation should absorb at about 500 mμ, because of its aza-amidinium system; and its *p*-dimethylaminophenyl substituent would lengthen its absorption some but not up to 660 mμ, as Sawicki proposes."

whole molecule. The question then arises as to the presence of the cation II. In this connection it is very important to note that the 670 mμ band overlaps another one with a hidden maximum somewhat above 600 mμ (Fig. 1). This hidden maximum is presumably due to the cation II. To secure more evidence on this point we decided to substitute the proton by other Lewis acids, in the expectation that the relative intensities and positions of the two bands could be somewhat changed and hence a better resolution be observed. This prediction was satisfactorily realized when diphenyl tellurium dichloride was the Lewis acid[10] (Fig. 2).

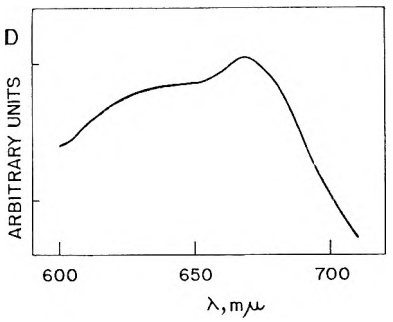


Fig. 2. Orange and red spectrum of 4′-N$(CH_3)_2$-DAB in the presence of diphenyl tellurium dichloride (solvent, ethyl alcohol).

The relatively high basicity of 4′-N$(CH_3)_2$-DAB makes it a useful detector of Lewis acid character, although high concentrations of the acceptor may be required. Thus, the green color is also developed with 1-benzyl-3-acetylpyridinium chloride (in ethanol), β-naphthyl sulfone (in benzene), diphenylselenium dichloride (in ethanol or benzene), and several derivatives of tellurium tetrachloride (in ethanol or benzene).

EXPERIMENTAL

4,4′-Bis(dimethylamino)azobenzene was a chromatographically pure product which melted sharply at 277°.

1-Benzyl-3-acetyl pyridinium chloride has recently been reported in the literature.[11] We have prepared it by a slightly different procedure. Benzyl chloride and 3-acetyl pyridine were refluxed during 3–4 hr. in ethanol. The desired product was precipitated from the reaction mixture by addition of cold ether, the temperature being kept well below zero. The crystals were washed with petroleum ether; they melted sharply at 189° (uncorr.). Reported m.p. 183–185°.[11]

All other chemicals were either available or gifts.

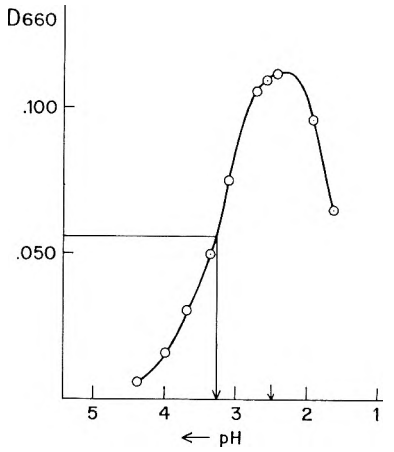
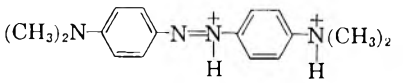


Fig. 3. Intensity of the longer wave length band in the visible spectrum of 4′-N$(CH_3)_2$-DAB *vs.* *p*H. The arrow indicates the limit of the existence of the bipositive cation.

pKa determinations. To ascertain the *p*Ka, the visible spectrum at various acidities in 50% aqueous ethanol was determined. A few representative curves are shown in Fig. 1. The solutions were prepared by adding to 12.5 ml. of aqueous HCl of various strengths, 2 ml. of the alcoholic solution of the dye and completing to 25 ml. with 95% ethanol. Final dye concentration was $8.5 \times 10^{-6} M$. Final *p*H measurements were carried out with a Beckman *p*H meter. Spectra were taken in a Beckman D.U. spectrophotometer at 25°, employing 1-cm. cells. Readings were reasonably constant and reproducible. To calculate the *p*Ka, the optical density at 660 mμ was plotted *versus* the *p*H (Fig. 3). At that wave length there is no absorption whatsoever by the free base. The curve goes through a maximum, a fact clearly to be ascribed to biprotonation; the arrow in Fig. 3 indicates the *p*H at which the red cation



starts forming in appreciable amounts. Evidently at this *p*H the curve is already leveling off. This observation allows one to take with reasonable approximation the *p*H corresponding to half maximum intensity as the *p*Ka of the dye.

Acknowledgment. The author wishes to thank Prof. J. A. Miller and Prof. E. C. Miller of Wisconsin University for valuable suggestions and also for a sample of 4,4′-bis(dimethylamino)azobenzene. He also thanks Prof. H. Hauptmann for his helpful criticism, and the Rockefeller Foundation as well as the Brazilian Conselho Nacional de Pesquisas for grants.

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(10) A small proportion of a third cation may also be present in the acid solutions of simple monodimethylaminoazobenzenes. Thus, the β-azonium band quite often shows a more or less pronounced shoulder on its longer wave length side. This shoulder can be made much more pronounced by using 1-benzyl-3-acetylpyridinium chloride as the Lewis acid.

(11) A. G. Anderson, Jr., and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958).

Use of Substituted α-Diazoacetophenones for the Preparation of Derivatives of Sulfonic Acids, *N*-Benzoylated Aminocarboxylic and Aminosulfonic Acids, *N*-Benzoylated Aminophenols, and a *N*-Benzoylated Amino Thiol[1]

THOMAS SUMNER, LAWRENCE E. BALL, AND JOHN PLATNER

Received February 17, 1959

The catalytic decomposition of α-diazoacetophenones in the presence of carboxylic acids yields esters of the acids in good yield.[2] This paper reports the extension of this reaction to sulfonic, aminosulfonic, and aminocarboxylic acids and also to amino phenols and an amino thiol.

The overall reaction is:

$$R{-}COCHN_2 + H^+ + A^- \xrightarrow{CuCl_2} R{-}COCH_2A + N_2$$

This reaction affords a rapid and convenient method for the conversion of many acids to their phenacyl esters. These compounds are usually crystalline, are easily purified, and have convenient melting points. They have long been widely used as derivatives for the identification of acids, but their preparation has frequently involved the use of disagreeable reagents.

Simple sulfonic acids react smoothly to give esters in good yield (Table I).

TABLE I

ESTERS[a] PREPARED BY THE REACTION OF *p*-BROMO-α-DIAZOACETOPHENONE WITH SULFONIC ACIDS

Acid	% Br Theory	% Br Found	M.P. of Esters (°C.)[3]
Methanesulfonic	27.27	27.09	118–119
Ethanesulfonic	26.01	25.83	87–88
Benzenesulfonic	22.50	22.77	110–111
p-Toluenesulfonic	21.64	21.60	127.5–129
2,5-Xylenesulfonic	20.85	20.62	114
m-Nitrobenzenesulfonic	19.60	19.78	125–126
p-Nitrobenzenesulfonic	19.60	19.82	173–174
2-Nitrobromobenzene-4-sulfonic	33.36	33.29	127
Thymolsulfonic	18.78	18.80	171–172
2-Chloro-5-nitrobenzenesulfonic	26.54	26.30	191–192
D-Camphorsulfonic	18.34	18.70	113–115
m-Benzenedisulfonic	25.70	24.70	68–69

[a] These esters were purified by method A.

The reaction of α-diazoacetophenones with aminosulfonic and aminocarboxylic acids fails to produce esters, probably because of the inner salt structures of these compounds which do not dissociate to produce the H^+ ion necessary for the reaction. Mixtures of the aminosulfonic acids and hydrochloric acid were also unsuccessful, the α-diazoacetophenones reacting preferentially with the mineral acid, producing α-chloroacetophenones. However, conversion of the amino group to its benzoyl derivative destroys the inner salt and permits the acid group to react to produce the desired esters (Table II).

TABLE II

ESTERS PREPARED BY THE REACTION OF *p*-NITRO-α-DIAZOACETOPHENONE WITH THE *N*-BENZOYLATED DERIVATIVES OF AMINOCARBOXYLIC ACIDS AND AMINOSULFONIC ACIDS

Acid	Purification Method	% N_2 Theory	% N_2 Found	M.P. of Esters (°C.)[3]
Glycine	B or C	8.13	8.12	134–134.5
p-Aminobenzoic	B or C	7.25	7.22	222–223
2-Aminoethyl hydrogen sulfate	D	6.86	6.83	135–136
p-Aminobenzenesulfonic	D	6.36	6.33	129–130
8-Amino-2-naphthalene sulfonic	D	5.71	5.70	128

The same substitution also allows the acid group of amino phenols and thiols to react to produce the respective ethers or thioethers.

The esters, ethers, and thioethers listed in Tables I, II, and III are believed to be new compounds.

TABLE III

ETHERS AND A THIOETHER PREPARED BY THE REACTION OF *p*-NITRO-α-DIAZOACETOPHENONE WITH THE *N*-BENZOYLATED DERIVATIVES OF AMINO PHENOLS AND AN AMINO THIOL

Phenol or Thiol	Purification Method	% N_2 Theory	% N_2 Found	M.P. of Ethers (°C.)[3]
p-Aminophenol	B	7.45	7.41	207–208
o-Aminophenol	B	7.45	7.40	183–184
m-Aminophenol	B	7.45	7.42	153–154
5-Amino-2-naphthol	B	6.57	6.64	204–205
o-Aminobenzenethiol	B	7.14	7.38	110–111

EXPERIMENTAL

p-Nitro-α-diazoacetophenone. A solution of 10 g. (0.05 mol.) of *p*-nitrobenzoyl chloride in ether is slowly added to a diazomethane solution prepared from 43 g. of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Eastman Kodak Co. 7066). The diazomethane must be present in more than an excess of 2:1 at all times during the reaction, as the HCl produced in the primary step will react with the diazo-compound to form the ω-chloro derivative unless it is removed by reaction with excess diazomethane. The product is isolated as lemon yellow prisms from the ether solution by evaporation and cooling; m.p. 109–110°. Other diazoacetophenones are prepared in the same manner using the appropriately substituted benzoyl chloride.

N-benzoyl derivatives of amino acids, amino phenols, and an amino thiol. The *N*-benzoyl derivatives were prepared by

(1) Based upon the theses presented by Lawrence E. Ball (1958) and John Platner (1954) to The University of Akron in partial fulfillment of the requirements for the degree of Master of Science.

(2) J. L. E. Erickson, J. M. Dechary, and M. R. Kesling, *J. Am. Chem. Soc.*, **73**, 5301 (1951).

(3) All melting points are uncorrected.

the reaction of the amino compounds with benzoyl chloride in pyridine solutions in the conventional manner.

Phenacyl esters and ethers. The sulfonic acids or substituted amino acids, amino phenols and amino thiols were placed in solution with equimolar quantities of the substituted α-diazo acetophenone in commercial dioxane. No appreciable reaction occurred until a trace (5 mg.) of anhydrous cupric chloride was added. The reaction mixture was then heated to 60–70° for 15 to 20 min. The reaction product was separated and purified by one of the following four methods:

Method A. The reaction mixture is poured slowly into 500 ml. of ice cold water containing 5–10 ml. of 10% K_2CO_3 solution. The ester precipitates and may be collected and recrystallized from alcohol.

Method B. The reaction mixture is heated to boiling and water is slowly added until the solution becomes permanently turbid. The solution is then cooled and the ester or ether crystallizes and may be recrystallized from alcohol.

Method C. Water is added as in method B and the mixture is shaken with an equal volume of chloroform. The chloroform layer is then washed first with 2% K_2CO_3 solution and then with distilled water, and then is dried over anhydrous calcium chloride. The chloroform solution is then concentrated and slowly cooled to −50° by the use of an acetone–dry ice bath. The ester crystallizes, may be rapidly filtered and then may be recrystallized from alcohol.

Method D. The anhydrous chloroform solution of the ester as obtained in method C is evaporated to dryness at low temperature under reduced pressure. The resulting material is recrystallized from alcohol with decolorizing charcoal added.

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Preparation and Degradation of 3α-Hydroxycholanic Acid[1]

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For another research program, a convenient method was desired for the preparation of 3α-hydroxynorcholanic acid on large scale and in high yield. Since the Barbier-Wieland degradation of 3α-hydroxycholanic acid has been described by several authors,[3,4] this degradation was undertaken.

The first step was the conversion of cholic acid into 3α-hydroxycholanic acid. This conversion was accomplished in 95% over-all yield by the modified Wolf-Kishner reduction[5] of the intermediate, methyl 3α - succinoxy - 7,12 - diketocholanate. The yield reported here could be obtained only when the modified procedure for alkali-sensitive carbonyls was adopted. Otherwise, the yields did not exceed 40%, and the purification of the reduction product was rather tedious. It appears that, unlike the monoketocholanic acids which are smoothly reduced by the ordinary Huang-Minlon modification,[5,6] the above mentioned diketocholanic acid derivative is sensitive to alkali.

The next step was the conversion of methyl 3-hydroxycholanate (I) into 3α-acetoxy-24,24-diphenylchol-23-ene (II). This conversion was accomplished in 90% yield by the known procedures.[3,4] The oxidation step of II with chromic acid in glacial acetic acid was found to be largely dependent upon reaction temperature. The highest yield (65%) of 3α-acetoxynorcholanic acid (III) was attained only when this oxidation was performed at 40–45°. Above and below this narrow temperature range, it was observed that the yield of III tended to decrease rather markedly.

The success of the ruthenium oxide–catalyzed oxidation of olefinic bonds with periodate[7] prompted the investigation of this new method for the oxidation of II into III. The present note describes the results of the use of ruthenium oxide as catalyst for the oxidation step involved in the Barbier-Wieland degradation of I.

The new method has proved to be successful with II. This involved the use of aqueous acetone (80–85%), 5 mole % of ruthenium tetroxide, and 140 mole % of solid sodium metaperiodate at 15–25°. II was readily oxidized to III and benzophenone in 78–83% yield. The over-all yield of 3α-hydroxynorcholanic acid from cholic acid was more than 70%. Osmium tetroxide,[8] used in place of ruthenium tetroxide, was found to be completely ineffective.

EXPERIMENTAL[9]

Preparation of 3α-hydroxycholanic acid. Methyl cholate (106 g.) was first converted into methyl 3α-succinoxy-7,12-diketocholanate (not isolated) by the procedure previously described,[10] and then it was mixed with 85% hydrazine hydrate (500 ml.) and ethylene glycol (1000 ml.) and the mixture was heated for 1 hr. at 100°. The resulting clear solution was cooled and then potassium hydroxide pellets (200 g.) were added portionwise through the condenser during 30 min. at room temperature. The condenser was then removed and the reaction mixture was slowly heated allowing the temperature to rise to about 200°. After re-

(1) Presented before the 21st meeting of the Israel Chemical Society, Jerusalem, 1957 [*Bull. Res. Council Israel*, 6A, 286 (1957)].

(2) Formerly Shalom Israelashvili.

(3) W. M. Hoehn and H. L. Mason, *J. Am. Chem. Soc.*, 62, 569 (1940).

(4) C. Meystre and K. Miescher, *Helv. Chim. Acta*, 29, 33 (1946).

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(8) R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, 21, 478 (1956).

(9) All m.p.s are uncorrected. Optical rotations were determined with a Zeiss polarimeter with circular scale 0.01°. Infrared spectra were taken with a Baird double beam recording spectrophotometer, Model B.

(10) H. Heusser and H. Wuthier, *Helv. Chim. Acta*, 30, 2165 (1947).

fluxing at this temperature for about 2 hr. the reaction mixture was cooled, diluted with water (3 l.), and the separated potassium salt of 3α-hydroxycholanic acid was centrifuged. The free acid (92 g.), obtained after adding concentrated hydrochloric acid to a solution of the potassium salt in hot water, was practically pure. Recrystallization from methanol yielded 90 g. of crystals melting at 184° α_D^{16} +36.5° ± 0.5° (0.68% in EtOH) (reported[10] m.p. 187–188° α_D^{11} +32.1°). The yield based upon methyl cholate used is 95%.

When the ordinary Huang-Minlon procedure was adopted for the reduction of methyl 3α-succinoxy-7,12-diketocholanate, as described previously,[11] the yield of 3α-hydroxycholanic acid was less than 40% and at the same time the free acid was obtained in an impure state requiring many recrystallizations for its purification.

Methyl 3α-hydroxycholanate (I). The esterification of 3α-hydroxycholanic acid (80 g.) was effected in quantitative yield on treatment with boiling methanolic hydrochloric acid (2.5%) (1500 ml.) for 2 hr. Recrystallization from petroleum-ether (40–60°), after chromatography over alumina, yielded the labile form of m.p. 90–92°,[12] transforming into the stable form, m.p. 125–126° (reported[12] m.p. 126–127°), after two days standing in a vacuum desiccator.

3α-Acetoxy-24,24-diphenylchol-23-ene (II). For the preparation of this compound, the usual Barbier-Wieland procedure was employed. I (0.2 mole) was treated with an excess of phenyl magnesium bromide (3.0 mole) in boiling benzene for 24 hr. The resulting carbinol (not isolated) was acetylated by means of acetic anhydride (60 ml.) and dry pyridine (100 ml.). After removal of solvents by vacuum distillation it was then dehydrated by boiling with glacial acetic acid (200 ml.) for 20 hr. The acetylated diphenylethylene (II), which crystallized out on cooling, was practically pure. Recrystallization from acetone afforded white needles melting at 160° (reported[4] m.p. 160–167°); α_D^{20} +67° (1% in $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 255–257 mμ, (log ε 4.18).

Anal. Calcd. for $C_{38}H_{50}O_2$: C, 84.7; H, 9.35. Found: C, 84.7; H, 9.39.

The infrared spectrum (KBr) showed bands (cm.$^{-1}$) at 3077, 2963, 2899 (CH), 1733 (acetate CO), 1650, 1595, 1495 (double bonds), 1246 [acetate (C—O)], 757–760, 696–700 (CH aromatic).

24,24-Diphenyl-chol-23-en-3α-ol. II was readily deacetylated by means of ethanolic potassium hydroxide. Recrystallization from ethanol gave crystals melting at 140–141° (reported[4] m.p. 110–140°); $\lambda_{max}^{CHCl_3}$ 255–258 mμ (log ε 4.23); α_D^{17} +52° ± 2° (0.2% in $CHCl_3$).

Anal. Calcd. for $C_{36}H_{48}O$: C, 87.0; H, 9.74. Found: C, 86.5; H, 9.70.

The infrared spectrum shows bands (cm.$^{-1}$) at 3460, 3413 (OH), 2950, 2878 (CH), 1653, 1600, 1493 (double bonds), 1499, 1445, 1418, 1375 (CH deformation), 757–760, 695 (phenyl).

3α-Acetoxynorcholanic acid (III). (a) *Ruthenium oxide-catalyzed periodate oxidation of* II. When the solutions of II (2 g.) in acetone (200 ml.) and ruthenium tetroxide[7] (120 mg.) in aqueous sodium periodate (5%) (10 ml.) were mixed at room temperature, an immediate black precipitate of ruthenium oxide was obtained. While the temperature of the stirred mixture was maintained at 20–25°, a total of 4.5 g. of finely powdered sodium metaperiodate was added in portions over a period of 4 hr. To the mixture (now dark brown) a few ml. of isopropanol was added to reduce the catalyst (now black), which was then removed by filtration. After removal of solvent, water was added and the mixture was extracted with ether. The extract proved to contain a mixture of benzophenone and III. They were easily separated on treatment of the ethereal extract with aqueous sodium carbonate (10%). The benzophenone, left in the ether extract, was identified by its 2,4-dinitrophenylhydrazone derivative. III was first chromatographed over silica gel (7.5 g.) using benzene as eluting solvent, and then recrystallized from aqueous acetone, giving 1.20–1.25 g. (80–83%) of pure 3α-acetoxynorcholanic acid (III) of m.p. 177–178° (reported[7] m.p. 175–176°), α_D^{20} +51° (1% in $CHCl_3$).

(b) *Chromium trioxide oxidation of* II. A suspension of II (3 g.) in glacial acetic acid (10 ml.) was mixed with a solution of chromium trioxide (3 g.) in glacial acid (80 ml.) and then left to stand in a thermostat at 40–45° for 12 hr. Excess of reagent was destroyed by the addition of dry methanol, followed by removal of solvent in vacuum and then ether extraction. The desired acid was isolated and purified in a fashion here reported, giving 1.5 g. (65%) of crystalline product of m.p. 177–178°. II was oxidized only partially at 35–36°, whereas at 100°, even after a short time, the required acid could not be obtained. This apparently led to the formation of a complex mixture of oxidation products.

3α-Hydroxynorcholanic acid. Deacetylation of III in a manner here reported, afforded in almost quantitative yield the pure 3α-hydroxynorcholanic acid after recrystallization from methanol, m.p. 185–186° (reported[12] m.p. 181–182°), α_D^{20} +32° ± 3° (0.4% in EtOH).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.55; H, 10.71. Found: C, 76.59; H, 10.82.

The infrared spectrum of this hydroxyacid shows bands (cm.$^{-1}$) at 3410–3390, 3096 (OH), 2920, 2857 (CH), 1716, 1688 (CO), 1468, 1455–1449, 1414, 1377 (CH deformation).

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Studies in Purine Chemistry. IV. Hypoxanthine-1-*N*-oxide[1]

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Purine-*N*-oxides are receiving current attention,[2–9] not only because of their potential as possible purine antimetabolites, but also because of the possibility that they may function as intermediates in biological interconversions of purines.

(1) This investigation was supported by a grant (C-2551-PET) to Princeton University from the National Cancer Institute of the National Institutes of Health.

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(8) H. von Euler and H. Hasselquist, *Arkiv för Kemi*, **13**, 225 (1959).

(9) G. M. Timmis, I. Cooke, and R. G. W. Spickett in *The Chemistry and Biology of Purines*, ed. by G. E. W. Wolstenholme and C. M. O'Connor, J. and A. Churchill, Ltd. London, 1957, p. 134.

The only purine-*N*-oxides known so far are the 1-*N*-oxides of adenine,[2-5,7] adenosine,[2,3,8] 2′,3′-isopropylideneadenosine,[2] and various adenine nucleotides,[6] mono-*N*-oxides of 2,6-diaminopurine[2] and ATP[8] and several 8-phenylpurine-7-*N*-oxides;[9] all but the latter were prepared by direct oxidation with hydrogen peroxide. This method suffers from the limitation that the position of oxidation cannot be assumed and must be determined independently, and that some purines are either degraded (*i.e.*, purine[2]) or are essentially unaffected (*i.e.*, hypoxanthine, guanine, 7-methyladenine, and uric acid[2]) by hydrogen peroxide.

We wish to report in the present paper an unambiguous synthesis of hypoxanthine-1-*N*-oxide by a route not involving peroxide oxidation. Methyl 4-nitroimidazole-5-carboxylate was prepared by known procedures and converted into the hydroxamic acid by reaction with hydroxylamine. Catalytic reduction in dimethylformamide solution, in the presence of Adams' catalyst, yielded 4-aminoimidazole-5-hydroxamic acid, which was then cyclized to hypoxanthine-1-*N*-oxide with ethyl orthoformate.[10] This cyclization is thus analogous to the previously described conversion of 2-aminopyrazine-3-hydroxamic acid to 4-hydroxypteridine - 3 - *N* - oxide (3 - hydroxy - 4(3*H*)-pteridinone).[11]

Hypoxanthine-1-*N*-oxide is moderately soluble in water, insoluble in most organic solvents, and very difficult to purify. Moreover, considerable difficulty was encountered in obtaining correct and reproducible microanalytical results because of its hygroscopicity. Samples prepared and dried in the usual manner were found to contain variable amounts of water by the time they reached the microanalyst's hand. Satisfactory microanalytical results were obtained only when the sample was allowed to equilibrate with the atmosphere, dried to constant weight at 137° (thus losing, on the average, 10.1% of its weight) and then immediately subjected to microcombustion.

Table I gives the paper chromatographic behavior and the ultraviolet absorption spectra of hypoxanthine-1-*N*-oxide. As one would expect, the R_f values for the *N*-oxide are generally higher than for hypoxanthine itself. The ultraviolet absorption spectra of hypoxanthine-1-*N*-oxide in alkaline and neutral solution exhibit two absorption maxima, the one at the shorter wave length being the more intense. The spectrum of adenine-1-*N*-oxide is similar,[3] and an intense absorption band at ~230 mμ (in neutral and in alkaline solution) may prove to be characteristic of purine-*N*-oxides in general. The spectrum of hypoxanthine-1-*N*-oxide in acid solution is similar to the spectrum of hypoxanthine itself.[12]

Catalytic reduction of hypoxanthine-1-*N*-oxide in the presence of Adams' catalyst yielded hypoxanthine, but the use of Raney nickel under conditions which sufficed for the reduction of adenine-1-*N*-oxide to adenine[3] was without effect.

TABLE I

Chromatographic Behavior Descending, 22°		Ultraviolet Absorption Spectra		
Solvent	R_f	Solvent	λ max	log ε
n-BuOH/5*N* HOAc	0.360 (0.335)[a]	0.1*N* NaOH	229	4.25
			261	3.82
3% NH_4Cl	0.603 (0.564)	H_2O	225 (s)	3.95
4% Sodium citrate	0.537 (0.537)		249	3.88
		0.1*N* HCl	248	3.91

[a] The values in parentheses are for hypoxanthine.

EXPERIMENTAL[13]

4-Nitroimidazole-5-hydroxamic acid. To a solution of 4.2 g. (0.061) mol. of hydroxylamine hydrochloride and 6.0 g. (0.15 mol.) of sodium hydroxide in 120 ml. of water was added portion-wise and with stirring 7.0 g. (0.04 mol.) of methyl 4-nitroimidazole-5-carboxylate.[14] After addition was complete, the deep yellow solution was stirred at room temperature for 2 hr. and then allowed to stand for 3 days. It was then acidified to *p*H 6 with dilute hydrochloric acid and the light yellow crystalline solid which separated was collected by filtration, washed with ice water, and dried at 100° *in vacuo* to give 6.0 g. (85.4%), m.p. 206° dec. Recrystallization from water raised the decomposition point to 220°. The material gave a very sensitive purple-red color with ferric chloride.

Anal. Calcd. for $C_4H_4N_4O_4$: C, 27.9; H, 2.34; N, 32.6. Found: C, 28.3, 28.4; H, 2.1, 2.6; N, 32.3.

Hypoxanthine-1-N-oxide. A solution of 3 g. of 4-nitroimidazole-5-hydroxamic acid in 40 ml. of dimethylformamide containing 0.3 g. of platinum oxide was hydrogenated at room temperature at 60 p.s.i. Hydrogen uptake was complete after 5 min. The reaction mixture was filtered from the catalyst and added quickly to 20 ml. of ethyl orthoformate. The resulting mixture, which now contained a light-brown solid, was heated under reflux at 155° (oil bath temperature) for 20 min. and was then poured into 100 ml. of ice water. The resulting solution containing a light-brown solid suspension was concentrated under reduced pressure to dryness and the residual solid recrystallized from methanol in the presence of a small amount of water and several drops of benzene. After three recrystallizations, 1.8 g. of a light yellow microcrystalline solid was obtained; m.p. >360°. Hypoxanthine-1-*N*-oxide gives an extremely sensitive ferric chloride test.

Anal. Calcd. for $C_5H_4N_4O_2$: C, 39.5; H, 2.7; N, 36.8. Found: C, 39.3; H, 3.3; N, 37.0, 36.6.

Reduction of hypoxanthine-1-N-oxide to hypoxanthine. A solution of 0.5 g. of hypoxanthine-1-*N*-oxide in 120 ml. of water containing 0.2 g. of platinum oxide was hydrogenated at 60 p.s.i. at 60° for 24 hr. The hot reduction mixture was

(10) A preliminary report of this synthesis was given by E. C. Taylor, T. S. Osdene, E. Richter, and O. Vogl in *The Chemistry and Biology of Purines*, ed. by G. E. W. Wolstenholme and C. M. O'Connor, J. and A. Churchill, Ltd., London, 1957, p. 23.

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(12) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

(13) All melting points are corrected. We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J.

(14) W. E. Allsebrook, J. M. Gulland, and L. F. Story, *J. Chem. Soc.* 232 (1942).

filtered from the catalyst and spotted on Whatman No. 1 paper using 3% ammonium chloride as solvent. Two spots were obtained, one corresponding to hypoxanthine and the other corresponding to unchanged hypoxanthine-1-*N*-oxide, thus indicating that reduction was incomplete. Fresh catalyst (0.29 g.) was therefore added to this solution, which was again hydrogenated at 60 p.s.i. at 80° for 2.5 days. After removal of the catalyst from the hot reduction mixture, the filtrate was again spotted on Whatman No. 1 paper, using 3% ammonium chloride as developing solvent. Only one absorption spot, corresponding to hypoxanthine, was obtained. This was confirmed by a simultaneous run with authentic hypoxanthine. Evaporation of this solution to dryness followed by recrystallization of the residue from water yielded a light tan solid which, although it still gave a positive ferric chloride test (indicating the presence of a small amount of unreduced hypoxanthine-1-*N*-oxide) apparently was essentially hypoxanthine, since it gave only one spot on paper chromatography (corresponding precisely in R_f value with authentic hypoxanthine) and its ultraviolet absorption spectrum in 0.1*N* NaOH was identical with the spectrum given by authentic hypoxanthine. It is interesting to note that the ferric chloride test in this instance is considerably more sensitive in detecting a small amount of hypoxanthine-1-*N*-oxide in the product than is paper chromatography.

Attempted reduction of hypoxanthine-1-*N*-oxide using Raney nickel under the conditions previously described for the reduction of adenine-1-*N*-oxide to adenine[3] was completely unsuccessful. No hypoxanthine could be detected in the reduction product.

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3-Substituted 1,8,8-Trimethyl-3-azabicyclo-[3.2.1]octanes

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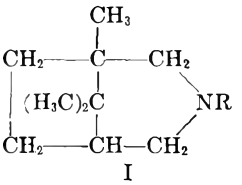
Received May 11, 1959

Recent publications[2-6] lead us to report certain aspects of our work on 3-substituted 1,8,8-trimethyl-3-azabicyclo[3.2.1]octanes, I. The 1,8,8-trimethyl-3-azabicyclo[3.2.1]octanes have been known as camphidines because of the mode of preparation from imides of camphoric acid.[7] We have made the several compounds from camphidine rather than through the imides; the method of Schmidt and Klavehn[8] provided a convenient route from camphene to camphidine.

The compounds showed only moderate activities as depressants on automatic ganglia and the central nervous system.



I

R

a. $-CH_2CH_2N(CH_3)_2$
b. $-(CH_2)_6-$

EXPERIMENTAL[9]

1,8,8-Trimethyl-3-azabicyclo[3.2.1]octane (Camphidine). The procedure was essentially that outlined by Schmidt and Klavehn,[8] wherein a ring expansion of camphene with hydrazoic acid[10] gave a mixture of 1,8,8-trimethyl-3-azabicyclo[3.2.1]octene-2 with the related octene-3 (α- and β-dehydrocamphidine) which was reduced catalytically to camphidine.

Camphene (260 g., 1.9 mol.) was dissolved in 2.8 l. of benzene which contained hydrazoic acid (160 g., 3.7 mol.).[10] The stirred solution was kept at 5 to 12° during the addition of tin (IV) chloride (1075 g., 4.12 mol.) over a 2 hr. period. It was warmed to room temperature for 0.5 hr. and allowed to stir for an hour longer before cooling to 15° and basified (*p*H 9–10) with sodium carbonate solution. Stirring was rendered difficult by the separation of white solid. The tin salt was collected after chilling and extracted well with benzene, giving a total of *ca.* 7 l. benzene solution which was then extracted with 2*N* hydrochloric acid. The dehydrocamphidines were liberated from the acidic extracts with 35% sodium hydroxide and taken up in benzene. Concentration of the dried extracts *in vacuo* was done with use of a column and a Dry Ice trap. The mixed bases were obtained in total yield of 80% (240 g.) by reworking the distillates.

A solution of 240 g. (1.58 mol.) of the mixed 1,8,8-trimethyl-3-azabicyclo[3.2.1]octenes in 500 cc. of methanol was treated with 1 g. of Adams' catalyst and 5 g. of charcoal for reduction at 25° under 1500 p.s.i. The temperature rose to 43° during the reduction, which was completed in 3 hr. Careful removal of solvent left a quantitative yield of camphidine (243 g.). The camphoraceous base was distilled with some difficulty because of its volatility b.p. *ca.* 150° (200 mm.); small quantities were purified by sublimation, m.p. 168–170°.

Anal. Calcd. for $C_{10}H_{19}N$: N,[11] 9.14. Found: N,[11] 8.84.

3-(2-Dimethylaminoethyl)-1,8,8-trimethyl-3-azabicyclo-[3.2.1]octane. A mixture of 7.7 g. (0.05 mol.) of camphidine and 5.5 g. (0.05 mol.) of 2-dimethylaminoethyl chloride was heated on the steam bath for 0.5 hr., an additional 7.7 g. of camphidine was added (because some camphidine had deposited in the condenser), and the mixture was heated for 3 hr. The cooled material was diluted with ether and a quantitative recovery (9.5 g.) of camphidine hydrochloride was obtained. The product was left as a golden oil (9.4 g., 84%) when the filtrates were concentrated. It passed over as a colorless oil at 64–65° (0.3 mm.).

(1) Present address: McNeil Laboratories, Inc., Philadelphia 32, Pennsylvania.

(2) G. Bilecki, *Med. Klinik*, **51**, 1516 (1956).

(3) Dr. Karl Thomae G.m.b.H., Belgian Patent **554,694**.

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(6) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, **22**, 1223 (1957).

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(9) Analyses were performed in the Analytical Laboratories of this Institute, under the direction of Mr. M. E. Auerbach and Mr. K. D. Fleischer.

(10) Prepared according to H. Wolff, Organic Reactions (R. Adams, editor-in-chief), J. Wiley and Sons, New York, 1946, Vol. 3, p. 327.

(11) Basic nitrogen determined by acetous-perchloric acid method of G. Toennies and T. P. Callan, *J. Biol. Chem.*, **125**, 259 (1938).

Anal. Calcd. for $C_{14}H_{28}N_2$: C, 74.94; H, 12.58; N,[11] 12.59. Found: C, 74.71; H, 12.70; N,[11] 12.12.

Methobromide was formed in 90% yield when the camphidine derivative was treated with methyl bromide in hot acetone. It crystallized from ethanol-acetone as long needles, m.p. 246–247° dec.

Anal. Calcd. for $C_{15}H_{31}BrN_2$: Br, 25.03; N, 8.77. Found: Br, 25.2; N, 8.72.

1,6-Bis 1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-3-yl hexane. Camphidine (7.7 g., 0.05 mol.), 1,6-dibromohexane (6.1 g., 0.025 mol.), anhydrous potassium carbonate (5.8 g., 0.04 mol.) and toluene (80 cc.) were stirred and refluxed for 20 hr., more camphidine (1.5 g., 0.01 mol.) and potassium carbonate (2.0 g., 0.015 mol.) were added and refluxing was resumed for 20 hr. longer. It was filtered and the filtrates extracted well with 4*N* hydrochloric acid. The base was liberated from the extracts, extracted with ether, and fractionated. 1,6-Bis 1,8,8-trimethyl-3-azabicyclo[3.2.1 octan-3-yl hexane was obtained as a golden oil (7.1 g., 73% yield) which boiled at 155–160° (0.22 mm.); $n_D^{25} = 1.5010$.

Anal. Calcd. for $C_{26}H_{28}N_2$: C, 80.34; H, 12.45; N, 7.21. Found: C, 80.33; H, 12.35; N, 7.17.

The *dihydrochloride* was prepared in ether and separated from ethanol-ether as a chalky solid, m.p. >300°.

Anal. Calcd. for $C_{26}H_{48}N_2 \cdot 2HCl$: C, 67.65; H, 10.92; Cl, 15.36. Found: C, 67.77; H, 10.61; Cl, 14.99.

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Dithiol Diesters of Long-Chain Acids[1]

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Glycol diesters of long-chain acids are well known and useful compounds. A literature search revealed that the corresponding dithiol diesters, however, apparently are not known.

Continuing our systematic study[2] of thiol esters, this paper describes the preparation and some of the properties of 1,2-ethanedithiol, 1,3-propanedithiol, 1,4-butanedithiol, and 1,5-pentanedithiol diesters of decanoic, dodecanoic tetradecanoic, hexadecanoic, and octadecanoic acids, as well as the 2-mercaptoethanol diesters of the above mentioned acids. Also prepared were 1,2-ethanedithiol and 1,4-butanedithiol dioctanoates.

The esters were prepared by the action of dithiols or 2-mercaptoethanol on acyl halides in the presence of pyridine.

$$2R{-}\overset{O}{\overset{\|}{C}}{-}Cl + HS{-}(CH_2)_n{-}SH \xrightarrow{\text{pyridine}} R{-}\overset{O}{\overset{\|}{C}}{-}S{-}(CH_2)_n{-}\overset{O}{\overset{\|}{C}}{-}SR + 2HCl$$

$$2R{-}\overset{O}{\overset{\|}{C}}{-}Cl + HS{-}CH_2{-}CH_2{-}OH \xrightarrow{\text{pyridine}} R{-}\overset{O}{\overset{\|}{C}}{-}S{-}CH_2{-}CH_2{-}O{-}\overset{O}{\overset{\|}{C}}{-}R + 2HCl$$

n = 2–5 R = C_9H_{19}, $C_{11}H_{23}$, $C_{13}H_{27}$, $C_{15}H_{31}$, $C_{17}H_{35}$

The properties of the esters, yields obtained and analytical data are summarized in Tables I and II.

When the reaction was carried out in the absence of pyridine, impure products were obtained and repeated recrystallizations of these products failed to purify them. Traces of unreacted acids were removed from the crude esters by chromatography on Florisil.

The dithiol diesters prepared are white crystalline solids. The lower members are sparingly soluble in ethanol and very soluble in acetone. Their solubility decreases in these solvents with increasing molecular weight. The lower members have a distinct mercaptan-like odor while the higher members are odorless.

Each of the five series of the dithiol diesters shows an alternation in melting points. Figure 1 represents the plot of the melting points of dithiol diesters against the number of carbon atoms in thiols. As in most homologous series, the even members melt at a higher temperature than the odd members. The reverse is true for alkanethiol esters.[3]

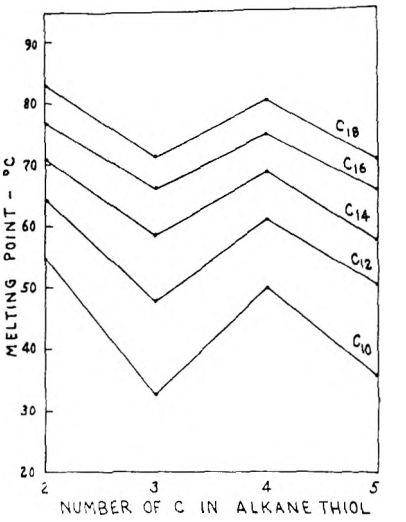

Fig. 1. Melting points of dithiol diesters

It is interesting to note that the 2-mercaptoethanol diesters melt at a lower temperature than either the corresponding 1,2-ethanedithiol or 1,2-ethane diesters.[4]

1,2-Ethanedithiol and 1,5-pentanedithiol dioctadecanoates reacted with methanol in the presence of a trace of sodium methoxide to form methyl octadecanoate by heating the reaction mixture on a steam bath for 12 hr.

(1) Taken in part from Senior Theses submitted by Paul A. Gwinner and Orestes T. Chortyk.

(2) Previous paper in this series is: *J. Org. Chem.*, **24**, 1143 (1959).

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TABLE I

DITHIOL DIESTERS

	M.P.	Yield, %	Formula	% Sulfur Calcd.	% Sulfur Found
1,2-Ethanedithiols					
Dioctanoate	42.2–42.8	62.3	$C_{18}H_{34}O_2S_2$	18.5	18.5
Didecanoate	54.7–56.0	54.7	$C_{22}H_{42}O_2S_2$	15.9	15.9
Didodecanoate	64.4–65.4	60.5	$C_{26}H_{50}O_2S_2$	13.9	13.7
Ditetradecanoate	70.8–71.4	71.0	$C_{30}H_{58}O_2S_2$	12.4	12.3
Dihexadecanoate	76.4–77.4	76.9	$C_{34}H_{66}O_2S_2$	11.2	10.9
Dioctadecanoate	82.8–83.4	41.5	$C_{38}H_{74}O_2S_2$	10.2	10.3
1,3-Propanedithiols					
Didecanoate	34.2–35.0	42.0	$C_{23}H_{44}O_2S_2$	15.4	15.4
Didodecanoate	46.0–47.0	60.4	$C_{27}H_{52}O_2S_2$	13.6	13.4
Ditetradecanoate	57.0–58.0	63.1	$C_{31}H_{60}O_2S_2$	12.1	12.2
Dihexadecanoate	64.4–65.4	70.5	$C_{35}H_{68}O_2S_2$	10.9	10.9
Dioctadecanoate	70.8–71.4	40.0	$C_{39}H_{76}O_2S_2$	10.0	10.3
1,4-Butanedithiols					
Dioctanoate	36.5–37.5	52.1	$C_{20}H_{38}O_2S_2$	17.1	17.0
Didecanoate	49.8–50.4	44.2	$C_{24}H_{46}O_2S_2$	14.9	15.0
Didodecanoate	61.6–62.0	53.5	$C_{28}H_{54}O_2S_2$	13.2	13.4
Ditetradecanoate	67.4–68.6	81.3	$C_{32}H_{62}O_2S_2$	11.8	12.0
Dihexadecanoate	73.0–74.0	74.4	$C_{36}H_{70}O_2S_2$	10.7	10.8
Dioctadecanoate	80.0–80.9	41.3	$C_{40}H_{78}O_2S_2$	9.78	9.84
1,5-Pentanedithiols					
Didecanoate	35.0–36.0	50.2	$C_{25}H_{48}O_2S_2$	14.4	14.5
Didodecanoate	50.0–51.0	52.2	$C_{29}H_{56}O_2S_2$	12.8	13.0
Ditetradecanoate	57.1–58.1	63.3	$C_{33}H_{64}O_2S_2$	11.5	11.2
Dihexadecanoate	65.5–66.5	73.2	$C_{37}H_{72}O_2S_2$	10.5	10.8
Dioctadecanoate	69.6–71.2	43.2	$C_{41}H_{80}O_2S_2$	9.57	9.67

TABLE II

2-MERCAPTOETHANOL DIESTERS

	M.P.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Didecanoate	36.0–37.0	47.2	$C_{22}H_{42}O_3S$	68.4	69.0	10.9	10.6
Didodecanoate	49.6–50.4	60.4	$C_{26}H_{50}O_3S$	70.6	70.4	11.3	11.1
Ditetradecanoate	60.2–60.6	63.1	$C_{30}H_{58}O_3S$	72.3	72.2	11.7	11.7
Dihexadecanoate	67.8–68.0	70.5	$C_{34}H_{66}O_3S$	73.8	73.8	11.9	12.0
Dioctadecanoate	73.8–74.4	46.5	$C_{38}H_{74}O_3S$	74.7	74.4	12.1	12.3

$$C_{17}H_{35}-\overset{O}{\overset{\|}{C}}-S(CH_2)_n-S-\overset{O}{\overset{\|}{C}}-C_{17}H_{35} + CH_3OH \xrightarrow{CH_3ONa} 2C_{17}H_{35}-\overset{O}{\overset{\|}{C}}-OCH_3 + HS-(CH_2)_n-SH$$

n = 2,5

The above mentioned compounds, however, unlike alkanethiol esters[5] did not undergo ester interchange reactions with phenol and thiophenol even when the reaction mixtures consisting of the dithiol diester, phenol or thiophenol, sodium methoxide, and pyridine were heated on a steam bath for 24 hr.

EXPERIMENTAL

Starting materials. Decanoic acid and dodecanoyl, tetradecanoyl and hexadecanoyl chloride were obtained from Eastman. All of the thiols were obtained from the Aldrich Chemical Co. The Humko Chemical Co. supplied S-97, commercial stearic acid. This was crystallized once from methanol and once from acetone and melted at 69°. The properties, yields obtained and analyses of the dithiol and monothiol diesters are summarized in Tables I and II.

Decanoyl chloride. This compound was prepared from decanoic acid and PCl_3 according to the method of Bauer.[6]

1,2-Ethanedithiol, 1,3-propanedithiol, 1,4-butanedithiol didecanoates, didodecanoates, ditetradecanoates, and dihexadecanoates. 2-Mercaptoethanol didecanoates, didodecanoates, ditetradecanoates, and dihexadecanoates. To 0.04 mol. of the acid chloride and 0.04 mol. of pyridine in a 200-ml. round bottomed flask, fitted with a reflux condenser, was added 0.02 mol. of the appropriate mercaptan or 2-mercaptoethanol and the mixture was allowed to stand overnight. It was heated on a steam bath for 3 hr. and then washed with two 50-ml. portions of boiling water. The solid which formed on cooling was crystallized from acetone-alcohol or acetone-benzene until successive crystallizations showed no increase in melting point.

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1,2-Ethanedithiol, 1,3-propanedithiol, 1,4-butanedithiol, and 1,5-pentanedithiol distearates. To 17 g. (0.06 mol.) of stearic acid and 100 ml. of petroleum ether in a 200-ml. round bottomed flask, fitted with a reflux condenser, was added 12 g. of PCl_5. The mixture was boiled under gentle reflux for 2 hr., cooled, and washed rapidly with four 25-ml. portions of ice water, and then dried over anhydrous Na_2SO_4.[7] To the dried solution of the acid chloride in petroleum ether was added a mixture of 0.03 mol. of the appropriate mercaptan and 0.06 mol. of pyridine in 100 ml. of petroleum ether. The rest of the procedure is identical to that used above.

2-Mercaptoethanol distearate. Stearoyl chloride was prepared by the method of Youngs *et al.* as described above. After the water wash and drying, the petroleum ether was removed by distillation and equivalent amounts of 2-mercaptoethanol and pyridine were added. The rest of the procedure is identical to that used above.

Chromatography. Analytical samples of the dithiol and monothiol diesters were chromatographed, using 20 g. of Florisil per gram of ester. The column was eluted with a total of 400 ml. of a solution containing 30% benzene–70% petroleum ether. The 1,2-ethanedithiol diesters were eluted with a total of 400 ml. of a solution containing 50% benzene–50% petroleum ether. After the solvent was removed by distillation, the product was crystallized from acetone-alcohol or acetone-benzene.

Reaction of methanol with 1,2-ethanedithiol and 1,5-pentanedithiol dioctadecanoate. To 0.005 mol. of 1,2-ethanedithiol or 1,5-pentanedithiol dioctadecanoate in a 200-ml. round bottomed flask, fitted with a reflux condenser, was added 0.05 g. of sodium methoxide and 70 ml. of methanol and the mixture was heated on a steam bath for 12 hr. At the end of the heating period, the methanol was removed by distillation and the product was dissolved in 100 ml. of ether. After the ether solution was washed with three 50-ml. portions of water, it was dried over anhydrous sodium sulfate. The ether then was removed by distillation and the methyl stearate was crystallized from methanol. The yield of product was 60–65% of the theoretical amount. Admixture of the products with an authentic sample of methyl stearate showed no depression of melting point.

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Benzilates and Related Esters of Aminophenylethanols

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Received May 28, 1959

In continuation of our exploration of derivatives of the aminophenylethanols,[1] a series of basic esters (Table I) of the formula $R_1COOCH(C_6H_5)$-$CH_2NR_2R_3.R_4X$ (I) has been synthesized and examined for pharmacological activity.

Esters evaluated included benzilates[2] as well as variants of R_1CO— of lesser molecular bulk.[3] Structural relationships with proven active drugs suggested examination of the basic esters I as central nervous system depressants,[4] anti-tremorine agents,[5] and local anesthetics.[3d]

Treatment of the aminophenylethanol[1] with the acid chloride R_1COCl gave the basic ester I, either isolated directly as the hydrochloride, or converted to its free base which was distilled. The corresponding benzilates were prepared from the α-chloro-α,α-diphenylacetates by hydrolysis.[6]

Selected compounds showed activity as anesthetic agents,[7] reversed the neurotoxicity of tremorine,[8] depressed motor activity,[9] and were active as hypotensive agents.[10]

EXPERIMENTAL[11]

The acid chlorides were available commercially, or were processed as described in the literature in the instance of ω-cyclohexylbutyryl chloride,[12] and α-chloro-α,α-diphenylacetyl chloride.[13]

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(5) (a) J. J. Denton, H. P. Schedl, V. A. Lawson, and W. B. Neier, *J. Am. Chem. Soc.*, 72, 3795 (1950) and preceding papers; (b) M. Harfenist and E. Magnien, *J. Am. Chem. Soc.*, 78, 1060 (1956).

(6) F. F. Blicke, J. A. Faust, and H. Raffelson, *J. Am. Chem. Soc.*, 76, 3161 (1954).

(7) Following the procedure outlined in ref. 3d, the data were reported in this order: compound no. of Table I/LD_{min} mg./kg./$ANED_{50}$ mg./ml.: 37/1000/7; 38/750/5.5; 39/100/6.7; 41/>1000/14; 43/1000/2.4; 46/1000/3.5; 50/750/1.5.

(8) Following the procedure outlined in ref. 3d, the compound No. of Table I/LD_{min} mg./kg./TED_{50} mg./kg. was noted: 34/750/75; 35/100/18; 36/450/89; 40/750/100; 49/250/56; 54/200/52.

(9) Following the procedure given by S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, 80, 1648 (1958), the compound No. of Table I/LD_{min} mg./kg./% depression of motor activity/test dose mg./kg. is given: 35/100/34/20; 40/750/30/100; 52/80/24/20.

(10) Following the procedure given by S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, 80, 2743 (1958), compound 47 had 3+ activity and compounds 35, 36, 42, 45, 49, and 52 had 2+ activity.

(11) Descriptive data shown in the table are not reproduced in the Experimental section. Typical examples of the synthesis are given.

(12) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, 15, 1082 (1950).

(13) F. E. King and D. Holmes, *J. Chem. Soc.*, 164 (1947).

			(0.1)									
16	C_2H_5— C_2H_5—	CH_3Br	132–133	A	39	$C_{23}H_{32}BrNO_2$	63.6	63.2	7.4	7.5	3.2	3.5
17	—$(CH_2)_4$—	HCl	197–198	D	69	$C_{22}H_{28}ClNO_2$					3.8	3.6
18	—$(CH_2)_4$—	CH_3Br	184–185	C	65	$C_{23}H_{30}BrNO_2$					3.2	3.1
19	—$(CH_2)_4$—	C_2H_5Br	125–127	A	55	$C_{24}H_{32}BrNO_2$	64.6	64.9	7.2	7.2	3.1	3.3
	R_1 = $C_6H_5CH(C_2H_5)$—											
20	C_2H_5— C_2H_5—		142–146 (0.03)		92	$C_{22}H_{29}NO_2$	77.8	77.9	8.6	8.7	4.1	3.9
21	—$(CH_2)_4$—	HCl	188–190	C	49	$C_{22}H_{28}ClNO_2$	70.7	71.1	7.6	7.3	3.8	4.0
22	—$(CH_2)_4$—	CH_3Br	153–155	A	67	$C_{23}H_{30}BrNO_2$	63.9	63.6	7.0	6.5	3.2	2.9
23	—$(CH_2)_4$—	C_2H_5Br	173–174	D	54	$C_{24}H_{32}BrNO_2$	64.6	64.5	7.2	7.2	3.1	3.1
	R_1 = $C_5H_{11}CH_2CH_2CH_2$—[f]											
24	CH_3— CH_3—	HCl	175–178	B	61	$C_{14}H_{28}ClNO_2$	60.5	60.0	10.2	10.0		
25	CH_3— CH_3—	CH_3I	143–145	G	60	$C_{21}H_{34}INO_2$	47.0	47.2	7.9	8.0		
27	—$(CH_2)_4$—	HCl	182–184	B	75	$C_{22}H_{34}ClNO_3$	69.5	69.8	9.0	9.3		
28	—$(CH_2)_4$—	CH_3I	118–121	G	72	$C_{23}H_{36}INO_2$	56.9	57.0	7.5	7.4		
29	—$(CH_2)_4$—	C_2H_5Br	157–159	H	13	$C_{24}H_{38}BrNO_2$	63.7	63.5	8.5	8.4	3.0	2.7
30	—$(CH_2)_5$—	HCl	128–131	B	66	$C_{23}H_{36}ClNO_2$[h]	65.1	64.6	10.3	10.4		
	R_1 = $(C_6H_5)_2CH$—											
31	C_2H_5— C_2H_5—		194–195 (0.2)		74	$C_{26}H_{29}NO_2$	80.6	80.3	7.5	7.3	3.6	3.8
32	C_2H_5— C_2H_5—	CH_3I	161–163	D	63	$C_{27}H_{32}INO_2$					2.7	2.8
33	C_2H_5— C_2H_5—	C_2H_5I	152–157	C	48	$C_{28}H_{34}INO_2$	61.9	61.9	6.3	6.4	2.6	2.6
	R_1 = $(C_6H_5)_2CCl$—											
34	CH_3— CH_3—	HCl	141–143	I	25	$C_{24}H_{25}Cl_2NO_2$					3.3	3.3
35	CH_3— i-C_3H_7—	CH_3I	151	I	25	$C_{17}H_{31}ClINO_2$	57.5	57.3	5.5	5.6	2.5	2.0
36	CH_3— C_6H_{11}—[f]	HCl	185–187	D	59	$C_{29}H_{33}Cl_2NO_2$	69.9	70.4	6.7	6.7		
37	C_2H_5— C_2H_5—	HCl	138–139	C	32	$C_{26}H_{29}Cl_2NO_2$	68.1	68.3	6.4	6.2	3.1	2.7
38	—$(CH_2)_4$—	HCl	178–181	C	31	$C_{26}H_{27}Cl_2NO_2$	68.4	68.2	6.0	5.9	3.1	3.0
39	—$(CH_2)_4$—[i]	HCl	182–184	C	25	$C_{26}H_{27}Cl_2NO_2$	68.4	67.9	6.0	5.8		
40	—$(CH_2)_5$	HCl	169–171	A	66	$C_{27}H_{29}Cl_2NO_2$	68.9	68.2	6.2	6.8	3.0	3.3
41	—$(CH_2)_2O(CH_2)_2$—	HCl	184–186	D	36	$C_{26}H_{27}Cl_2NO_3$	66.1	66.1	5.8	6.0	3.0	3.1
42	i-C_3H_7— $C_6H_5CH_2$—	HCl	153–155	C	21	$C_{32}H_{33}Cl_2NO_2$	71.9	72.1	6.2	6.2		

TABLE I

$R_1COOCH(C_6H_5)CH_2NR_2R_3.R_4X$

No.	R_2	R_3	R_4X	M.P.[a] or B.P. (Mm.)	RS[b]	Yield,[c] %	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
	$R_1 = C_3F_7$—												
1	C_2H_5—	C_2H_5—	HCl	117–118	A	17	$C_{16}H_{19}ClF_7NO_2$	45.1	45.3	4.5	5.1	3.3	3.1
	$R_1 = C_6H_5CH_2$—												
2	C_2H_5—	C_2H_5—	HCl	146–148	B	43	$C_{20}H_{26}ClNO_2$	69.0	69.2	7.5	7.3		
3	C_2H_5—	C_2H_5—	C_2H_5I	132–134	A	40	$C_{22}H_{30}INO_2$	56.5	56.6	6.5	6.5	3.0	2.8
4	C_2H_5—	C_2H_5—	EBA[e]	162–163	C	49	$C_{24}H_{32}BrNO_4$	60.2	60.1	6.7	6.8	2.9	2.8
	$R_1 = C_6H_{11}CH_2$—[f]												
5	C_2H_5—	C_2H_5—		155–157 (0.6)		56							
6	C_2H_5—	C_2H_5—	Pic[g]	76–78	D		$C_{26}H_{34}N_4O_9$	57.1	57.4	6.2	6.2		
7	C_2H_5—	C_2H_5—	EBA[e]	163–165	B	68	$C_{24}H_{38}BrNO_4$	59.5	59.7	7.9	7.8	2.9	3.3
8		—$(CH_2)_4$—	HCl	195–197	E	66	$C_{20}H_{30}ClNO_2$	68.3	68.1	8.6	8.4	4.0	4.0
9		—$(CH_2)_4$—	CH_3Br	189–191	C	52	$C_{21}H_{32}BrNO_2$	61.3	61.4	8.1	7.6		
10		—$(CH_2)_4$—	C_2H_5Br	157–158	A	67	$C_{22}H_{34}BrNO_2$	62.3	62.3	8.1	7.9		
11		—$(CH_2)_4$—	EBA[e]	150–151	A	57	$C_{24}H_{36}BrNO_4$	59.7	60.2	7.5	7.3	2.9	2.8
	$R_1 = C_6H_5CH_2CH_2$—												
12	C_2H_5—	C_2H_5—	HCl	114–116	F	69	$C_{21}H_{28}ClNO_2$	69.7	70.0	7.8	7.6		
13	C_2H_5—	C_2H_5—	CH_3Br	127–129	A	38	$C_{22}H_{30}BrNO_2$	62.9	63.0	7.2	7.3	3.3	3.3
14	C_2H_5—	C_2H_5—	EBA[e]	129–132	A	47	$C_{25}H_{34}BrNO_4$	61.0	61.3	7.0	6.9	2.8	2.7
	$R_1 = C_6H_5CH_2CH_2CH_2$—												
15	C_2H_5—	C_2H_5—		146–150 (0.1)		31	$C_{22}H_{29}NO_2$	77.8	77.9	8.6	8.4	4.1	3.8

TABLE I (*Continued*)

No.	R_2	R_3	R_4X	M.P.[a] or B.P. (Mm.)	RS[b]	Yield,[c] %	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
	$R_1 = (C_6H_5)_2C(OH)$—												
43	CH_3—	CH_3—	HCl	183–185	C	71	$C_{24}H_{26}ClNO_3$	70.0	70.2	6.4	6.1	3.4	3.1
44	CH_3—	CH_3—	CH_3I	176–178	C	69	$C_{25}H_{28}INO_3$	58.0	58.0	5.5	5.5	2.7	2.5
45	CH_3—	*i*-C_3H_7—	HCl	170–172	C	39	$C_{26}H_{30}ClNO_3$	71.0	70.5	6.9	7.0	3.2	2.8
46	C_2H_5—	C_2H_5—	HCl	164–165	C	80	$C_{26}H_{30}ClNO_3$	71.0	70.9	6.9	6.9	3.2	3.4
47	C_2H_5—	C_2H_5—	CH_3I	178–179	C	58	$C_{27}H_{32}INO_3$	59.5	59.3	5.9	6.1	2.6	2.6
48	CH_3—	C_6H_{11}—[f]	HCl	193–196	D	23	$C_{29}H_{34}ClNO_3$	72.6	72.7	7.1	7.2	2.9	3.1
49	CH_3—	C_6H_{11}—[f]	CH_3I	125–127	C	24	$C_{30}H_{36}INO_3$	61.5	61.9	6.2	6.6	2 4	2.8
50	—$(CH_2)_4$—		HCl	193–195	E	46	$C_{26}H_{28}ClNO_3$	71.3	71.2	6.4	6.6	3.2	2.8
51	—$(CH_2)_4$—		CH_3I	141–143	C	64	$C_{27}H_{30}INO_3$					2.6	2.7
52	—$(CH_2)_4$—		EBA[e]	168–169	D	49	$C_{30}H_{34}BrNO_5$	63.4	63.3	6.0	6.2	2.5	2.4
53	—$(CH_2)_5$—		HCl	203–205	D	49	$C_{27}H_{30}ClNO_3$	71.7	71.4	6.7	6.9	3.1	3.0
54	—$(CH_2)_5$—		CH_3I	178–181	C	43	$C_{28}H_{32}INO_3$	60.3	60.0	5.8	5.6	2.5	2.9
55	—$(CH_2)_2O(CH_2)_2$—		HCl	198–200	D	65	$C_{26}H_{28}ClNO_4$	68.8	69.1	6.2	6.2	3.1	2.8
56	*i*-C_3H_7	$C_6H_5CH_2$—	HCl	161–163	D	29	$C_{32}H_{36}ClNO_4$[j]	72.1	71.6	6.8	6.6	2.6	2.8

[a] Melting points are not corrected. [b] RS = recrystallizing solvent: A = methyl ethyl ketone; B = isopropyl alcohol–isopropyl ether; C = isopropyl alcohol; D = ethanol; E = acetonitrile; F = benzene; G = not recrystallized; H = chloroform-ether; I = *n*-propanol. [c] Yields are expressed as % of recrystallized or distilled product. [d] Analyses by Weiler and Strauss, Oxford, England. [e] EBA = ethyl bromoacetate quaternary salt. [f] C_6H_{11} = cyclohexyl. [g] Pic = picric acid. [h] Chlorine, Calcd.: 10.7. Found: 10.9. [i] The compound is derived from the isomeric 2-(1-pyrrolidino)-2-phenylethanol (described in ref. 1). [j] The formula represents a monohydrate.

2-Diethylamino-1-phenylethyl diphenylacetate (Compound 31). To a stirred solution of 23.1 g. (0.1 mol.) of diphenylacetyl chloride in 100 ml. of benzene was added 19.3 g. (0.1 mol.) of 2-diethylamino-1-phenylethanol in 100 ml. of benzene at a rate sufficient to maintain reflux. After heating under reflux for 3 hr., the benzene was removed and the residue treated with 250 ml. of water, cautiously basified with 40% aqueous sodium hydroxide and the separated free base extracted with five 60-ml. portions of ether. The combined extracts were dried (anhydrous magnesium sulfate), filtered, and distilled to give 74% of product, b.p. 194–195° (0.2 mm.).

2-Diethylamino-1-phenylethyl diphenylacetate methiodide (Compound 32). To a cooled solution of 3.9 g. (0.01 mol.) of 2-diethylamino-1-phenylethyl diphenylacetate in 20 ml. of acetonitrile was added 1 ml. (0.016 mol.) of methyl iodide. The solution was allowed to stand 20 hr. at room temperature and then poured into 150 ml. of dry ether. Trituration of the precipitated gum with several additional portions of dry ether gave 4.9 g. (93%) of product, m.p. 154–159°.

2-Piperidino-1-phenylethyl α-chloro-α,α-diphenylacetate hydrochloride (Compound 40). A solution of 19.9 g. (0.075 mol.) of α-chlorodiphenylacetyl chloride in 70 ml. of acetonitrile was added to a suspension of 14.3 g. (0.07 mol.) of 2-piperidino-1-phenylethanol in 30 ml. of acetonitrile. After storage at 20° for 24 hr. there was obtained 30.2 g. of product.

2-Diethylamino-1-phenylethyl benzilate hydrochloride (Compound 46). A suspension of 18 g. (0.039 mol.) of 2-diethylamino-1-phenylethyl α-chloro-α,α-diphenylacetate hydrochloride in 900 ml. of water upon warming on a steam bath for 20 min., yielded a clear solution. Sodium chloride (180 g.) was then added and the precipitate and solution extracted with a total of 2 l. of chloroform. The chloroform was removed and the residue recrystallized (isopropyl alcohol) to give 13.8 g. (80%) of product; m.p. 164–165°.

2-Diethylamino-1-phenylethyl benzilate methiodide (Compound 47). Methyl iodide (2.9 g., 0.02 mol.) was added to a cooled solution of 5.4 g. (0.013 mol.) of 2-diethylamino-1-phenylethyl benzilate in 26 ml. of acetonitrile. Upon storage for 20 hr. at 20° and scratching, the product crystallized, and was separated and recrystallized (isopropyl alcohol) to give 4.1 g. (58%) of product; m.p. 178–179°.

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Bicarbonate-catalyzed Displacement of a Nitro Group of 1,3,5-Trinitrobenzene

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During an investigation of methods for the selective reduction of one of the nitro groups of *sym*-trinitrobenzene, reduction by means of sodium sulfide and sodium bicarbonate in aqueous methanol was tried.[1] Among the reaction products none of the desired 3,5-dinitroaniline could be detected, but 3-amino-5-nitroanisole was isolated in 20% yield. Since the displacement of aromatic nitro groups by alcohols has previously been reported to occur only in strongly alkaline media,[2,3] this result was unexpected. The conditions for this displacement were then investigated and at the same

(1) H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, 794 (1945) used this method for the mono-reduction of dinitro- and trinitronaphthalenes.

(2) C. A. Lobry de Bruyn and F. H. van Leent, *Rec. trav. chim.*, 14, 150 (1895).

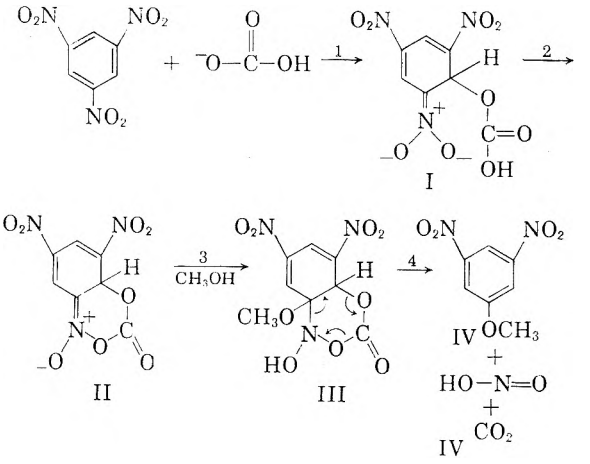
(3) F. Reverdin, *Org. Syntheses*, Coll. Vol. I, 219 (1941).

time the sequence of the substitution and reduction reactions was readily demonstrated. It was found that heating *sym*-trinitrobenzene in 76% aqueous methanol in the presence of either sodium or potassium bicarbonate or sodium carbonate in the absence of sulfide likewise resulted in the displacement of a nitro group, 3,5-dinitroanisole being obtained in 60–80% yield. In contrast, 3,5-dinitroaniline was inert under these conditions and since the mono-reduction of 3,5-dinitroanisole to 3-amino-5-nitroanisole under similar conditions had been observed previously,[4] the sequence of steps were clearly established as substitution followed by reduction.

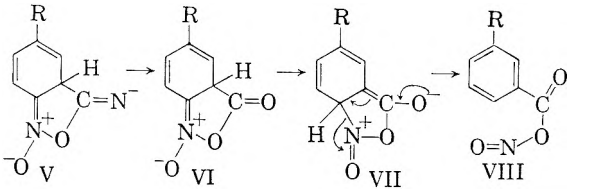
Attempts were made to effect the displacement of a nitro group in *sym*-trinitrobenzene by treatment in aqueous methanolic solutions with other catalysts such as sodium acetate, dibasic sodium phosphate, sodium iodide, ammonium carbonate, and carbon dioxide. Starting trinitrobenzene was recovered in each case in 70–100% yields. In contrast heating *sym*-trinitrobenzene in 0.6*N* aqueous methanolic sodium hydroxide solution gave only dark-colored, amorphous substances. When the bicarbonate-catalyzed substitution was carried out in aqueous ethanol, the reaction likewise gave tarry, dark-colored substances from which no 3,5-dinitrophenetole could be isolated. In this case, it appeared that the prevailing reactions were those brought about by the reducing action of ethanol.[2] On the supposition that the displacement might be the result of a weakly alkaline effect, the trinitrobenzene was boiled with 76% aqueous methanol containing sufficient sodium hydroxide to give it an initial *p*H of 11. But in this case also, no 3,5-dinitroanisole was obtained, the only identifiable substance at the end of the reaction being starting material. In contrast to trinitrobenzene, *m*-dinitrobenzene was totally inert to aqueous methanol and sodium bicarbonate.

The above experiments seem to point up a rather unique specificity of the bicarbonate and carbonate anions in their roles as catalysts in the displacement of the nitro group. A mechanism that seems reasonable for these conditions and which is in harmony with the chemical behavior of trinitrobenzene and the bicarbonate anion is shown in the scheme top of column 2:

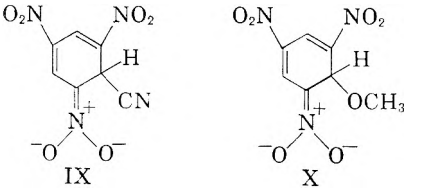
This mechanism, through the formation of the intermediates I and II, is analogous to that presented by Bunnett and Rauhut[5] for the von Richter reaction. Their mechanism is characterized by cyanide attack on the position *ortho*- to the nitro group, followed by local interaction of the two groups to give rise to V which upon hydrolysis becomes VI. The transition complex III resembles VII to a degree, an essential difference between the



two being that in III, the position occupied by the nitro group bears a methoxyl group instead of a proton. The presence of the methoxyl group in III is the expected result of a nucleophilic attack on II by methanol from the basic medium. In an attempt to substantiate a nucleophilic attack at this point,



a bicarbonate-catalyzed reaction was conducted in the presence of potassium iodide in the hope that iodide might compete with methanol to give rise to some 3,5-dinitroiodobenzene. Only 3,5-dinitroanisole was isolated. The addition of bicarbonate ion to give I finds further analogy in structures IX and X which were assigned by Meisenheimer[6] to the stable adducts of *sym*-trinitrobenzene with



potassium cyanide and potassium methylate respectively. These compounds are responsible for the deep red colors developed when trinitrobenzene comes in contact with bases, bicarbonates included.

EXPERIMENTAL[7]

3-Amino-5-nitroanisole. To a refluxing solution of 10 g. (0.047 mol.) of 1,3,5-trinitrobenzene in 150 ml. of methanol was added 2.4 g. (0.028 mol.) of sodium bicarbonate. This was followed by the dropwise addition of a solution com-

(4) J. J. Blanksma, *Rec. trav. chim.*, **28**, 105 (1909).

(5) J. F. Bunnett and M. M. Rauhut, *J. Org. Chem.*, **21**, 944 (1956).

(6) J. Meisenheimer, *Ann.*, **323**, 205 (1902).

(7) Melting points are uncorrected. The microanalyses were carried out under the direction of Dr. J. A. Kuck, Stamford Laboratories, American Cyanamid Company, Stamford, Conn.

posed of 25 g. (0.10 mol.) of sodium sulfide nonahydrate, 8 g. (0.1 mol.) of sodium bicarbonate, 60 ml. of water, and 40 ml. of methanol. When one half of this mixture had been added, another 2.4 g. (0.028 mol.) of sodium bicarbonate was added to the reaction mixture in one lot. The addition of the sulfide-bicarbonate solution was carried out over a 1.5 hr. period. After that, the reaction was refluxed for an additional 0.5 hr. and allowed to cool. A rust-colored material precipitated from the dark solution. It weighed 1.4 g. (20%). Recrystallization from 40% aqueous ethanol gave material of m.p. 119–120°. Another recrystallization from 50% aqueous ethanol gave matted, orange needles melting at 118.5–119°. A mixed m.p. with an authentic sample of 3-amino-5-nitroanisole (Lit. m.p. 118°)[8] was not depressed.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.84; N, 16.66. Found: C, 49.75; H, 4.79; N, 16.95.

Another crop of crystalline material weighing 2.1 g. was obtained from the original reaction solution. This substance melted at 100–115° after a recrystallization from water containing a small amount of ethanol. Further recrystallizations from other solvents did not change this m.p. The material appeared to be a mixture of two or more compounds, one of which is probably the aminonitroanisole. It was not purified further.

3,5-Dinitroanisole. To a hot solution of 10 g. (0.047 mol.) of 1,3,5-trinitrobenzene in 150 ml. of methanol, was added a slurry of 12.8 g. (0.15 mol.) of sodium bicarbonate in a mixture of 60 ml. of water and 40 ml. of methanol. The red mixture was refluxed and stirred for 2.5 hr. and allowed to cool over a period of several hours. The tan crystals which precipitated were filtered and dried in a desiccator. Recrystallization from 200 ml. of hot methanol gave 5.5 g. (60%) of nearly colorless product, m.p. 104–106°. This melting point was not depressed by admixture with an authentic sample of 3,5-dinitroanisole (Lit. m.p. 105°).[3] Additional crystalline fractions were obtained from the mother liquors indicating a higher yield of product. These fractions, however, were not brought to a constant melting point.

When the reaction was run with potassium bicarbonate a more easily purified product melting at 104–106° was obtained in 86% yield, while sodium carbonate (0.15 mol. under the same conditions as described above) gave the product in 70% yield.

Attempted reactions with sodium acetate, dibasic sodium phosphate dodecahydrate, sodium iodide, ammonium carbonate, and carbon dioxide. A mixture of 0.05 mol. of 1,3,5-trinitrobenzene, 0.15 mol. of the requisite salt, and 250 ml. of 76% aqueous methanol was refluxed for 3 hr. In all cases, at least 70% of the trinitrobenzene was easily recovered by cooling the reaction mixture and washing the pale yellow crystals with water and cold methanol. The identity of starting material was shown by mixed m.p.'s.

In the case of the carbon dioxide experiment, this gas was bubbled through a boiling 76% aqueous methanol solution of trinitrobenzene for 3 hr. The recovery of the starting material was quantitative.

Behavior of 1,3,5-trinitrobenzene with strong alkali. To a hot solution of 10 g. (0.05 mol.) of 1,3,5-trinitrobenzene in 150 ml. of methanol was added 6 g. (0.15 mol.) of sodium hydroxide dissolved in a mixture of 60 ml. of water and 40 ml. of methanol. The dark red solution was stirred under reflux for 3 hr. No crystalline product was obtained from the black, amorphous reaction product.

Behavior of 1,3,5-trinitrobenzene with sodium bicarbonate in the presence of potassium iodide. To a hot solution of 10 g. (0.05 mol.) of 1,3,5-trinitrobenzene in 150 ml. of methanol was added a slurry of 12.8 g. (0.15 mol.) of sodium bicarbonate and 16.6 g. (0.1 mol.) of potassium iodide in a mixture of 60 ml. of water and 40 ml. of methanol. The red mixture was stirred under reflux for 2.5 hr., and cooled. A crystalline material precipitated which was filtered and recrystallized from 100 ml. of methanol. The crystals weighed 3.7 g. and melted at 104–106°. A mixed m.p. with an authentic sample of 3,5-dinitroanisole was not depressed. The original reaction solution was evaporated to about one-half volume whereupon another 1.6 g. of crude crystals was obtained. Two recrystallizations from ethanol gave a compound melting at 120–122°, which by mixed m.p. was shown to be unreacted 1,3,5-trinitrobenzene. The mother liquor was concentrated further to a small, dark, aqueous solution, which was extracted with ether several times. Evaporation of the ether gave a negligible amount of solid which was recrystallized from ethanol and melted at 120–122°. A mixed m.p. with 1,3,5-trinitrobenzene was not depressed. The yield of 3,5-dinitroanisole calculated on recovered TNB was 47%.

Attempted reaction of m-dinitrobenzene with sodium carbonate. To a solution of 4 g. (0.024 mol.) of *m*-dinitrobenzene in 75 ml. of methanol was added a suspension of 8 g. of sodium carbonate (0.075 mol.) in a mixture of 30 ml. of water and 20 ml. of methanol. No color change occurred. The mixture was stirred under reflux for 2.5 hr. and cooled in ice. The precipitated crystals were filtered and recrystallized from aqueous ethanol giving 4 g. of crystals melting at 89–90°. This m.p. remained undepressed by admixture with authentic *m*-dinitrobenzene.

Attempted reaction of 3,5-dinitroaniline with sodium bicarbonate. A 1 g. (0.005 mol.) sample of 3,5-dinitroaniline (m.p. 161–162°)[9] was dissolved in 15 ml. of not methanol. A slurry of 1.3 g. (0.015 mol.) of sodium bicarbonate in a mixture of 6 ml. of water and 7 ml. of methanol was added, and the reaction was refluxed for 3 hr. On cooling, yellow crystals precipitated. These were filtered and air-dried, giving 0.9 g. of material melting at 159–161°. A mixed m.p. with 3,5-dinitroaniline was not depressed.

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(8) J. J. Blanksma, *Rec. trav. chim.*, **24**, 40 (1905).

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Synthesis of 2,4,5-Trichloro-Cl^{36}-phenol

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2,4,5-Trichlorophenol is a versatile compound in agricultural pest control, appearing in many products either as such, or as an integral part of some other chemical molecule. Our investigations required the use of the chlorine-36 labeled compound; since it was not available, its synthesis was undertaken.

Because we had a quantity of the compound[1] 1,2,4,5 - tetrachloro - *1-*Cl^{36} - benzene, the obvious

(1) R. W. Meikle, *J. Org. Chem.*, **24**, 277 (1959).

pathway to 2,4,5-trichloro-Cl^{36}-phenol was through hydrolysis.[2]

EXPERIMENTAL

2,4,5-Trichloro-Cl^{36}-phenol. The compound[1] 1,2,4,5-tetrachloro-*1*-Cl^{36}-benzene (84.8 mg., 0.39 mmol., specific activity 20.8 μc./mmol.) and 2 ml. of 5*M* sodium hydroxide in methanol[3] were sealed in a Pyrex test tube (1.4 × 14 cm.). The atmosphere in the tube was dry nitrogen. The tube was put in a Parr high-pressure bomb together with sufficient methanol to equalize the pressure within the tube. The bomb was heated without shaking for a total of 5 hr.[4,5] and then cooled as rapidly as possible under tap water. Fifty min. was required for the temperature of the bomb to reach the operating temperature of 160°.

As soon as the bomb was cool, the tube was removed. Sodium chloride was visible as a precipitate in the bottom of the tube. The contents were quantitatively transferred to a steam distillation apparatus (commonly used for Kjeldahl nitrogen determinations) and any unreacted starting material or such by-products as trichloroanisole, or both, were removed by steam distillation. None of these compounds were found in the first 30 ml. of distillate. The reaction mixture was then acidified with dilute sulfuric acid and again steam distilled until 60 ml. of distillate had been collected. The 2,4,5-trichloro-Cl^{36}-phenol sublimed very rapidly. The distillate was extracted with methylene chloride, and the extracts were dried over a minimal amount of anhydrous magnesium sulfate.

The 2,4,5-trichloro-Cl^{36}-phenol was isolated by evaporating the solvent through a column of glass tubing 0.6 × 84 cm.[7] The yield of product was 69 mg. (89%); the specific activity was 15.6 μc./mmol. The m.p. of the product was 66° (for unlabeled compound, lit.[2] 66°). The infrared absorption spectrum of the compound was identical with that of unlabeled 2,4,5-trichlorophenol, and a mixed m.p. with an authentic specimen thereof showed no depression in melting point.

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(2) W. S. W. Harrison, A. T. Peters, and F. M. Rowe, *J. Chem. Soc.*, 235 (1943).

(3) 1.1*M* Potassium hydroxide in Carbitol was also investigated as a hydrolyst, but this system was not nearly so efficient as the methanolic sodium hydroxide in the conversion.

(4) During the course of preliminary work it was found that the effect of reaction time on the yield of product was quite marked: as the time of reaction increased beyond the optimum of 5 hr., the yield decreased. This showed that the product was being subjected to hydrolysis or methanolysis, or both, resulting in the formation of polyphenols and some or all of their methyl esters. However, the method of isolation was such that these by-products could not have been detected, and no attempt was made to isolate them.

(5) Trichloroanisole is to be expected as a by-product in the methanolic sodium hydroxide hydrolysis of 1,2,4,5-tetrachlorobenzene. Holleman[6] found the anisole derivative, but he used a higher temperature (180° instead of 160°) and a longer time (12 hr. instead of 5 hr.). No trichloroanisole was detected when the shorter reaction time and lower temperature were used.

(6) A. F. Holleman, *Rec. trav. chim.*, **39**, 736 (1920).

(7) It was found in preliminary work that the use of a 1.4 × 20-cm. Vigreux column resulted in a loss of 5–6 mg. of product.

Aryl and Aryl-alkyl Isocyanosilanes[1]

J. J. MCBRIDE, JR.

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Alkylisocyanosilanes have been prepared by Eaborn[2] and by McBride and Beachell.[3] While the present work was in progress, the first arylisocyanosilane, triphenylisocyanosilane, was reported by Bithner and co-workers.[4] The structure of these compounds has been the subject of some controversy. The "iso" structure was favored by Eaborn and by McBride and Beachell. Infrared studies have been made by Bithner and co-workers who suggest that the trialkyl compounds are temperature-dependent equilibrium mixtures of the normal and isocyanide forms. Linton and Nixon[5] studied isotopic shifts in the CN-stretching frequency of the trimethyl compound and concluded that this compound is the normal rather than the isocyanide. The Raman spectra of the trimethyl compound permitted no definite differentiation.[6]

This paper reports the preparation of diphenyldiisocyanosilane, dimethylphenylisocyanosilane, and the recently described triphenylisocyanosilane. The molar refractions of the first two compounds (dimethylphenylisocyanosilane is a liquid and diphenyldiisocyanosilane a low-melting solid with a strong tendency to supercool) are much closer to the calculated values for isocyanides than for normal cyanides.

The aryl and aryl-alkyl isocyanosilanes, like the alkyl compounds, are, with the exception of the triphenyl compound, extremely susceptible to hydrolysis and react violently with water. Triphenylisocyanosilane did not hydrolyze appreciably on standing in air for 0.5 hr. The great reactivity of the compounds is also shown by the reaction of diphenyldiisocyanosilane with the phenyl Grignard at the temperature of refluxing ethyl ether. Tetraphenylsilane was obtained in 80% yield. With diphenyldibromosilane and the phenyl Grignard under the same conditions, no tetraphenylsilane was obtained.

A new isothiocyanate, dimethylphenylsiliconisothiocyanate, and a new bromide, methylphenyldibromosilane, are described.

(1) Florida Agricultural Experiment Stations Journal Series, No. 909.

(2) C. Eaborn, *J. Chem. Soc.*, 2757 (1949); 3077 (1950).

(3) J. J. McBride, Jr., and H. C. Beachell, *J. Am. Chem. Soc.*, **74**, 5427 (1952).

(4) T. A. Bithner, W. H. Knoth, R. V. Lindsey, Jr., and W. H. Sharkey, *J. Am. Chem. Soc.*, **80**, 4151 (1958).

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(6) J. Goubeau and J. Rehying, *Z. anorg. u. allgem. Chem.*, **294**, 92 (1958).

ISOCYANOSILANES

Compound	M.P.	B.P.	n_D^t	D_4^t	% CN Calcd.	% CN Found	M_R Obs.	M_R Calcd.[a] —NC	M_R Calcd.[a] —CN
$(C_6H_5)_2Si(NC)_2$[b]	46–48°	142°/2 mm.	1.559932	1.090432	22.0	20.5	69.48	69.51	68.07
$(CH_3)_2(C_6H_5)SiNC$		230–232°	1.499828	0.957328	16.1	16.2	49.44	49.60	48.88
$(C_6H_5)_3SiNC$	136–138°[c]	210°/5 mm.			9.12	9.05			

[a] Using Auwers' [*Ber.*, *60*, 2122 (1927)] values for —NC and —CN. [b] Density and refractive index measured on supercooled liquid. [c] Ref. 3 gives 136–138° for the b.p. of $(C_6H_5)_3SiNC$—obviously a typographical error.

EXPERIMENTAL

Diphenyldiisocyanosilane. To 0.055 mol. of silver cyanide was added 0.025 mol. diphenyldibromosilane. There was immediate evolution of heat and yellowing of the solid. The mixture was kept at 110–120° for 1 hr. and then distilled. The distillate, a straw-colored liquid, b.p. 135–140°/2 mm. was redistilled over a little silver cyanide. There was obtained 4.7 g. (80% of theory) of diphenyldiisocyanosilane, a pale yellow viscous liquid, b.p. 142–144°/2 mm.

Dimethylphenylisocyanosilane. To 0.11 mol. silver cyanide was added 0.10 mol. dimethylphenylbromosilane. There was immediate evolution of heat and yellowing of the solid. The mixture was heated to reflux and maintained at reflux for 2 hr. Distillation gave 12.4 g. (77% of theory) of colorless liquid, b.p. 230–232°.

Triphenylisocyanosilane. A mixture of 0.030 mol. triphenylbromosilane and 0.036 mol. silver cyanide was heated for 2 hr. at 200°. Distillation at reduced pressure gave 6.9 g. (81% of theory) of pure white solid, b.p. 210°/5 mm.

Dimethylphenylsiliconisothiocyanate. A mixture of 0.024 mol. of dimethylphenylisocyanosilane and 0.024 mol. of sulfur were heated at reflux (*ca.* 250°) for 0.5 hr. Distillation gave 2.2 g. (57% of theory) of straw-colored liquid, b.p. 252–254°, n_D^{30} 1.5556, d_4^{30} 1.0384, M_R calcd. 59.91; M_R obs. 59.81.

An identical product was obtained in 60% yield by the reaction of dimethylphenylchlorosilane with silver thiocyanate.

Methylphenyldibromosilane was prepared in 18% yield by the reaction of phenylmagnesiumbromide with methyltribromosilane in ethyl ether. The pure compound had b.p. 140–144°/60 mm., n_D^{30} 1.5537, D_4^{30} 1.599, Br, calcd. 57.2%; found: 57.2%.

Reaction of diphenyldiisocyanosilane with phenylmagnesiumbromide. When 0.01 mol. diphenyldiisocyanosilane in 15 ml. of ether was added dropwise with stirring to 0.030 mol. phenylmagnesiumbromide in 25 ml. ether, a very vigorous reaction occurred. After addition was complete, the mixture was stirred under reflux for 1 hr. After working up in the usual way, there was obtained 2.77 g. (81% of theory) of tetraphenylsilane, m.p. and mixed m.p. 233–234°. When this reaction was run using a 25% deficiency of the phenyl Grignard, a 61% yield of tetraphenylsilane was obtained.

This high reactivity is in contrast to the reactivity of diphenyldibromosilane with excess phenylmagnesiumbromide under the same conditions. No tetraphenylsilane was formed.

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Synthesis of 1,2,3,4-Tetrahydroquinolin-3-ols

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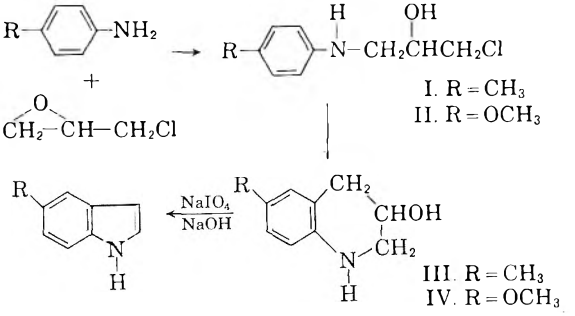
Received June 5, 1959

Recently, a new indole synthesis involving periodate oxidation of substituted tetrahydroquinolin-3-ols was reported.[1] The tetrahydroquinolin-3-ols were conveniently prepared by condensing α- and β-naphthylamine with epichlorohydrin. We have found that if substituted anilines, such as *p*-toluidine and *p*-anisidine, are used in place of the naphthylamines, a modified procedure is required.

The reaction of the amines with epichlorohydrin actually involves two reactions, and since *p*-toluidine readily adds to epichlorohydrin to give I,[2] the step giving difficulty is the cyclization of I to a substituted tetrahydroquinolin-3-ol (III). In studying the conversion of I to III, we found that relatively dilute reaction mixtures are necessary and that adding a base such as diethylaniline helps to prevent the formation of undesirable by-products. For example, a cyclization yield of 50% was obtained by heating a 0.042*M* solution of I with an equivalent amount of diethylaniline in boiling bromobenzene for 48 hr.



When *p*-anisidine was treated with epichlorohydrin, II was obtained as an oil. Therefore, it was more convenient to prepare IV without isolating II.

Periodate oxidation of III and IV led to the picrates of 5-methylindole and 5-methoxyindole, respectively, although in the case of 5-methoxyindole the yield was but 10%.

EXPERIMENTAL

N-(γ-Chloro-β-hydroxypropyl)-p-toluidine (I). The synthesis of this compound[2] and analogous compounds[3] has

(1) F. C. Pennington, M. Jellinek, and R. D. Thurn, *J. Org. Chem.*, **24**, 565 (1959).

(2) P. Cohn and P. Friedlaender, *Ber.*, **37**, 3034 (1904); N. N. Vorozhtsov, Jr., and S. I. Kutkevichus, *Zhur. Obschei. Khim.*, **27**, 2152–2160 (1957).

(3) H. L. Yale, E. J. Pribyl, W. Braker, F. H. Bergein, and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 3715 (1950); B. J. Ludwig, W. A. West, and D. W. Farnsworth, *J. Am. Chem. Soc.*, **76**, 2893 (1954).

been described previously, but a more convenient method was developed. *p*-Toluidine (4.00 g.) was dissolved in 500 ml. of warm water and epichlorohydrin (3.30 ml.) was added over a 15-min. period while the temperature was held at 35–40°. The solution was stirred and the temperature held at 35–40° for 2 hr. When the mixture began to get cloudy, seed crystals of the product were added. The mixture was allowed to stand 20 hr., and the product (I) was recovered and washed with cold water, 5.37 g. (72%), m.p. 79–81° (lit. 81–82°[2]). Although a larger excess of epichlorohydrin gave greater yields, the product was not as pure.

N-(*γ-Chloro-β-hydroxypropyl*)-*p-anisidine* (II). This compound was prepared by the procedure used for the synthesis of I except that *p*-anisidine was condensed with epichlorohydrin (10% excess). The product was obtained as an oil. It was extracted with bromobenzene and used without purification for the synthesis of IV.

1,2,3,4-Tetrahydro-6-methyl-quinolin-3-ol (III). Compound I (3.78 g.) was dissolved in bromobenzene (450 ml.) and diethylaniline (3.00 ml.) added. The mixture was boiled under reflux for 48 hr. The product was extracted with 5% hydrochloric acid (100 ml.), and the extract washed with benzene. The acidic extract was made basic with sodium hydroxide, and a benzene extraction carried out. The benzene extract was dried over anhydrous sodium sulfate and passed over an alumina column. The column was washed with benzene, and the product eluted with benzene ether and ether. Although recrystallization of eluted product was possible, further purification was best achieved by converting III to its hydroiodide salt using a mixture of butanol (20 ml.), hydroicdic acid (5 ml.) and ether (150 ml.). The salt was recovered, and washed with ether 2.74 g. (50%).

A purified sample of the hydroiodide salt melted at 237–239° with some decomposition.

Anal. Calcd. for $C_{10}H_{14}NOI$: neut. equiv., 291. Found: neut. equiv., 292.

Neutralization of an aqueous solution of the hydroiodide salt gave III, which was recrystallized from hexane for analysis, m.p. 101.5–103°.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.77; H, 8.26; N, 8.58.

It was possible to follow the cyclization of I to III by mixing an aliquot (1 ml.) from the reaction mixture with benzene (5 ml.) and 5% hydrochloric acid (3 ml.). The aqueous layer was added to a mixture of 6*N* sodium hydroxide (4 ml.) and 1.28% sodium periodate (4 ml.). The indole that was formed was steam distilled out of the mixture, and aliquot parts of the distillate in 50% alcohol were analyzed. A sample (2 ml.) was mixed with 2.5% alcoholic dimethylaminobenzaldehyde solution (1 ml.) and 6*N* hydrochloric acid (1 ml.), and the absorption at 570 mμ was determined. Although the procedure is not a good method of analyzing for III, it gives some measure of the amount of cyclization occurring in the reaction.

1,2,3,4-Tetrahydro-6-methoxy-quinolin-3-ol (IV). This compound was prepared from a bromobenzene solution of II. The bromobenzene extract obtained from the reaction of *p*-anisidine (4.60 g.) and epichlorohydrin (3.0 ml.) was adjusted to a volume of 900 ml. of bromobenzene, and the residual water distilled with a small amount of bromobenzene. Diethylaniline (6 ml.) was added, and the mixture was boiled under reflux for 48 hr. The product was isolated by chromatography in a manner similar to the isolation of III. The product was recrystallized from a mixture of benzene and hexane, 1.30 g. (19.5%), m.p. 73.5–74.5°. An analytical sample melted at 75°.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.95; H, 7.03; N, 7.79.

5-Methylindole. Compound III was oxidized by periodate using essentially the procedure previously reported.[1] A solution of III (200 mg. in 35 ml. of ethanol) and a solution of sodium periodate (626 mg. in 35 ml. of water) were added at about the same rate over a 1.5-hr. period to 100 ml. of an 8% sodium hydroxide solution, and 5-methylindole steam-distilled from the reaction mixture as soon as it was formed. A small amount of 5-methylindole crystallized in the steam distillate which had been saturated with salt, m.p. 57.5–58° (lit. 58.5[4]), but a more efficient recovery was obtained by extracting the indole with ether, removing the ether, extracting the product with a small volume of hot water and adding the hot solution to a saturated, aqueous picric acid solution. The orange-red picrate was recovered, 121 mg. (27%), m.p. 145–148°, with some decomposition (lit. 151°[4]).

5-Methoxyindole. Compound IV was oxidized by the same method that was used for the oxidation of III. The red picrate of 5-methoxyindole was obtained in 10% yield, m.p. 142–144° with some decomposition (lit. 145°[5]).

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Some Properties of Benzenesulfonyl Peroxide

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The published chemistry of benzenesulfonyl peroxide consists of one paper[1] describing its preparation and another[2] describing its decomposition in water to form phenol, sulfuric acid, and (probably) benzenesulfonic acid. We now wish to report our unsuccessful attempts to improve the unsatisfactory yields in its preparation and the results of some exploratory work involving its use as a polymerization initiator and concerning the products of its decomposition in benzene.

Adaptations of several procedures for the preparation of benzoyl peroxide[3–6] involving interaction of benzenesulfonyl chloride and sodium peroxide or hydrogen peroxide failed to give isolable amounts of the sulfonyl peroxide. Benzenesulfonyl chloride failed to react with the urea hydrogen peroxide complex[3] and formed only the sulfonamide with the hydrogen peroxide dicyclohexylamine complex.[7]

(1) R. F. Weinland and H. Lewkowitz, *Ber.*, **36**, 2702 (1903).
(2) F. Fichter and E. Stocker, *Helv. Chim. Acta*, **7**, 1071 (1924).
(3) M. S. Karasch, S. S. Kane, and H. C. Brown, *J. Am. Chem. Soc.*, **63**, 526 (1941).
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(5) S. Gambarjan, *Ber.*, **42**, 4004 (1909).
(6) A. Kergomard and J. Bigou, *Bull. soc. chim. France*, 486 (1956).
(7) D. F. DeTar and L. A. Carpino, *J. Am. Chem. Soc.*, **77**, 6370 (1955).

TABLE I

POLYMETHYL METHACRYLATE STUDIES

Sample No.	Cat.	Temp.	Time, Hr.	Cat., Mg.	Monomer, G.	Polymer, G.	Conv., %	Softening Point	Av. Mol. Wt.
I	BSP[a]	25	7	18.2	14.2	2.91	20.4	260–265	2.9×10^5
II	BSP	25	24	18.2	14.2	10.68	75.0	—	9.3×10^5
III	BSP	33	7	18.2	14.2	10.91	77.0	290–300	6.8×10^5
IV	BSP	41	7	18.2	14.2	10.51	74.0	295–300	11.4×10^5
V	BSP	48	7	18.2	14.2	9.96	67.8	290–300	11.6×10^5
VI	BSP	55	7	18.2	14.2	3.31	23.3	260–270	6.2×10^5
VII	BSP	56	7	18.2	14.2	2.54	17.9	—	—
VIII	BSP	70	7	18.2	14.2	1.74	12.3	260–270	—
IX	BP[b]	25	7	14.2	14.2	0.0	—	—	—
X	BP	33	7	14.2	14.2	0.0	—	—	—
XI	BP	41	7	14.2	14.2	0.0	—	—	—
XII	BP	48	7	14.2	14.2	0.0	—	—	—
XIII	BP	55	7	14.2	14.2	2.69	18.9	270–280	14.8×10^5
XIV	BP	70	7	14.2	14.2	9.93	70.0	290–295	9.9×10^5

[a] Benzenesulfonyl peroxide. [b] Benzoyl peroxide.

Thus, our only contribution to the preparation of this compound lies in our procedure for crystallization.

In order to determine the ability of benzenesulfonyl peroxide to initiate polymerization, bulk polymerization of methyl methacrylate was effected at several temperatures with the sulfonyl peroxide and with benzoyl peroxide (Table I). It was found through per cent conversion data that benzenesulfonyl peroxide satisfactorily initiated polymerization at temperatures from 25° to 48° whereas benzoyl peroxide did not. Above 54°, the sulfonyl peroxide rapidly lost its effectiveness while benzoyl peroxide began to become effective. Determination of intrinsic viscosities permitted an estimation of average molecular weights.

A more superficial study of the polymerization of styrene (Table II) indicated that benzoyl peroxide was superior to benzenesulfonyl peroxide, while with acrylonitrile (Table III), the two initiators were of comparable effectiveness, the sulfonyl peroxide again being the more effective at lower temperatures. The results of some copolymerizations may be seen in Table IV.

TABLE II

POLYSTYRENE STUDIES

Catalyst	Temp.	Time, Hr.	Cat., Mg.	Monomer, G.	Polymer, G.	Conv., %
BSP[a]	45	112.2	11.8	9.1	0.14	1.5
BP[b]	45	112.2	9.1	9.1	1.29	14.2
BSP	80	7.5	11.8	9.1	0.0	0.0
BP	80	7.5	9.1	9.1	2.68	29.5

[a] Benzenesulfonyl peroxide. [b] Benzoyl peroxide.

Since the results of the polymerizations led us to believe that benzenesulfonyl peroxide decomposed to form radicals, the products of its decomposition in benzene were investigated. As anticipated, the reaction effected at room temperature afforded

TABLE III

POLYACRYLONITRILE STUDIES

Catalyst	Temp.	Time, Hr.	Cat., Mg.	Monomer, G.	Polymer, G.	Conv., %
BSP[a]	25	0.58	15.5	12.0	0.33	2.7
BSP	35	0.58	15.5	12.0	1.83	15.3
BSP	45	0.58	15.5	12.0	1.99	16.6
BSP	55	0.58	15.5	12.2	2.10	17.5
BSP	65	0.58	15.5	12.0	1.01	8.4
BP[b]	25	0.58	12.0	12.0	0.0	—
BP	35	0.58	12.0	12.0	0.0	—
BP	45	0.58	12.0	12.0	0.0	—
BP	55	0.58	12.0	12.0	0.5	4.2
BP	65	0.58	12.0	12.0	2.79	23.2

[a] Benzenesulfonyl peroxide. [b] Benzoyl peroxide.

phenyl benzenesulfonate in 48–52% yield together with benzenesulfonic acid:

$$(C_6H_5—SO_2—O)_2 + C_6H_5 \longrightarrow C_6H_5—SO_2—O—C_6H_5 + C_6H_5—SO_3H$$

EXPERIMENTAL

Benzenesulfonyl peroxide was prepared essentially by the procedure of Weinland[1] from 6 g. of sodium peroxide, water, and 4 g. of benzenesulfonyl peroxide in the cold. The waxy product was separated by decantation, washed with water, dissolved in 10 cc. of ether. Crystallization was effected by addition of 10 cc. of methanol, cooling in Dry Ice–ethanol, filtration, and washing with very cold methanol. The product, obtained in 8–10% yield, melted with decomposition at 53–54°. The melting point was not altered by recrystallization. The peroxide decomposes, sometimes violently, when kept overnight at room temperature but may be kept for several weeks at −20°.

Polymerization of methyl methacrylate. The monomer was distilled under deoxygenated nitrogen and 15 cc. samples were added to each of 18 tubes (6 containing 18.2 mg. benzenesulfonyl peroxide, 6 containing 14.0 mg. benzoyl peroxide, and 6 controls). The tubes were frozen until placed in the heating bath. After heating at the indicated temperature and time, the tubes were immersed in Dry Ice–methanol and opened. The contents were dissolved in benzene and the polymer was precipitated by excess methanol. Conversion

TABLE IV

COPOLYMERIZATION DATA

System	Cat.	Temp.	Time, Hr.	Cat., Mg.	Monomer, Mixture, G.	Polymer, G.	Conv., %	N, %	Molar Ratio Acrylonitrile to Styrene or Vinyl Acetate
Acrylonitrile-styrene	BSP[a]	45	66.7	11.5	8.9	0.66	7.4	6.66	2:3
Acrylonitrile-styrene	BP[b]	45	66.7	8.9	8.9	2.37	26.6	6.9	2:2.88
Acrylonitrile–vinyl acetate	BSP	45	14.8	17.9	13.8	0.28	2.0	20.8	1:5.7
Acrylonitrile–vinyl acetate	BP	45	14.8	13.0	12.1	0.24	2.0	20.6	1:5.7

[a] Benzenesulfonyl peroxide. [b] Benzoyl peroxide.

is defined as the weight of precipitated polymer obtained from a given weight of monomer expressed as per cent. Molecular weights were estimated by standard procedures[8] from the viscosities of a series of standard solutions of the polymer in benzene.

Other polymerizations. Styrene and acrylonitrile were polymerized in tubes as described above. Polyacrylonitrile, being insoluble in its monomer, precipitated as it was formed and was filtered, washed with methanol and dried *in vacuo*. The copolymerizations likewise were effected in tubes, the "monomers" consisting of equimolar mixtures of acrylonitrile-styrene and acrylonitrile-vinyl acetate. Both copolymers were removed by filtration, washed with methanol, and dried.

Reaction of benzenesulfonyl peroxide with benzene. The peroxide (58.2 mg.) was dissolved in 10 cc. of cold benzene and allowed to stand for three days. The benzene was extracted with water and evaporated to dryness. This residue was extracted with carbon tetrachloride leaving a small dark tarry residue. The carbon tetrachloride extract was concentrated to a volume of 2.0 cc. The infrared spectrum of this solution was identical with that of authentic phenyl benzenesulfonate. When compared with standard solutions of the latter at 7.25 and 11.65μ, a yield of 21.4 mg. (49%) was estimated. Two like experiments gave yields of 48% and 52%.

On a larger scale, 0.81 g. (0.0026 mol.) of the peroxide was dissolved in 150 cc. of benzene and the solution was allowed to stand at room temperature for 3 days before warming briefly on the steam bath. Water (50 cc.) was added and the mixture titrated to the phenolphthalein end point with standard base, 0.0029 mol. being consumed. The aqueous layer, shown to be free of sulfate, was separated, clarified with Norit, concentrated to 10 cc. and a saturated aqueous solution containing 0.8 g. of benzylisothiuronium chloride was added. The precipitate so obtained was recrystallized from water to give 0.61 g. of benzylisothiuronium benzenesulfonate melting at 146.5–148.5° alone and when mixed with an authentic sample. The benzene solution was evaporated to dryness and the tarry residue was extracted with 25 cc. of carbon tetrachloride. This solution was poured through a 2.5 cm. high column of alumina of about 0.5 cm. diameter and eluted with carbon tetrachloride. This afforded a water white solution which after evaporation left 0.24 g. of a white solid melting from 30–34°. After crystallization from ethanol, the material melted at 34–35°, alone and when mixed with authentic phenyl benzenesulfonate.

(8) F. Daniels, J. H. Mathews, *et al.*, *Experimental Physical Chemistry*, 4th edition, McGraw-Hill, Inc., New York, 1949, p. 243; P. J. Flory, *Principles of Polymer Chemistry*, Cornell University Press, New York, 1953, p. 246; R. E. Burke and O. Grumitt, *High Molecular Weight Organic Compounds*, Vol. VI, Interscience Publishers, New York, 1949, p. 90; H. I. Goldberg, W. P. Hohenstein, and H. O. Mark, *J. Polymer Sci.*, **2**, 502 (1947).

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Preparation of 2,4-Dialkylhexahydropyrano-[2,3-d]-*m*-dioxins

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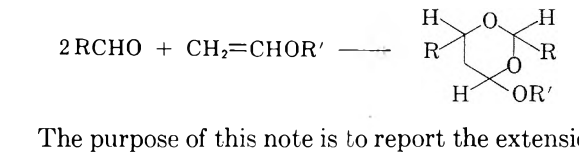
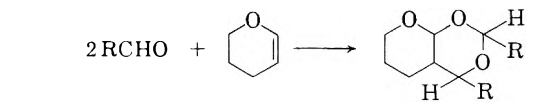
The preparation of 4-alkoxy-2,6-dialkyl-*m*-dioxanes by the acid-catalyzed addition of two moles of an aldehyde to one mole of a vinyl ether has been previously described.[1]



The purpose of this note is to report the extension of this reaction to include the addition of aldehydes to dihydropyran. The products are 2,4-dialkylhexahydropyrano[2,3-d]-*m*-dioxins.



The structure was assigned by analogy with the aldehyde–vinyl ether reaction products and was supported by the infrared spectra.

EXPERIMENTAL

2,4-Diisopropylhexahydropyrano[2,3-d]-m-dioxin. A mixture of isobutyraldehyde, 317 g. (4.4 mol.), and dihydropyran, 168 g. (2 mol.), was added dropwise over a 1.25-hr. period to a stirred solution of 0.5 ml. of boron trifluoride etherate in 20 ml. of ethyl ether. Moderate cooling was used to main-

(1) R. I. Hoaglin and D. H. Hirsh, U. S. Patent 2,628,257 (1953).

tain the temperature at 50–55°. Stirring was continued for 2.75 hr., and the catalyst was neutralized by addition of a solution of 10 ml. of potassium acetate in 10 ml. of water. The organic phase was separated and distilled to give 66 g. of recovered isobutyraldehyde, b.p. 62–64° at atmospheric pressure. The distillation was then continued under vacuum to give 66 g. of the isobutyraldehyde trimer, 2,4,6-triisopropyl-s-trioxane (b.p. 88° at 12 mm., m.p. 61°). 271 g. (59%) of 2,4-diisopropylhexahydropyrano[2,3-d]-*m*-dioxin, b.p. 128° (12 mm.), n_D^{20} 1.4562; and 72.5 g. of residue.

The infrared spectrum showed strong bands at 8.6 and 9.1 μ, which are the positions of C—O—C absorption in s-trioxane and tetrahydropyran, respectively. No other functional group, such as C=O or C=C, was indicated to be present.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60. Found: C, 68.62; H, 10.73.

2,4-Dipropylhexahydropyrano[2,3-d]-m-dioxin. Under conditions similar to those described above, butyraldehyde (2 mol.) and dihydropyran (2 mol.) gave, after a small forerun, 269 g. (59%) of 2,4-dipropylhexahydropyrano[2,3-d]-*m*-dioxin, b.p. 115–121° (4–5 mm.), n_D^{20} 1.4578. The infrared spectrum was similar to that of the product from isobutyraldehyde.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60. Found: C, 68.54; H, 10.54.

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Rate of Reduction of Some Steroid Ketones with Sodium Borohydride

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In connection with a previous investigation on the rate of reduction of steroid ketones in the A and B rings,[1] some other ketones in the C and D rings and in the chain inserted on C-17 were studied.

Although the experimental data (Table I) gave results as normally expected, they showed the reason for the selectivity found sometimes when polycarbonyl compounds are treated with sodium borohydride.[2]

The more interesting facts are that a C-11 ketone is reduced 1000 times slower than a 3-ketone, and that the introduction of a bromine atom in the α-position of a carbonyl increases the rate of reduction by a factor of ten. It is known[3] that sodium borohydride reduction of α-halo ketones proceeds normally to give bromohydrins and the rate increase is very probably due to the interaction between the carbonyl and halogen dipoles that is released when the keto group is reduced.

TABLE I

RATE OF REDUCTION WITH SODIUM BOROHYDRIDE[a]

	$k \times 10^4$	Ratio[b]
Cholestan-3-one	397[c]	100
2-Bromo-cholestan 3-one	5000[d]	1260
11-Keto-tigogenin	0.5[d]	0.126
Hecogenin (12 keto)	42	10.6
Estrone methyl ether	28	7.05
Estrone	30	7.55
Cyclopentanone	34[c]	8.55
Δ^5-Androsten-3β-ol-17-one	23.5	5.94
Δ^5-Pregnen-3β-ol-20-one	5.8	1.45
16-β-Methyl-Δ^5-isopregnen-3β-ol-20-one	4.5	1.13

[a] In 2-propanol at 25. Rate constants in liter mol.$^{-1}$ sec.$^{-1}$ [b] Ratio of rate constants to cholestan-3-one = 100.0. [c] From ref. (1). [d] Approximate result.

When a 3,11 diketone or a 3,20,11 triketone is reduced with one or two equivalents of sodium borohydride, the 11 keto group remains unaltered. The explanation can be seen in the kinetic values, since in the reduction of a 3,11 diketone only 0.1% of the 11-ketone would be reduced. The reason for the lack of reactivity of the C-11 position is steric in nature and it has been discussed elsewhere.[4]

The kinetic results also explain the high selectivity in the reduction of 3,17 and 3,20 diketones.[5]

The relative rates of reduction of the 3,17 and 20 keto group are 100, 5, and 1. Therefore, a minimum percentage of the 17 and 20 alcohols is obtained allowing an easy purification of the reduced product.

The 12 ketone is more reactive than the 17,11 or 20 ketones but nevertheless is reduced 12 times slower that the 3-ketone. The relative rates of reduction for steroidal keto groups can be summarized as follows: 3 keto, 100; 2-bromo 3 keto, 1000; 12 keto, 8.4; 17 keto, 5.2; 20 keto, 1.08; 11-ketone, 0.1.

Taking these results together with the data already reported[1] it is possible to establish the following order of reactivity on sodium borohydride reduction for most of the ketones in the steroid molecule: Δ^5 —3 keto > $\Delta^{5(14)}$ —3 keto > 3 keto A/B *cis* > 3 keto A/B *trans* > 6 keto > 7 keto > Δ^4 —3 keto > 12 keto > 17 keto > 20 keto > 11 keto.

The C-2 ketone is expected to be as reactive as the C-3, the C-16 as reactive as the 3-17, and the C-1 and C-4 as reactive as the C-6 ketone.

EXPERIMENTAL

The ketones used were samples carefully purified and whose melting point agreed with the ones reported in the

(1) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1049 (1958).

(2) H. Heyman and L. F. Fieser, *J. Am. Chem. Soc.*, **73**, 5252 (1951); E. Elisberg, H. Vanderhaeghe, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 2814 (1952).

(3) C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.*, 1657 (1958).

(4) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Co., New York, 1949, p. 408.

(5) A. H. Soloway, A. S. Deutsch, and T. F. Gallagher, *J. Am. Chem. Soc.*, **75**, 2356 (1953).

literature. Since all of the ketones are known their preparations can be found elsewhere.

Kinetics. The kinetic method was the same used previously.[1] In all cases the rate constants were calculated from a second order rate plot.

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Studies in Purine Chemistry. V. 7-Methyladenine-3-*N*-oxide[1]

EDWARD C. TAYLOR AND PAULA K. LOEFFLER

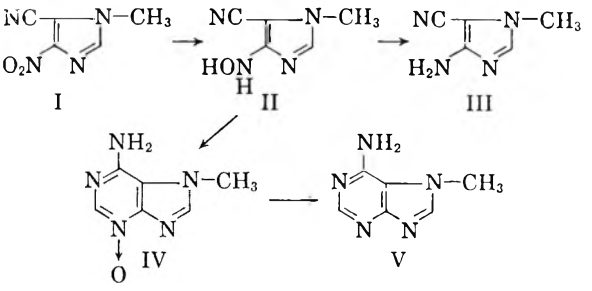
Received June 17, 1959

Of the four possible structural types of purine-mono-*N*-oxides, representatives of only the 1- and 7-oxides have been reported.[2] The present paper describes the synthesis and properties of 7-methyladenine-3-N-oxide.

Although reduction of 1-methyl-4-nitro-5-cyanoimidazole (I) with Raney nickel is known to yield 1-methyl-4-amino-5-cyanoimidazole (III),[3] we have found that yields in the reduction are variable and dependent upon the quality of the Raney nickel employed. In an attempt to improve on this conversion by the use of other catalysts, reduction of I was carried out with platinum oxide. Absorption of hydrogen either in ethanol or in ethanolic hydrogen chloride solution was complete within 8 minutes, but the reduction product proved to be 1-methyl-4-hydroxylamino-5-cyanoimidazole (II). Complete reduction to III had occurred only to a negligible (2.5%) extent. The structure of II was readily confirmed by further reduction with hydrogen in the presence of Raney nickel to 1-methyl-4-amino-5-cyanoimidazole (III).

Attempted cyclization of II by heating with formamide led only to extensive decomposition, but smooth cyclization to 7-methyladenine-3-*N*-oxide (IV) was effected by refluxing II in ethanol solution with formamidine acetate. 7-Methyladenine-3-*N*-oxide (IV) was similar in properties to previously described purine-1-*N*-oxides[2] in the following respects: (a) it was extremely hygroscopic and readily formed a stable monohydrate (b) it was appreciably more soluble in water than the parent purine, and (c) its ultraviolet absorption spectrum in dilute sodium hydroxide solution showed two absorption maxima, the more intense peak being at the shorter wave length. Compound IV also exhibited two absorption maxima in 0.1 *N* hydrochloric acid solution, in contrast to adenine-1-*N*-oxide, which has been reported to have only one maximum in this solvent.[4]

The structure of 7-methyladenine-3-*N*-oxide follows not only from its method of preparation and its physical properties, but also from its facile reduction with hydrogen and Raney nickel to 7-methyladenine. It is of interest to note that similar conditions, which have been successfully employed for the reduction of adenine-1-*N*-oxide to adenine,[5] were without effect on hypoxanthine-1-*N*-oxide.[2] Apparently the N—O bond in hypoxanthine-1-*N*-oxide (which is a cyclic hydroxamic acid) is appreciably stronger than the N—O bond of the adenine-*N*-oxides.



EXPERIMENTAL[6]

1-Methyl-4-hydroxylamino-5-cyanoimidazole (II). A solution of 10 g. of 1-methyl-4-nitro-5-cyanoimidazole in 200 ml. of ethanol containing 1 g. of platinum oxide was hydrogenated at room temperature and 3 atmospheres pressure until hydrogen absorption ceased (about 8 minutes). The reduction mixture was heated to boiling, filtered from the catalyst, and the filtrate chilled to give 6.0 g. (66%) of 1-methyl-4-hydroxylamino-5-cyanoimidazole as pale yellow needles which were recrystallized from ethanol; m.p. 178° (dec.).

Anal. Calcd. for $C_5H_6N_4O$: C, 43.5; H, 4.4; N, 40.6. Found: C, 43.8; H, 4.2; N, 40.4.

Evaporation of the filtrate yielded 0.2 g. (2.5%) of 1-methyl-4-amino-5-cyanoimidazole, identical with an authentic sample.[3]

Reduction of 1-Methyl-4-hydroxylamino-5-cyanoimidazole to 1-Methyl-4-amino-5-cyanoimidazole (III). A solution of 2.0 g. of 1-methyl-4-hydroxylamino-5-cyanoimidazole in 30 ml. of ethanol was hydrogenated in the presence of 2 g. of Raney nickel catalyst (wet with ethanol) at room temperature and at 3 atmospheres pressure for 12 hr. The reduction mixture was filtered from the catalyst, the filtrate concentrated under reduced pressure and the residue recrystallized from benzene to give 0.65 g. (37%) of light yellow crystals, m.p. 178–179, identical in all respects with an authentic sample of 1-methyl-4-amino-5-cyanoimidazole.[3]

7-Methyladenine-3-N-oxide (IV). A solution of 5 g. of 1-methyl-4-hydroxylamino-5-cyanoimidazole and 6.5 g. of

(1) This investigation was supported by a research grant (C-2551-PET) to Princeton University from the National Cancer Institute of the National Institutes of Health.

(2) For a summary of and appropriate references to previous work in this field, see the accompanying paper: E. C. Taylor, C. C. Cheng, and O. Vogl, *J. Org. Chem.*, 24, 2019 (1959).

(3) R. N. Prasad and R. K. Robins, *J. Am. Chem. Soc.*, 79, 6401 (1957).

(4) M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, 80, 2759 (1958).

(5) M. A. Stevens, D. J. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, 80, 2755 (1958).

(6) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J. All melting points are uncorrected.

formamidine acetate in 500 ml. of ethanol was heated under reflux for 20 hr. The product gradually separated from the hot reaction mixture in the form of colorless, fluffy plates. The chilled mixture was filtered to yield 4.0 g. of 7-methyladenine-3-*N*-oxide, while concentration of the filtrate yielded an additional 1.5 g.; total yield, 5.5 g. (92%). Recrystallization from ethanol yielded colorless needles, m.p. 278° dec. The product was extremely hygroscopic and was rapidly converted to a monohydrate upon exposure to air.

Anal. Calcd. for $C_6H_7N_5O \cdot H_2O$: C, 39.3; H, 4.95; N, 38.2. Found: C, 39.0; H, 4.8; N, 38.3.

Careful drying just prior to analysis resulted in the loss of 10.1% of the weight of the monohydrate (calculated loss: 9.9%):

Anal. Calcd. for $C_6H_7N_5O$: C, 43.6; H, 4.3; N, 42.4. Found: C, 43.7; H, 4.2; N, 42.5.

$\lambda_{max}^{0.1\ N\ NaOH}$ 229, 296 mμ; log ε 4.23, 4.07

$\lambda_{max}^{0.1\ N\ HCl}$ 224.5, 278 mμ; log ε 4.06, 4.12

Reduction of 7-Methyladenine-3-N-oxide to 7-Methyladenine (V). A solution of 1.0 g. of 7-methyladenine-3-*N*-oxide in 80 ml. of water containing 1 ml. of concentrated ammonium hydroxide was hydrogenated in the presence of 1 g. of freshly prepared Raney nickel catalyst (wet with ethanol) at 3 atmospheres pressure and at room temperature for 20 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. Recrystallization of the residue from aqueous ethanol yielded 0.85 g. of 7-methyladenine, m.p. 345°, identical in every respect with an authentic sample.[3]

Acknowledgment. The authors are indebted to Joseph E. Loeffler for stimulating discussions during the course of this work.

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Effect of Sodium in the Preparation of *n*-Butyllithium

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Received June 19, 1959

n-Butyllithium is routinely prepared in this laboratory from 1-bromobutane and lithium metal in diethyl ether by the method of Gilman *et al.*,[1] in yields of 80–95%. Recently metallic lithium of higher grade was made commercially available[2] so it was of interest to determine the effect of this metal on the yield of *n*-butyllithium. According to information supplied by the manufacturer, the main difference between this new lithium metal and the regular grade lithium is the sodium content, which is approximately 0.005% for the new metal compared to 0.05% for the regular grade metal. By following the usual procedure[1] we obtained a maximum yield of only 48% with the "low sodium" lithium compared to 80–95% for the regular grade lithium. Moreover the reaction differs in that a precipitate forms during the reaction, the lithium does not become shiny but turns a dull brownish color, and the temperature fluctuates and is difficult to control.

Reaction conditions have been varied in order to improve the yield. Small pieces of sodium were added with no significant result. The temperature was varied from the usual −30 to −40° to the reflux temperature of the ether. Somewhat better yields were obtained at the higher temperatures with a maximum of 59% at 10°. Special stirrers were designed in an effort to minimize the coating of the lithium, but these were unsuccessful. An increase in addition time of 1-bromobutane from the usual 30 min. to 3 hr. at −35° resulted in a yield of 29%. However, the use of half "low sodium" lithium and half regular grade lithium using routine procedures increased the yield to 76%. In another experiment some of the "low sodium" lithium was melted under oil and approximately 0.1% sodium was added. This metal also gave *n*-butyllithium in 76% yield. "Low sodium" lithium[3] to which 0.8% sodium was added resulted in an 84.2% yield of *n*-butyllithium by conventional procedures.

In the literature are reports of good yields of *n*-butyllithium from 1-chlorobutane and lithium metal in benzene.[4] This reaction was attempted in the conventional way with regular grade lithium metal and resulted in low yields of *n*-butyllithium (32–57%). Since the lithium appeared to be heavily coated, more vigorous stirring was used but this did not improve the yield even though the metal was finely dispersed by the stirrer. The use of a lithium dispersion also did not improve the yield. However, when "low sodium" lithium to which 0.8% sodium was added was used, the yields by the conventional method were increased to 70–80%.

In *n*-heptane "low sodium" lithium and 1-chlorobutane resulted in yields from 71.9–73.7%. Regular lithium gave yields from 64–69.6%, but again "low sodium" lithium, to which 0.8% sodium was added,[3] gave higher yields of 79.2–81.3% by conventional methods.

Apparently the amount of sodium in the lithium metal appreciably affects the yield of *n*-butyllithium[5] from *n*-butyl halides and lithium metal, though the reason for this effect is not clear. The

(1) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(2) Available from the Lithium Corp. of America, Inc., Rand Tower, Minneapolis 2, Minn.

(3) This sample of lithium was kindly provided by the Lithium Corp. of America.

(4) K. Ziegler and H. Colonius, *Ann.*, **479**, 135 (1930); H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **54**, 1957 (1932); G. Wittig, *Angew. Chem.*, **53**, 241 (1940).

(5) Recently "sodium free" lithium was found to be unreactive toward *t*-butyl chloride. However, lithium containing 1–2% sodium gave good yields of *t*-butyllithium. See M. Stiles and R. P. Mayer, *J. Am. Chem. Soc.*, **81**, 1497 (1959).

sodium has to be intimately mixed with the lithium as the addition of pieces of sodium or sodium sand to the "low sodium" lithium does not change the yield. In the case of *n*-butyl bromide in diethyl ether the surface of the "low sodium" lithium coated badly which did not happen with regular lithium. The significance of this coating has not been evaluated. Further work is in progress on this effect of sodium on the preparation of *n*-butyllithium and other organolithium compounds. In this connection the yield of phenyllithium from bromobenzene and lithium seems to be unaffected by the amount of sodium in the lithium. It is considered likely that metals other than sodium may have an effect on the production of organolithium compounds and that this effect may apply to other organometallic compounds as well.

EXPERIMENTAL

Preparation of n-butyllithium in diethyl ether. The procedure outlined by Gilman *et al.*[1] using 1-bromobutane and lithium metal was followed. The resulting solution was filtered through glass wool, and the yield determined by the double titration method.[6] Any variations in procedure together with yields from specific runs are listed in Table I.

Preparation of n-butyllithium in benzene. As a basic procedure the lithium metal wire was cut into small pieces and washed several times with benzene to remove any grease. Then approximately 100 ml. of benzene was added before adding the 1-chlorobutane in benzene over a period of 0.5 hr. The temperature of the reaction was not controlled, and after the addition the reaction mixture was stirred for 3 hr. The double titration method[6,7] was used to determine the yield after filtering through glass wool. Any variations used in the procedure together with yields from specific runs are listed in Table II.

TABLE I

PREPARATION OF *n*-BUTYLLITHIUM FROM 1-BROMOBUTANE AND LITHIUM IN DIETHYL ETHER

Trial	Li, G.-Atoms	1-Bromobutane, Mole	Total Vol., Ml.	Temp.	Yield, %
1	0.67[a,b]	0.30	175	−35	37.0
2	0.34[a]	0.15	96	0	55.9
3	0.34[a]	0.15	135	−40	47.5
4	0.34[a]	0.15	105	−50	38.8
5	0.34[a]	0.15	94	10	58.8
6	0.34[a]	0.15	90	25	54.1
7	0.34[a]	0.075	100	0	57.7
8	0.34[a]	0.15[c]	135	−35	29.0
9	0.34[a,d]	0.15	112	−35	24.1
10	0.17[a] 0.20[e]	0.15	115	−35	76.0
11	0.36[f]	0.15	115	−35	72.5
12	0.41[g]	0.15	117	−35	76.8
13	0.34[a,h]	0.15	106	−35	53.4
14	0.40[a,i]	0.15	89	−35	53.4
15	0.40[a,i]	0.15	98	−35	41.5
16	0.40[a,j]	0.15	106	−35	49.8
17	0.40[a,j]	0.15	98	−35	45.0
18	0.40[a,h]	0.15	100	−35	47.0
19	0.40[k]	0.15	104	−35	84.2

[a] "Low sodium" lithium (0.002% Na). [b] Several small pieces of sodium added. [c] Addition time of halide was 3 hr. rather than the usual 30 min. [d] Lithium pressed to expose more surface. [e] Regular lithium (0.05% Na). [f] Sodium added to melted lithium. [g] Approximately 0.1% sodium added to melted lithium. [h] Small pieces of carefully handled sodium added. [i] Sodium bromide (0.1 g.) added. [j] Sodium sand (0.1 g.) added. [k] "High sodium" lithium (0.8% Na) from the Lithium Corp. of America, Inc.

TABLE II

PREPARATION OF *n*-BUTYLLITHIUM FROM 1-CHLOROBUTANE AND LITHIUM IN BENZENE

Trial	Li, G.-Atoms	1-Chlorobutane, Mole	Total Vol., Ml.	Temp.	Yield, %
1[a]	0.44[b]	0.19	147	—	32.3
2[a]	0.44[b]	0.19	125	—	57.5
3[a]	0.52[c]	0.19	250	—	37.0
4[e]	0.60[b]	0.19[d]	90	—	31.6
5[f]	0.60[b]	0.19[d]	173	—	39 5
6[g]	0.60[b]	0.19[d]	86	50–60	50.8
7[g]	0.60[h]	0.19[d]	109	—	77.2
8[i]	0.60[h]	0.19[j]	112	—	70.2

[a] Stirred 3 hr. at room temperature. [b] Regular lithium (<0.05% Na). [c] Lithium dispersion obtained from Lithium Corp. of America, Inc. [d] Entire amount of halide added at one time. [e] Mixture was shaken intermittently for 4 hr. [f] Stirred for 24 hr. with wire brush stirrer. [g] Stirred for 4 hr. with wire brush stirrer. [h] "High sodium" lithium (0.8% Na) from Lithium Corp. [i] Stirred with glass stirrer for 4 hr. [j] Halide was added during a period of 15 min.

Preparation of n-butyllithium in heptane. After washing the small pieces of lithium wire (0.56 g.-atom) several times in benzene, 35 ml. of heptane was added. Then a solution of 1-chlorobutane (0.15 mole) in 15 ml. of heptane was added rapidly (10 to 15 min.). When the addition was complete, the reaction mixture was stirred for 3 hr. After filtering through a sintered glass filter the yield was determined by the double titration method.[6,7] The yields are actually better than indicated because some of the *n*-butyllithium remained with the debris on the filter and could not be washed out with any reasonable amount of heptane. Any variations in

TABLE III

PREPARATION OF *n*-BUTYLLITHIUM FROM 1-CHLOROBUTANE AND LITHIUM IN HEPTANE

Trial	Li, G.-Atoms	1-Chlorobutane, Mole	Total Vol., Ml.	Temp.	Yield, %
1	0.56[a]	0.15[b]	54	65–75	52
2	0.56[a]	0.15[b]	66	65–75	52
3	0.56[a]	0.15[c]	58	65–75	61.8
4	0.56[d]	0.15[c]	66	65–75	67.6
5	0.65[d]	0.19[c]	65	65–75	69.9
6	0.56[e]	0.15[c]	62	65–75	65.1
7	0.65[e]	0.19[c]	61	65–75	65.7

[a] Regular lithium (<0.05% Na). [b] Addition time of halide was 15 min. [c] Addition time of halide was 10 min. [d] "High sodium" lithium (0.8% Na) from Lithium Corp. [e] "Low sodium" lithium (0.002% Na) from Lithium Corp.

(6) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, 66, 1515 (1944).

(7) There seems to be some question about the accuracy of the double titration method in benzene and heptane solutions. However, the yields are consistent with each other though quite possibly low.

this procedure together with yields from specific runs are listed in Table III.

Acknowledgment. We wish to express our grateful appreciation to the Research Corp. for a grant which made this study possible.

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Oxidation of Nitrosoaromatic Compounds with Peroxytrifluoroacetic Acid[1]

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The previously unreported oxidation of *o*-dinitrosobenzene into *o*-dinitrobenzene has now been observed using peroxytrifluoroacetic acid.[2] Similar oxidations of 4-methyl-1,2-dinitrosobenzene into 4-methyl-1,2-dinitrobenzene and *p*-dinitrosobenzene into *p*-dinitrobenzene have occurred.

3-Nitro- and 3,5-dinitro-1,2-dinitrosobenzene, diphenylfuroxan, and the fused ring molecules, 1,2-dinitrosonaphthalene and 9,10-dinitrosophenanthrene apparently are not oxidized under similar conditions by peroxytrifluoroacetic acid into nitro derivatives and may be recovered. Poor recovery of the fused ring compounds indicates ring oxidation and degradation. Attempts to oxidize 4-chloro-5-methoxy-1,2-dinitrosobenzene with this reagent result in extensive destruction.

Peroxytrifluoroacetic acid oxidizes nitrosobenzene to nitrobenzene and catalyzes a self-condensation to *p*-nitrosodiphenylhydroxylamine.[3] Oxidation is predominant at higher temperatures and the condensation is predominant at lower temperatures.

$$C_6H_5NO \xrightarrow{F_3CCO_3H} C_6H_5NO_2 + p\text{-}ONC_6H_4N(C_3H_5)OH$$

EXPERIMENTAL

Oxidation of nitrosobenzene. To a solution of 3.21 g. (0.03 mol.) of nitrosobenzene in 25 ml. of methylene chloride, maintained at 5–10° with an ice bath, was added over a period of 45 min. with good stirring a solution of 1.2 ml. (0.04 mol.) of 90% hydrogen peroxide in 15 ml. (0.20 mol.) of trifluoroacetic acid. After the addition the solution was stirred another 15 min. at 5–10° and poured into 100 ml. of ice water. The mixture was made alkaline with solid sodium bicarbonate and allowed to stand for 4 hr. before the precipitated solid was collected, washed with 75 ml. of ether and air dried. The weight of crude yellow-brown *p-nitroso-N,N-diphenylhydroxylamine*, m.p. 138–141° dec. (lit.[3] m.p. 147–152° dec.), was 1.12 g. (35%). Recrystallization twice from aqueous ethanol (Norit) yielded 0.35 g. of yellow-brown solid, m.p. 137–138° (dec.).

A sample of the crude product dissolved in boiling aqueous ethanol was treated with zinc dust until the yellow color was discharged. After treating the mixture with Norit it was filtered and rapidly cooled. Grey platelets (which darkened in air) of *p*-aminodiphenylamine, m.p. 75–76° (lit.[4] m.p. 75°), separated from the solution. An attempt to carry out this reduction with sulfur dioxide as previously reported[3] allowed recovery of starting material.

The ether and methylene chloride layer of the filtrate from the oxidation reaction was separated and the aqueous phase was extracted with two 25-ml. portions of ether. The organic layer and the ether extracts were combined, washed with 25 ml. of water, and dried over anhydrous sodium sulfate. The solvent was removed, followed by distillation of a trace of a blue-green liquid (assumed to be nitrosobenzene), which was not isolated. Finally, 0.91 g. (25%) of nitrobenzene, b.p. 209–210°, n_D^{25} 1.5474, distilled as a dark yellow liquid. Redistillation gave a product b.p. 208–209°, n_D^{25} 1.5487, 0.63 g. (17%).

In another experiment nitrosobenzene was dissolved in 50 ml. of methylene chloride and, to the gently refluxing solution, a solution of hydrogen peroxide in trifluoroacetic acid was added over a period of 30 min. After refluxing another 15 min., the red-brown solution was poured into 150 ml. of ice water and worked up in the manner outlined above except that after filtering and washing the solid product with 25 ml. of cold methylene chloride, the combined filtrate and wash was steam distilled. The aqueous phase of the steam distillate was separated and extracted with two 15-ml. portions of methylene chloride. The combined extracts and methylene chloride layer of the distillate were dried over anhydrous sodium sulfate. By distillation of this solution there was obtained 1.31 g. (35.5%) of nitrobenzene, b.p. 208–210°, n_D^{25} 1.5484. The crude dry *p*-nitroso-*N,N*-diphenylhydroxylamine filtered from the reaction mixture weighed 0.49 g. (15%), m.p. 120° (dec.). Recrystallization from aqueous ethanol furnished 0.25 g. (8%) of material, m.p. 128–132° (dec.).

Oxidation of 1,2-dinitrosobenzene. To a solution of 2.70 g. (0.12 mol.) of the dinitroso compound in 15 ml. (0.20 mol.) of trifluoroacetic acid was added with stirring 1.7 ml. (0.06 mol.) of 90% hydrogen peroxide. The solution was heated to reflux and the heat of reaction was sufficient to maintain reflux for a few minutes. After a total reflux time of 45 min. the solution was poured into 200 ml. of ice water, the crude yellow precipitate of *o*-dinitrobenzene was filtered, washed with water, and recrystallized from dilute ethanol as light yellow needles, m.p. and mixture m.p. 118–119° (lit.[5] m.p. 116–116.5°), 0.71 g. (21%). Comparable yields of *o*-dinitrobenzene were obtained when the reaction was carried out in the presence of urea, a scavenger for oxides of nitrogen, either at room temperature for 17 hr. or at reflux for 1 hr.

In a similar manner, 3,4-dinitrosotoluene was oxidized into dinitrotoluene, m.p. and mixture m.p. 58–59°,[6] in 15% yield and *p*-dinitrosobenzene into *p*-dinitrobenzene, m.p. and mixture m.p. 174–175°,[5] in 92% yield.

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(1) Financial support by the Office of Ordnance Research, U. S. Army under contracts No. DA-01-009-ORD-428 and DA-01-009-ORD-669.

(2) A. S. Bailey and J. R. Case, *Tetrahedron*, **3**, 113 (1958) report that performic and peracetic acids do not react with *o*-dinitrosobenzene.

(3) E. Bamberger, H. Büsdorf, and H. Sand, *Ber.*, **31**, 1513 (1898).

(4) O. Fischer and L. Wacker, *Ber.*, **21**, 2609 (1888).

(5) J. W. Williams and C. H. Schwingel, *J. Am. Chem. Soc.*, **50**, 362 (1928).

(6) F. Beilstein and A. Kuhlberg, *Ann.*, **155**, 1 (1870).

Structure of Aryl Azo Pyrazolone Compounds and Their Copper Derivatives

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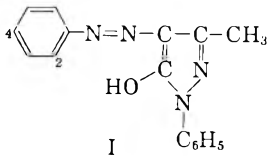
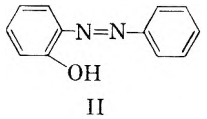
The simple aryl azo pyrazolone compounds (I) have been shown to be different from the simple *o*-hydroxy aryl azo compounds (II) in their



I



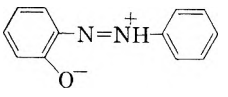
II

complexing ability with metal ions.[1] Although pyrazolone dyes are stronger acids, their metal derivatives are considerably more stable to dissociation into ions than the metal derivatives of type II. For example, the formation quotients of divalent copper, nickel, cobalt, and zinc with 1-phenyl-3-methyl-4-(4-methoxyphenylazo)-5-pyrazolone[2] are readily measured in 75 volume % dioxane-water while only the copper compound of 2-(4-methoxyphenylazo)-4-methyl-1-phenol[3] weakly forms under the same conditions.

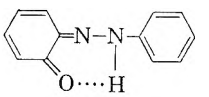
It has also been reported that there is only a small color shift in going from the undissociated dye, HCh, to the dissociated dye, Ch^-, of type (I)[1,2,4,5] while there is usually a significant color shift with type II, many of them serving as common indicators.

A preliminary infrared investigation of four simple aryl azo pyrazolone compounds, (Ia) 4-NO_2, (Ib) 4-OCH_3, (Ic) 2-OCH_3, and (Id) 2-SCH_3 and their copper(II) derivatives (2:1, dye to metal) shows no significant bands above 1700 cm.$^{-1}$ which are assignable to either the hydroxy or the NH group. However, a sharp, well defined band was found at 1670 cm.$^{-1}$ for dye (Ia), 1655 cm.$^{-1}$ for (Ib), and at 1665 cm.$^{-1}$ for (Ic) and (Id). This band disappeared completely in the copper derivatives.

Dolinsky and Jones[6] interpreted spectra of type II compounds as showing no evidence of either OH or of C=O absorption with the *o*-hydroxy compounds but that there was definite evidence in favor of the OH group with the *p*-hydroxy compounds. They proposed a zwitterion structure III as the most reasonable for the *o*-hydroxy (type II) derivatives. Recently Hadzi[7] interpreted his work with compounds of type II as arguing in favor of quinonehydrazone form (IV).



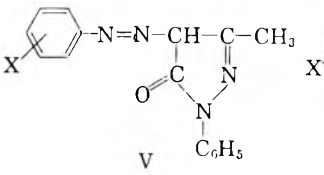
III



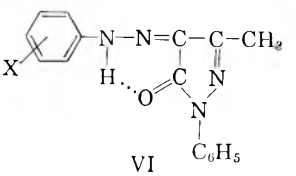
IV

Burawoy, *et al.*,[8] have used electronic spectra to show the existence of two distinct forms, the true hydroxy azo form II and the quinonehydrazone form IV.

We propose that either structure (V) or (VI) can represent the aryl azo pyrazolone compounds (the 1665 band is the carbonyl stretching band) and that (VII) represents the copper derivatives. The absence of significant absorption above 1700

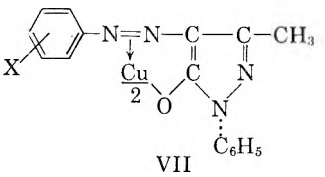


V



VI

cm.$^{-1}$ suggests that V is more reasonable than VI. However, as noted by Hadzi,[7] the band due to NH stretching would probably be broadened, weak, and shifted to longer wave lengths.



VII

EXPERIMENTAL

The azo compounds were prepared by coupling the appropriate diazotized amines to 1-phenyl-3-methyl-5-pyrazolone; they were recrystallized from dioxane. (Ia) 1-phenyl-3-methyl-4-(4-nitrophenylazo)-5-pyrazolone, red platelets, m.p. 199–200°, reported,[9] 198–199°; (Ib) 1-phenyl-3-methyl-4-(4-methoxyphenylazo)-5-pyrazolone, orange powder, m.p. 139–140°, reported[2] 139–140°; (Ic) 1-phenyl-3-methyl-4-(2-methoxyphenylazo)-5-pyrazolone, orange crystals, m.p. 166–167°, reported[2] 165–167°; (Id) 1-phenyl-3-methyl-4-(2-thiomethyoxyphenylazo)-5-pyrazolone, orange powder, m.p. 149–150°, reported[2] 149–150°. Each of the azo compounds was tested for purity, as previously reported.[4] Determination of neutral equivalents gave values within 0.1% of the calculated values.

The copper derivatives were prepared by the slow addition of 2 ml. of 1*N* NaOH solution to 100 ml. of boiling 75–25% dioxane-water which contained 2 mmoles of the dye and 1 mmole of copper(II) nitrate. The solutions were evaporated on a steam bath until precipitation of the com-

(1) F. A. Snavely and W. C. Fernelius, *Science*, **117**, 15 (1953).

(2) F. A. Snavely, B. D. Krecker, and C. G. Clark, *J. Am. Chem. Soc.*, **81**, 2337 (1959).

(3) C. G. Clark, Senior Honor Dissertation, Franklin and Marshall College (1957).

(4) F. A. Snavely, W. C. Fernelius, and B. P. Block, *J. Am. Chem. Soc.*, **79**, 1028 (1957).

(5) F. A. Snavely and B. D. Krecker, *J. Am. Chem. Soc.*, **81**, 4199 (1959).

(6) M. Dolinsky and J. H. Jones, *J. Assoc. Offic. Agr. Chemists*, **37**, 197 (1954).

(7) D. Hadzi, *J. Chem. Soc.*, 2143 (1956).

(8) A. Burawoy, *Ann.*, **509**, 60 (1934); A. Burawoy, A. G. Salem, and A. R. Thompson, *J. Chem. Soc.*, 4793 (1952).

(9) P. Karrer and E. B. Hershberg, *Helv. Chim. Acta*, **17**, 1014 (1934).

pound occurred. The metal derivatives were recrystallized from chlorobenzene, washed with ethyl ether, and dried in a vacuum desiccator. The copper derivative of (Ia), red-purple needles, m.p. 269–270°, reported[4] 268–270°.

The copper derivative of (Ib), brown crystalline powder, m.p. 237–238°.

Anal. Calcd. for Cu $(C_{17}H_{15}O_2N_4)_2$: C, 60.20; H, 4.46; N, 16.53. Found: C, 60.73; H, 4.29; N, 16.29.

The copper derivative of (Ic), brown crystalline powder, m.p. 286–287°, reported[10] 285°.

Anal. Calcd. for Cu $(C_{17}H_{15}O_2N_4)_2$: C, 60.20; H, 4.46; N, 16.53. Found: C, 60.67; H, 4.39; N, 16.28.

The copper derivative of (Id), brown powder, m.p. 233–234°.

Anal. Calcd. for Cu $(C_{17}H_{15}ON_4S)_2$: C, 57.48; H, 4.25; N, 15.77. Found: C, 57.37; H, 4.25; N, 15.43.

The spectra were measured, using the KBr disk technique on a Baird-Atomic two-beam infrared spectrophotometer.

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(10) V. I. Mur, *Zhur. Obshchei Khim.*, **24**, 572 (1954); *Chem. Abstr.*, **49**, 6198 (1955).

Some 4-Halo-2-butynyl *N*-Substituted Carbamates

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Many carbamates have been synthesized and screened for their biological activity as pesticides in the past few years. Although none are employed commercially as pesticides in this country at this time, certain acetylenic carbamates have been reported as having herbicidal activity.[1,2] Due to the fact that acetylenic compounds are rarely encountered in nature and that the carbamate linkage is known to be biologically active, the carbamates described herein were prepared and evaluated as pesticides. Several members of the series were found to be active, both as selective and as nonselective herbicides. The highly selective herbicidal activity of one of these compounds, 4-chloro-2-butynyl *N*-(3-chlorophenyl)carbamate, toward wild oats (*Avena fatua*) has been recently reported.[3] The variables regulating its use as a herbicide as well as the biological activities of the analogs in Table I will be reported elsewhere. No 4-chloro-2-butynyl *N*-substituted carbamate has been reported to have biological activity and only 4-chloro-2-butynyl *N*-phenylcarbamate, which is a member of this class of compounds, has been reported prior to this work.[4]

The compounds in Table I were prepared by four different methods:

(A) $ArN{=}C{=}O + HOCH_2C{\equiv}CCH_2X \longrightarrow ArNHCOOCH_2C{\equiv}CCH_2X$

(B) $RNH_2 + ClCOOCH_2C{\equiv}CCH_2X \longrightarrow RNHCOOCH_2C{\equiv}CCH_2X + HX$

(C) $ArN{=}C{=}O + HOCH_2C{\equiv}CCH_2OH \longrightarrow ArNHCOOCH_2C{\equiv}CCH_2OH$

$ArNHCOOCH_2C{\equiv}CCH_2OH + SOCl_2 \longrightarrow ArNHCOOCH_2C{\equiv}CCH_2Cl$

(D) $RNHCOOCH_2C{\equiv}CCH_2Cl + KI \longrightarrow RNHCOOCH_2C{\equiv}CCH_2I + KCl$

Method (C) has been used primarily for the preparation of 4-hydroxy-2-butynyl *N*-(3-chlorophenyl)carbamate. No solvent is necessary if the isocyanate addition is carried out above the melting point of the diol. The molar ratio of freshly distilled diol to isocyanate is important as regards the yield of the desired product. At a molar ratio of 1.25/1 the reaction mixture, when washed free of diol, contains 67% 4-hydroxy-2-butynyl *N*-(3-chlorophenyl)carbamate. At a molar ratio of 20/1 the yield of product in the reaction mixture is increased to 93%. The reaction mixtures were analyzed by their infrared absorption spectra, the band at 9.73μ being utilized to determine the concentration of the desired product.

The major impurity in the diol free reaction product would be expected to be 2-butynylene bis[*N*-(3-chlorophenyl)carbamate], which would be formed from the reaction of 4-hydroxy-2-butynyl *N*-(3-chlorophenyl)carbamate with isocyanate. The presence of the bis carbamate was confirmed by isolation from a reaction mixture. When an aliquot portion of the diol free reaction product was treated with excess isocyanate to convert the hydroxy carbamate to bis carbamate, only the bis carbamate was isolated.

The preparation of both the bromo and chloro halohydrins has been previously described by Bailey.[5] The chlorocarbonates were synthesized by the conventional reaction of phosgene with the halohydrin. These compounds were difficult to purify and were usually employed as the reaction mixture.

(1) J. A. Tursich, U. S. Patent **2,788,268** (1957).

(2) Badische Amlin, Ger. Patent **1,034,912** (1958).

(3) A paper entitled "Wild Oat Control with 4-Chloro-2-butynyl *N*-(3-Chlorophenyl)carbamate" by Otto L. Hoffmann, T. R. Hopkins, and Joe W. Pullen (in press) was presented at Winnipeg before the Proceedings of the 12th Annual Meeting, Western Section, National Weed Committee, Canada, on November 23, 1958 and before the North Central Weed Control Conference in Cincinnati on December 9, 1958. A paper entitled "Wild Oats—A New Chemical Control" by T. R. Hopkins, Otto L. Hoffmann, and Joe W. Pullen was presented before the Western Weed Conference at Salt Lake City on March 19, 1959.

(4) G. Dupont, R. Dulon, and G. Lefebure, *Bull. soc. chim. France*, 816 (1954).

(5) W. J. Bailey and E. J. Fufiwara, *J. Am. Chem. Soc.*, **77**, 165 (1955).

TABLE I

4-HALO-2-BUTYNYL *N*-SUBSTITUTED CARBAMATES
$RNHCOOCH_2C{\equiv}CCH_2X$

R	X	Formula	M.P., °C.	Crude Yield, %	Method	Cryst. Solv.	Analyses Calcd. C	Calcd. H	Found C	Found H
H	Cl	$C_6H_6ClNO_2$	95–96	65	B	1	40.7	4.1	40.6	3.9
$HOOCCH_2$	Cl	$C_7H_8ClNO_4$	90–91	26	B	1, 9, 3	40.9	3.9	41.0	3.9
2-C_3H_3NS[a]	Cl	$C_8H_7ClN_2O_2S$	142–143	18	B	1, 2, 3	41.6	3.1	41.7	2.9
C_4H_8O[b]	Cl	$C_9H_{12}ClNO_3$	Liq.	60	B	1	49.7	5.6	49.8	5.4
2-C_5H_4N[c]	Cl	$C_{10}H_9ClN_2O_2$	152–154	11	B	1, 3	53.5	4.0	53.5	4.2
C_5H_5O[d]	Cl	$C_{10}H_{10}ClNO_3$	52–53	38	B	1	52.8	4.5	52.8	4.5
C_5H_{10}[e]	Cl	$C_{10}H_{14}ClNO_2$	Liq.	64	B	1	55.7	6.5	55.4	6.2
3-$C_6H_{10}NO$[f]	Cl	$C_{11}H_{15}ClN_2O_3$	162–164	17	B	3, 2	51.1	5.8	51.4	5.7
cyclo-C_6H_{11}	I	$C_{11}H_{16}INO_2$	78–80	56	D	1, 4	41.1	5.0	41.0	5.0
n-C_6H_{13}	Cl	$C_{11}H_{18}ClNO_2$	Liq.	47	B	1, 9	57.0	7.8	57.4	7.8
$C_6H_5CH_2$	Cl	$C_{12}H_{12}ClNO_2$	66–68	30	B	1	60.6	5.1	61.0	5.0
4-HOC_6H_4	Cl	$C_{11}H_{10}ClNO_3$	122–123	75	B	3	55.0	4.2	54.9	3.9
2-BrC_6H_4	Cl	$C_{11}H_9BrClNO_2$	55–56	43	B	6	43.7	3.0	43.8	3.0
3-BrC_6H_4	Cl	$C_{11}H_9BrClNO_2$	78–79	86	B	1	43.7	3.0	44.0	3.3
4-BrC_6H_4	Cl	$C_{11}H_9BrClNO_2$	101–103	92	B	1	43.7	3.0	43.9	3.0
3-ClC_6H_4	Br	$C_{11}H_9BrClNO_2$	81–82	50	B	6	43.7	3.0	43.7	3.1
2-ClC_6H_4	Cl	$C_{11}H_9Cl_2NO_2$	37–39	44	A	6	51.2	3.5	51.1	3.5
3-ClC_6H_4	Cl	$C_{11}H_9Cl_2NO_2$	75–76	93	C	2	51.2	3.5	51.4	3.6
4-ClC_6H_4	Cl	$C_{11}H_9Cl_2NO_2$	102–104	72	A	1	51.2	3.5	51.2	3.4
3-ClC_6H_4	I	$C_{11}H_9ClINO_2$	87–88	96	D	1	37.8	2.6	37.9	2.9
2-$CH_3C_6H_4$	Cl	$C_{12}H_{12}ClNO_2$	48–49	42.6	B	6	60.6	5.1	60.3	5.0
3-$CH_3C_6H_4$	Cl	$C_{12}H_{12}ClNO_2$	47–48	60.0	B	6	60.6	5.1	60.3	5.0
4-$CH_3C_6H_4$	Cl	$C_{12}H_{12}ClNO_2$	93–94	67.5	B	6	60.6	5.1	60.2	5.0
2-$NO_2C_6H_4$	Cl	$C_{11}H_9ClN_2O_4$	67–68	29	A	1	49.2	3.4	49.3	3.4
3-$NO_2C_6H_4$	Cl	$C_{11}H_9ClN_2O_4$	92–94	75	A	1	49.2	3.4	49.5	3.4
4-$NO_2C_6H_4$	Cl	$C_{11}H_9ClN_2O_4$	129–130	44	A	1	49.2	3.4	49.1	3.3
3-$(CH_3O)C_6H_4$	Cl	$C_{12}H_{12}ClNO_3$	74–75	79	B	1	56.8	4.8	56.9	4.9
3-Cl-2-$CH_3C_6H_3$	Cl	$C_{12}H_{11}Cl_2NO_2$	88–89	81	B	1	52.9	4.1	53.0	4.1
2-Cl-5-$CH_3C_6H_3$	Cl	$C_{12}H_{11}Cl_2NO_2$	63–64	61	B	1	52.9	4.1	53.2	4.0
3-Cl-6-$CH_3C_6H_3$	Cl	$C_{12}H_{11}Cl_2NO_2$	103–105	69	B	1	52.9	4.1	53.2	4.2
4-Cl-2-$CH_3C_6H_3$	Cl	$C_{12}H_{11}Cl_2NO_2$	90–91	59	B	1	52.9	4.1	52.9	4.1
2-Br-4-$CH_3C_6H_3$	Cl	$C_{12}H_{11}BrClNO_2$	81–82	44	B	1	45.5	3.5	45.8	3.8
5-NO_2-2-$CH_3C_6H_3$	Cl	$C_{12}H_{11}ClN_2O_4$	133–134	80	B	1	51.0	3.9	50.9	3.8
2-NO_2-4-$CH_3C_6H_3$	Cl	$C_{12}H_{11}ClN_2O_4$	65–66	74	B	1	51.0	3.9	51.3	4.2
2,4-$Cl_2C_6H_3$	Cl	$C_{11}H_8Cl_3NO_2$	70–71	33	A	6, 7	45.2	2.8	45.1	2.8
2,3-$Cl_2C_6H_3$	Cl	$C_{11}H_8Cl_3NO_2$	71–72	47	B	1	45.2	2.8	45.0	2.8
2,4-$(CH_3)_2C_6H_3$	Cl	$C_{13}H_{14}ClNO_2$	81–83	90	B	1	62.0	5.6	61.7	5.7
2,5-$(CH_3O)_2C_6H_3$	Cl	$C_{13}H_{14}ClNO_4$	45–46	85	B	1	55.0	4.9	55.3	5.1
4-$HOOCC_6H_4$	Cl	$C_{12}H_{10}ClNO_4$	180–184	90	B	2	53.9	3.7	53.9	4.0
4-$C_6H_5C_6H_4$	Cl	$C_{17}H_{14}ClNO_2$	90–91	81	B	1	68.1	4.7	68.2	5.0
4-NCC_6H_4	Cl	$C_{12}H_9ClN_2O_2$	133–134	85	B	1	57.9	3.7	58.2	3.7
4-$CH_3COC_6H_4$	Cl	$C_{13}H_{12}ClNO_3$	142–144	90	B	1	58.8	4.6	58.9	4.8
4-$C_6H_5N{=}NC_6H_4$	Cl	$C_{17}H_{14}ClN_3O_2$	130–131	69	B	1	62.2	4.3	62.4	4.5
1-$C_{10}H_7$[g]	Cl	$C_{15}H_{12}ClNO_2$	103–104	77	B	1	65.8	4.4	66.0	4.5
2-$C_{10}H_2$[g]	Cl	$C_{15}H_{12}ClNO_2$	84–85	73	B	1	65.8	4.4	65.8	4.5
2-C_7H_4NS[h]	Cl	$C_{12}H_9ClN_2O_2S$	197 (dec.)	66	B	5	51.3	3.2	51.6	3.2
2-(CH_3O)-5-ClC_6H_3	Cl	$C_{12}H_{11}Cl_2NO_3$	76–77	61	B	1	50.0	3.9	50.2	3.9

[a] 2-Thiazoyl. [b] Morpholino. [c] 2-Pyridyl. [d] Furfuryl. [e] Piperidino. [f] 3-Cyclohexamethyleneimine-2-oxo. [g] Naphthyl. [h] 2-Benzothiazoyl.

Crystallization solvents: (1) benzene-*n*-hexane, (2) ethanol-water, (3) benzene, (4) ligroin, (5) ethanol, (6) *n*-hexane, (7) acetone-hexane, (8) ethyl acetate–hexane, (9) ethanol-hexane.

Several carbamates were obtained which were liquids. This normally occurred when the nitrogen was disubstituted, when lower alkyl groups were involved, or in some cases where an *ortho*- substituted aromatic amine was employed. All attempts to purify these materials by conventional methods usually failed. Those products which are reported as being liquids at room temperature in Table I were purified by successive low temperature extractions.

EXPERIMENTAL[6]

The following examples are representative of each method of preparation of the carbamates.

Method A

Preparation of 4-chloro-2-butynyl N-(3-nitrophenyl)carbamate. A mixture of 4-chloro-2-butyn-1-ol (20.9 g., 0.2 mol.), 3-nitrophenylisocyanate (32.8 g., 0.2 mol.), 300 ml. of benzene and 5 drops of pyridine was stirred and heated to the reflux temperature. The mixture was refluxed 3 hr.,

(6) All melting points are uncorrected.

cooled to room temperature, and poured into 300 ml. of *n*-hexane. The crude product (49.9 g.; 93% yield; m.p. 85–89°) was removed by filtration and air dried. Recrystallization from a benzene-*n*-hexane mixture gave 45 g. (83% yield) of product (m.p. 92–93.5°).

Method B

Preparation of 4-chloro-2-butynyl N-(2,5-dimethoxyphenyl)-carbamate. A mixture of 2,5-dimethoxyaniline (7.66 g., 0.05 mol.), pyridine (3.96 g., 0.05 mol.) and 50 ml. of benzene was cooled to 10°. 4-Chloro-2-butynyl chloroformate (8.5 g., 0.05 mol.) was added dropwise at 10–15°. The mixture was stirred for 3 hr. at ambient temperature then diluted with an equal volume of water. The benzene layer was separated, dried over anhydrous calcium chloride, diluted with 2 volumes of *n*-hexane and chilled to 0°. The crude product (12.2 g.; 85% yield; m.p. 42–45°) was collected by filtration. Recrystallization from benzene-*n*-hexane gave 11.4 g. (m.p. 45–46°, 80% yield).

Method C

Chlorination of 4-hydroxy-2-butynyl N-(3-chlorophenyl)-carbamate. A mixture of 4-hydroxy-2-butynyl *N*-(3-chlorophenyl)carbamate (0.25 mol., 60.0 g.), ethylene dichloride (120 ml.) and 0.5 ml. pyridine was heated to 60°. Thionyl chloride (31.2 g., 0.262 mol.) was added dropwise at 60–65° (20 min.) and held at 60–65° for 2 hr. after addition was complete. The reaction mixture was cooled to 25°, poured into 300 ml. of *n*-hexane, and chilled to 0°. The product (60.3 g.; 93.4% yield; m.p. 70–72°) was collected by filtration and air dried.

Method D

Metathesis with 4-chloro-2-butynyl N-(3-chlorophenyl)-carbamate and potassium iodide. To a solution of 7.0 g. of potassium iodide and 1.5 l. of absolute acetone was added 4-chloro-2-butynyl *N*-(3-chlorophenyl)carbamate (10.0 g., 0.039 mol.). The solution was heated to reflux for 2 hr. and filtered. The solvent was removed under reduced pressure, the residue was dissolved in 15 ml. of benzene, filtered, diluted with 50 ml. of *n*-hexane, and allowed to cool. The product was collected by filtration (13.0 g., 96% yield). A small portion was recrystallized from benzene-hexane several times to give a colorless product melting at 87–88°.

4-Hydroxy-2-butynyl N-(3-chlorophenyl)carbamate. The following example is representative of the method of preparing this compound regardless of the mole ratios employed. Actual ratios studied were 1.25/1, 2.5/1, 5/1, 10/1, and 20/1. Yields obtained were, respectively, 67%, 82%, 87%, 91%, and 93%.

3-Chlorophenyl isocyanate (30.7 g., 0.2 mol.) was added dropwise, with stirring, to molten 2-butyn-1,4-diol (86.0 g., 1.0 mol.). The temperature was maintained at 60 ± 5° during the addition and stirring was continued for an additional 30 min. The reaction mixture was poured into 500 ml. of water at 85°, the slurry cooled to 0°, and filtered. The residue was washed with 250 ml. of water at 85°, cooled to 0°, and filtered. The crude carbamate was dried to give 47.0 g. of product melting at 80–98°. An infrared analysis determined the material to be 87% pure. The crude carbamate was recrystallized two times from ethylene dichloride and once from toluene to give 28.1 g. (57% yield) melting at 87–88°.

Anal. Calcd. for $C_{11}H_{10}ClNO_3$: C, 55.2; H, 4.2. Found: C, 55.4; H, 4.5.

Isolation of 2-butynylene-1,4-bis[N-(3-chlorophenyl)carbamate]. The reaction product from a reaction using a 5/1 mole ratio of 2-butyn-1,4-diol to 3-chlorophenyl isocyanate was washed free of diol with water as described above. Forty-six and seven-tenths grams of the residual solid was recrystallized 3 times from 5 parts of ethylene dichloride to yield 33.0 g. of 4-hydroxy-2-butynyl *N*-(3-chlorophenyl)-carbamate, m.p. 85–86° analyzing 96% pure by infrared. The filtrates were combined and evaporated and the residual solid, 13.1 g., was extracted nine times with 200-ml. portions of boiling water leaving 7.0 g. of tan solid, m.p. 90–125°. This residue was recrystallized twice from ethanol-water and then from chloroform to yield 1.6 g. of white solid, m.p. 143–143.5°. A small sample was recrystallized from absolute alcohol to yield white needles, m.p. 146.5–147°.

Anal. Calcd. for $C_{18}H_{14}Cl_2N_2O_4$: C, 55.0; H, 3.6; N, 7.1. Found: C, 55.2; H, 3.8; N, 7.2.

Five grams of the above carbamate mixture containing 87% 4-hydroxy-2-butynyl *N*-(3-chlorophenyl)carbamate (0.018 mol.) was dissolved in acetone and refluxed with 2.8 g. (0.18 mol.) of 3-chlorophenyl isocyanate for 4 hr. The volatile materials were removed under reduced pressure (final conditions 100° at 5 mm.) leaving 7.6 g. of tan solid (97% crude) melting at 130–138°. Recrystallization from benzene-hexane gave 5.6 g. (72%) melting at 140–141°. A mixed melting point with an authentic sample of 2-butynylene-1,4-bis[*N*-(3-chlorophenyl)carbamate] gave no depression.

Preparation of 4-chloro-2-butynyl chlorocarbonate. Phosgene (50 ml., 0.7 mol.) was condensed in a 200-ml. flask. 4-Chloro-2-butyn-1-ol (44 g., 0.42 mol.) was added dropwise at a rate which maintained the reaction temperature at approximately 0°. After the chlorohydrin addition the mixture was allowed to rise to room temperature whereupon the excess phosgene was removed under reduced pressure. The product was distilled. There was obtained 48.8. g. (70%) of the desired chlorocarbonate boiling at 100–103°/16 mm.; n_D^{25} 1.4830.

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Synthesis of 2-Oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]-quinolizine

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Synthesis of 2-oxo-3-ethyl-9,10-dimethoxy-1,2,-3,4,6,7-hexahydro-11bH-benzo [a] quinolizine (IV), a key intermediate in the synthesis of emetine and allied compounds, has been described by two different groups of authors.[2a,b] In this paper we are reporting a third synthesis of this compound.

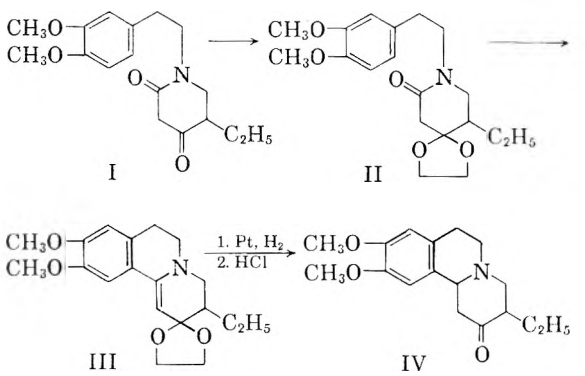
N-3,4-Dimethoxyphenylethyl-2,4-dioxo-5-ethyl-piperidine (I) was converted to the corresponding ethyleneketal derivative, *N*-3,4-dimethoxyphenyl-ethyl - 2 - oxo - 4,4 - ethylenedioxy - 5 - ethyl-piperidine (II), by the standard method, and the ketal underwent a cyclization when treated with a mixture of phosphorus pentoxide and sea sand in boiling pyridine.[3] $\Delta^{1:11b}$-2,2-Ethylenedioxy-3-ethyl - 9,10 - dimethoxy - 3,4,6,7 - tetrahydro - 2H-benzo[a]quinolizine (III) thus obtained was reduced catalytically followed by acid hydrolysis to furnish 2-oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-

(1) Present address: No. 40, 3-chome, Iogi, Suginami-ku, Tokyo.

(2) (a) A. R. Battersby, H. T. Openshaw, and H. C. S. Wood, *J. Chem. Soc.*, 2436 (1953). (b) A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, 41, 119 (1958).

(3) N. Itoh and S. Sugasawa, *Tetrahedron*, 6, 16 (1959).

hexahydro-11bH-benzo[a]quinolizine (IV) in a fair yield.



EXPERIMENTAL

1-(3,4-Dimethoxyphenylethyl)-4,4-ethylenedioxy-5-ethyl-2-piperidone (II). A mixture of 5 g. of 1-(3,4-dimethoxyphenylethyl)-5-ethyl-2,4-dioxopiperidine (I)[4] in 150 ml. of benzene, 2 g. of ethylene glycol and 0.2 g. of *p*-toluenesulfonic acid was boiled for 3 hr. surmounted with a constant water separator. On cooling the reaction mixture was shaken with 10% sodium hydroxide solution to remove the starting ketone and toluenesulfonic acid, washed with water, and dried. Benzene was then removed to leave a colorless clear sirup, yield 5 g. (85%), in which the absence of the original ketone was proved by inspection of the infrared spectrum. This was directly used in the next step.

$\Delta^{1:11}$-2,2-Ethylenedioxy-9,10-dimethoxy-3,4,6,7-tetrahydro-2H-benzo[a]quinolizine (III). To a boiling solution of 1 g. of the foregoing compound in 50 ml. of pyridine was added an intimate mixture of 5 g. of phosphorus pentoxide and 50 g. of purified sea sand in 4 portions with stirring.[5] After being refluxed for 6 hr. altogether the pyridine solution was decanted while still hot and the resultant residue was extracted with 3 × 10 ml. portions of hot pyridine. Pyridine was distilled from the combined pyridine solution. The residue was mixed with 10 ml. of benzene, which was distilled off to remove the residual pyridine. This manipulation was repeated twice more, thus leaving 0.7 g. of a reddish brown sirup, which was characterized as the picrate, yellow prisms from ethanol, m.p. 109–110°.

Anal. Calcd. for $C_{25}H_{28}O_{11}N_4$: C, 53.6; H, 5.0; N, 10.0. Found: C, 53.6; H, 5.2; N, 10.3.

2-Oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[a]quinolizine (IV). A solution of 0.5 g. of aforementioned crude base in 20 ml. of ethanol, acidified with a few drops of 10% hydrochloric acid, was hydrogenated over platinum catalyst, 53 ml. of hydrogen being absorbed. One-half g. of a colorless sirup thus obtained was dissolved in a few ml. of 10% hydrochloric acid and warmed on a steam bath for 1 hr. The solution was filtered through a wet filter paper and the filtrate was made alkaline with potassium carbonate with cooling. The base that separated was taken up in benzene and dried, and the solvent was removed to leave 0.43 g. of a colorless glass, which solidified on standing. This formed colorless needles from *n*-hexane, m.p. 109°, which was not depressed on admixture with an authentic sample prepared according to the method of Battersby *et al.*,[2a] yield 0.2 g. The total yield from II was 31%.

The picrate formed yellow prisms from ethanol, m.p. 182–183° (decomp.).

Anal. Calcd. for $C_{25}H_{26}O_{10}N_4$: C, 53.3; H, 5.0; N, 10.8. Found: C, 53.65; H, 5.3; N, 10.7.

(4) Y. Ban, *Pharm. Bull. (Japan)*, **3**, 53 (1955).

(5) After some time stirring became impossible through caking.

Acknowledgment. The authors are grateful to Mr. M. Nakamura, vice-president of Yawata Chemical Industries Ltd., for a generous donation of pure pyridine.

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Synthesis of 1-*p*-Methoxybenzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline

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1-Substituted 3,4,5,8-tetrahydroisoquinolines are precursors of 1,2,3,4,5,6,7,8-octahydroisoquinolines, which, when suitably substituted in the 1-position, form key intermediates for the synthesis of morphinans. Bischler-Napieralski cyclization of *N*-acyl-2-(1,4-cyclohexadienyl)ethylamine to yield 1-substituted 3,4,5,8-tetrahydroisoquinolines has been described by the present authors.[2]

We now report the acylation of 2-(1,4-cyclohexadienyl)ethylamine with *p*-methoxyphenylacetyl chloride to form the corresponding amide which was then cyclized to give 1-*p*-methoxybenzyl-3,4,5,8-tetrahydroisoquinoline. Since the latter is unstable in air it was catalytically reduced without purification to yield 1-*p*-methoxybenzyl-1,2,3,4,-5,6,7,8-octahydroisoquinoline. The identity of the latter was confirmed by a mixed melting point with an authentic sample prepared according to the procedure of Schnider and Hellerbach.[3] It was converted to 3-hydroxy-*N*-methylmorphinan by the method of these authors.

EXPERIMENTAL

N-2-(1,4-Cyclohexadienyl)ethyl-p-methoxyphenylacetamide. 2-(1,4-Cyclohexadienyl)ethylamine (6.2 g.) in 80 ml. of benzene was treated with *p*-methoxyphenylacetyl chloride (9.4 g. in benzene) in the presence of sodium bicarbonate (5%, 200 ml.) with cooling and stirring. An oily amide was obtained, which solidified on scratching and was purified from a mixture of *n*-hexane and benzene, colorless scales, m.p. 86–86.5°, yield 12.5 g. or 92%.

Anal. Calcd. for $C_{17}H_{21}O_2N$: C, 75.3; H, 7.75; N, 5.2. Found: C, 75.5; H, 7.7; N, 5.1.

1-p-Methoxybenzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline. A mixture of *N*-2-(1,4-cyclohexadienyl)ethyl-*p*-methoxyphenylacetamide (3 g.), phosphoryl chloride (3 ml.) and benzene (50 ml.) was refluxed for 30 min., giving a reddish yellow solution, a copious evolution of hydrogen chloride being observed. On cooling enough petroleum ether was added to the reaction solution to produce a reddish precipitate, which

(1) Present address: No. 40, 3-chome, Iogi, Suginami-ku, Tokyo, Japan.

(2) S. Sugasawa and R. Tachikawa, *Tetrahedron*, **4**, 205 (1958).

(3) O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1437 (1950).

was separated from the supernatant liquid after some time and dissolved in dilute hydrochloric acid. The acid solution, after being shaken with benzene and filtered through a wet filter paper, was made alkaline cautiously with caustic soda solution with cooling and stirring. The benzene layer was washed and dried and the solvent was removed in vacuo in a hydrogen atmosphere. The reddish residue thus obtained was dissolved in methanol (50 ml.) and reduced over Raney nickel (1.5 g.), *ca.* 2 molar equivalents of hydrogen being absorbed. The catalyst and the solvent were removed and the residue was dissolved in benzene and purified through an alumina column. After evaporation of the solvent there remained a yellow oily base, which was again dissolved in methanol, neutralized with hydrobromic acid and evaporated. The residue solidified on scratching and was purified from a minimum amount of hot water (charcoal) to give the hydrobromide salt of 1-*p*-methoxybenzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline as colorless prisms, m.p. 197–198°, undepressed when admixed with an authentic specimen, yield 1.55 g. or 41.3%. Both specimens also gave the identical IR spectra.

Anal. Calcd. for $C_{17}H_{23}ON \cdot HBr$: C, 60.4; H, 7.1; N, 4.1. Found: C, 60.0; H, 6.7; N, 4.1.

Catalytic reduction of the 2-methyl quarternary salt of the tetrahydro base did not give a satisfactory result. Methylation was accomplished by catalytic reduction in the presence of formaldehyde and the 1-*p*-methoxybenzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline was converted to 3-hydroxy-*N*-methylmorphinan, m.p. 250–252°, by the procedure of Schnider and Hellerbach.[3] Its identity was confirmed by mixed melting point with an authentic sample.

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Pyrolysis of 1,1-Dichloro-2-vinylcyclopropane. Synthesis of 2-Chlorocyclopentadiene

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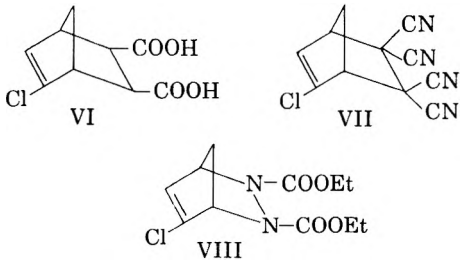
The reaction of chloroform with butadiene in the presence of potassium *t*-butoxide gives 1,1-dichloro-2-vinylcyclopropane (I).[1] This material is remarkably stable, being resistant to the action of bases, to zinc and magnesium in refluxing ethanol or tetrahydrofuran and is not attacked by molecular oxygen.[2] However, on vacuum pyrolysis at about 500° (5 mm. nitrogen atmosphere), the compound was converted essentially completely to a mixture of new chloroolefins. Low temperature vacuum distillation of the mixture permitted isolation in about 90% purity of a monochlorocyclopentadiene (II) which on the basis of its Diels-Alder reactions was concluded to have the chlorine atom in the 2- position.

Vapor phase chromatography of the reaction product on a silicone column resulted in separation into four major peaks and several additional minor ones. While the structures of these materials have not been conclusively demonstrated, evidence was obtained for the existence of 4,4-dichlorocyclopentene (III), 1,1-dichloropenta-1,4-diene (IV), and 1,1-dichloropenta-1,3-diene (V) in the pyrolysis mixture.

Evidence for the interesting chlorocyclopentadiene structure consisted of hydrogenation with palladium on charcoal in alcoholic potassium hydroxide to cyclopentane; a mass spectrum indicating a molecular weight of 100 and the presence of one chlorine atom (from the size of the isotopic 102 peak); the infrared spectrum showing a strong band at 6.3μ attributable to a conjugated diene structure; the nuclear magnetic resonance spectrum which showed the presence of two types of hydrogens in the ratio of 3 to 2 with resonance at +9.0 and +42.5 parts per ten million from benzene, respectively; the ultraviolet spectrum with maxima at 254 (ϵ 3200) and 250 (ϵ 3200) with a shoulder at 238 (ϵ 2500) mμ; the exothermic reactions with maleic anhydride and tetracyanoethylene; and the spontaneous dimerization of the material on standing.

The conclusion that the molecule reacted as if the chlorine atom were in the 2- rather than the 1-position on the cyclopentadiene ring was made on the basis of the absence of the 14.2μ *cis*-hydrogen band in the infrared spectra of all the Diels-Alder derivatives which were prepared. This band was present in all authentic bicyclo(2,2,1)hept-5-ene derivatives unsubstituted in the 5- and 6-positions which were examined.



In addition, the nuclear magnetic resonance (NMR) spectrum of VI showed the presence of four kinds of hydrogens in the approximate ratios of 4:2:2:1. The lone hydrogen atom had its resonance peak at the position of resonance of the olefinic hydrogens in bicyclo(2,2,1)hept-5-ene-2,3-dicarboxylic acid. The existence of a dynamic equilibrium between 1- and 2-chlorocyclopentadiene with more rapid reaction of the 2- isomer cannot be ruled out, however, though an attempt to find even a small amount of an isomeric adduct in the maleic anhydride reaction was unsuccessful.

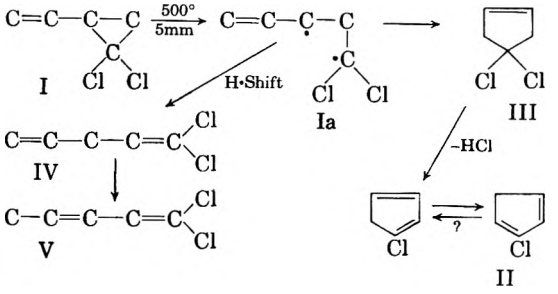
The evidence for the 4,4-dichlorocyclopentene (III) consisted of the infrared, NMR, and mass spectrum of a fraction which had been collected by vapor phase chromatography. Also, in a series of

(1) R. C. Woodworth and P. S. Skell, *J. Am. Chem. Soc.*, 79, 2542 (1957).

(2) All of these observations are in sharp contrast to the behavior of 1,1-dibromo-2-vinylcyclopropane, N. P. Neureiter, unpublished results; see also W. E. Doering and P. M. LaFlamme, *Tetrahedron*, 2, 75 (1958).

pyrolyses the yield of III decreased in direct proportion to an increase in II with an increase in the pyrolysis temperature. This suggested that at the higher temperatures III was dehydrochlorinating to give II. Such a precursor to the cyclopentadiene structure would mean that initially 1-chlorocyclopentadiene was formed, followed either by immediate rearrangement to the 2- isomer or the existence of the two compounds in dynamic equilibrium.

The most plausible course for the transformation would involve initial rupture of the cyclopropane ring to form the resonance stabilized diradical Ia which then has a number of alternate paths by which it can subsequently react.



One path of reaction of Ia leading to the linear structures IV and V is indicated. A small amount of isopentane which was obtained on hydrogenation of the reaction mixture can be explained through formation of a different initial diradical.

It has recently been concluded that carbenes add to double bonds by a three-center transition state.[3] Perhaps as a result of such a mechanism no 1,4-additions of carbenes to conjugated double bond systems have been observed.[4] It seems reasonable to interpret the present work as further evidence for the reaction of carbene species in the singlet state. If a carbene were a true diradical one might fairly expect some conjugate addition. It appears that when the diradical intermediate Ia does exist, conjugate addition can be observed. Of course, in the present work, the three-membered ring is unstable with regard to the diradical Ia at the high temperatures of the reaction. This, then, is one way of forcing the 1,4- addition of a carbene to a conjugated system.

EXPERIMENTAL[5]

Chlorocyclopentadiene. The 1,1-dichloro-2-vinylcyclopropane was obtained by the method of Woodworth and Skell.[1] In a typical pyrolysis run 16.8 g. (0.123 mol.) of this product was introduced during 1 hr. to an empty 28 × 300 mm. (heated length) Vycor tube inclined at a 40° angle through a furnace heated to 475–500°. A slow stream of nitrogen (100 ml./min.) was passed through the tube, while a vacuum pump was regulated to hold the total pressure at about 5 mm. The sample was charged in two different ways. A small three-neck flask equipped with dropping funnel, nitrogen inlet, and heating mantle was attached *via* a short, bent exit tube to the pyrolysis tube. The material could be added through the dropping funnel at any desired rate and immediately vaporized. Later the dropping funnel was eliminated by placing the full charge in the precooled flask and slowly warming to vaporize the material into the nitrogen stream. The exit gases from the pyrolysis tube were passed directly into a Dry Ice trap, then to a liquid nitrogen trap which was attached to the vacuum pump. The liquid product remained in the Dry Ice trap while the hydrogen chloride collected in the liquid nitrogen trap. At the end of the reaction the product in the Dry Ice trap (13.7 g., brown liquid) was dried over a little calcium chloride to remove some cloudiness and distilled immediately under nitrogen through an 8 × 200 mm. Vigreux column. The distillate was collected in a Dry Ice trap at 33 mm. pressure until the vapor temperature reached 39° (b.p. of starting material). The distillate (6.3 g.) was immediately redistilled (after removing a little cloudiness with calcium chloride) under nitrogen through a 14-cm. Vigreux column. The fractions were collected at 0°. After a small forerun, a fraction (1.92 g.) was collected, b.p. 30.7–35.5° (60 mm.) (flat at 33°), n_D^{27} 1.4822. From mass spectral data the material was estimated to be about 90% pure monochlorocyclopentadiene, though in the low voltage mass spectrum there were small peaks at mass 136, 104, and 88. The NMR spectrum at 60 megacycles on the neat liquid showed two kinds of hydrogen (peaks at +9.0 and +42.5 parts per ten million from benzene) in the ratio of 3 to 2. There were some smaller impurity bands —in part ascribable to the presence of some of the dimer. The infrared spectrum showed bands at 3.23 (mw), 3.47 (mw), 6.17 (vw), 6.32 (s), 6.69 (s), 7.30 (s), 7.42 (s), 7.89 (s), 8.02 (ms), 8.19 (m), 8.90 (s), 9.00 (m), 9.29 (ms), 9.34 (ms), 10.21 (ms), 10.60 (ms), 10.90 (ms), 11.23 (s), 11.62 (s), 11.76 (s), 12.48 (m), 13.40 (s), 14.60 (ms), 14.95 (s) μ. The ultraviolet spectrum in isooctane showed λ_{max} 254 mμ (ϵ 3200), 250 mμ (ϵ 3200), and 238 mμ (ϵ 2500).

For rapid, rough analyses of the product mixture vapor phase chromatography on an 8 ft. silicone grease on firebrick column operated at 80° with 22 lb. of helium pressure was used. There were only four significant peaks with at least five minor ones (all less than 5%). The first peak corresponded to chlorocyclopentadiene.

The second large peak (whose relative percentage was strongly dependent on the temperature of the pyrolysis) had a mass of 136 and contained two chlorine atoms. In the mass spectrometer from the size of the 100 and 101 peaks it was clear that the material had a structure which readily lost hydrogen chloride. The infrared spectrum had a C—H stretching pattern in the 3–4μ range similar to cyclopentene. Also, the shape of the C=C band at 6.18μ and the broad band at 14.35μ were similar to cyclopentene. The NMR spectrum in carbon disulfide at a frequency of 30 megacycles showed two kinds of hydrogens in the ratio of about 2 to 1 with bands centered at +38.0 and +13.0 parts per ten million from benzene. On the basis of these data this material has been assigned the structure 4,4-dichlorocyclopentene.

The third and fourth large peaks overlapped slightly. A mixture of the two was hydrogenated with palladium (10%) on charcoal in ethanol containing potassium hydroxide to give *n*-pentane. Both compounds had mass 136 and contained two chlorine atoms. The materials did not readily lose hydrogen chloride in the mass spectrometer. The third compound appeared to have a vinyl group and no methyl group from the infrared. No evidence was obtained for the

(3) W. von E. Doering and W. A. Henderson, Jr., *J. Am. Chem. Soc.*, **80**, 5274 (1958). P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **78**, 4496 (1956).

(4) The evidence for the small amount of 1,4- addition of $:CCl_2$ to isoprene reported by M. Orchin and E. C. Herrick, *J. Org. Chem.*, **24**, 139 (1959), hardly seems sufficient to warrant the conclusion.

(5) All boiling points and melting points are uncorrected. Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

location of the chlorine atoms. It was felt that the material was a linear, nonconjugated, dichloropentadiene. The fourth compound was thought to be the conjugated isomer of the third, but no conclusive information was obtained.

In a series of pyrolyses using only 1 or 2 ml. samples the effect of temperature on the pyrolysis was examined. Under the conditions described above, varying only the temperature produced a change in the composition of the product. Below 300° there was no conversion, at 325° it was only 0.5%. At 375° with 12% conversion there was 5% of peak 1, 5% of peak 2 and 2% of peak 3. Peak 4 appeared (2%) at 425° (~50% conversion). In the 400–450° range, the relative amounts of 1 and 2 were essentially the same; however, above 500° as the temperature was raised to 570° the percentage of 2 dropped sharply as 1 increased. The percentage and number of small by-product peaks increased at these high temperatures. In the normal pyrolysis range (475–525°) a typical product (by relative peak areas in the vapor phase chromatograms) showed 25–30% peak 1, 15–20% peak 2, 30–35% peak 3, 10% peak 4, and 10–20% others.

Hydrogenation of reaction mixture. A sample of the pyrolysis product (0.8971 g.) was dissolved in 30 ml. of ethanol containing 1.3 g. of potassium hydroxide pellets and 80 mg. of 10% palladium on charcoal catalyst. The mixture was stirred in a hydrogen atmosphere at room temperature for 20 hr. Hydrogen absorption was very rapid at the beginning —but in the last 12 hr. only 10 ml. was absorbed. The mixture was filtered and distilled through a short Vigreux column until the vapor temperature reached 78°. The distillate was transferred to a narrow tube and water added. The supernatant layer (0.1–0.2 ml.) was analyzed by vapor phase chromatography. It was about 30% cyclopentane, 70% *n*-pentane. In a larger run 2.039 g. of pyrolysis mixture gave 0.35 ml. of hydrocarbon. This was analyzed as 61% *n*-pentane, 2% isopentane, 37% cyclopentane. From treatment of the residue with nitric acid and silver nitrate 2.47 g. of silver chloride was recovered corresponding to 0.61 g. of chloride ion having been eliminated from the original material. This suggests that hydrogenolysis under the reaction conditions was not complete.

From a fractional distillation of the pyrolysis product mixture the first fraction was hydrogenated as described above. The recovered hydrocarbon was 73% cyclopentane, 15% *n*-pentane and 12% a combination of several smaller peaks (C_1's to C_4's).

Isolation of dimer. The pyrolysis mixture from 20 g. of 1,1-dichloro-2-vinylcyclopropane was distilled giving 5.0 g., b.p. up to 30° (28 mm.). This was added to 15 ml. of ethyl ether containing a pinch of hydroquinone and let stand at room temperature for 5 days. The ether was removed under a column and the brown residue distilled giving 3.1 g. of colorless liquid, b.p. 85–93° (3 mm.). This was redistilled giving 2.4 g., b.p. 78–84° (2.2 mm.), n_D^{20} 1.5388.

Anal. Calcd. for $C_{10}H_{10}Cl_2$: C, 59.7; H, 5.0; Cl, 35.3. Found: C, 59.6; H, 4.9; Cl, 29.0, 29.2.

Hydrogenation of dimer. A sample of this dimer (0.9586 g., 4.77 mmol.) was dissolved in 30 ml. of ethanol with 2.5 g. of potassium hydroxide and 130 mg. of 10% palladium on charcoal. The mixture was stirred at room temperature for several hours in 1 atmosphere of hydrogen—uptake being very rapid. After about 200 ml. had been absorbed, continued hydrogen absorption became very slow even though the temperature was raised to 60°. At the end of 4 days 351 ml. (15.65 mmol.) of hydrogen had been absorbed. Most of the ethanol was removed under a small column at slightly reduced pressure. The residue was added to 4 vol. of water and extracted with petroleum ether. Washing the extracts with water, drying with calcium chloride and distilling gave 0.46 g. of material distilling to 120° (20–30 mm.). About $^2/_3$ of this material solidified on standing. The mass spectrum showed it to be a mixture of masses 136 and 170. The 170 material still contained one chlorine atom as evidenced by the 172 isotope peak, while the 136 peak was apparently due to the saturated hydrocarbon. This shows that the hydrogenolysis was not complete. The odor of the product was similar to that of tetrahydrodicyclopentadiene.

Reaction with maleic anhydride. From the initial distillation of the pyrolysis mixture 2.4 g. of the first cut was added to 2.6 g. of maleic anhydride in 12 ml. of benzene. Within 1 min. there was a considerable development of heat. The solution was left standing overnight and concentrated *in vacuo*. The highly viscous residue was boiled with 20 ml. of water for 1 hr. The clear solution was concentrated *in vacuo* until crystals formed (1.0 g.). The slightly moist material was recrystallized from an ether–petroleum ether mixture giving 0.35 g. of white crystals of *5-chlorobicyclo(2,2,1)hept-5-ene-2,3-dicarboxylic acid* (VI), m.p. 140.1–141.3°. It was interesting that the material was insoluble in ether when dry, but readily dissolved on the addition of a drop of water. The only other product present from subsequent crops seemed to be maleic acid.

Anal. Calcd. for $C_9H_9ClO_4$: C, 49.9; H, 4.2; Cl, 16.4. Found: C, 49.8; H. 4.5; Cl, 16.2.

The NMR spectrum of the compound was recorded in 1,4-dioxane and deuterated acetone. There were four kinds of hydrogens present with resonance at −6(COOH), +12(=CH), +40 and +43(α and β to COOH), and +59 (bridge) parts per ten million from benzene. The relative ratios were 2.3:0.9:3.9:1.9 (theor. 2:1:4:2), respectively. The spectrum of bicyclo(2,2,1)hept-5-ene-2,3-dicarboxylic acid (in 1,4-dioxane) showed essentially the same peaks but in the order of 2.3:1.7:4.3:1.7 (theor. 2:2:4:2). In the monochloro compound there was one less olefinic hydrogen.[6] Though no conclusive information was obtained concerning the *endo* or *exo* configuration of the adduct, the apparent absence of splitting of the bridge hydrogens in the NMR spectrum suggests the *endo* form.

Reaction with tetracyanoethylene. Immediately upon mixing tetracyanoethylene (1.3 g.) with the crude chlorocyclopentadiene (1.3 g.) in tetrahydrofuran (12 ml.), there was sudden development of heat. After standing overnight the mixture was concentrated *in vacuo* leaving 2.0 g. of dark solid. A portion of the material was decolorized with norite and recrystallized from ethyl acetate–petroleum ether. On standing in the refrigerator, a very small quantity of white crystals of *5-chloro-2,2,3,3-tetracyanobicyclo(2,2,1)hept-5-ene* (VII) was obtained, m.p. 202–204° (dec.), darkening at 183°.

Anal. Calcd. for $C_{11}H_5ClN_4$: C, 57.8; H, 2.2; N, 24.5. Found: C, 57.8; H, 2.4; N, 24.6.

Reaction with diethyl azodicarboxylate. When the crude chlorocyclopentadiene (1.3 g.) was mixed with the azodicarboxylic ester (1.7 g.) in 15 ml. of ether, there was no development of heat whatsoever. After 4 days at room temperature the solvent was removed *in vacuo* leaving a viscous orange residue. After standing for 3 weeks at −10° the material crystallized (1.7 g. of yellow-white solid). The crystals were washed with ether which removed the color (excess azodicarboxylic ester). The residue (0.13 g.) after two recrystallizations from ethyl acetate–petroleum ether gave white crystals of *5-chloro-2,3-dicarbethoxy-2,3-diazabicyclo(2,2,1)hept-5-ene* (VIII), m.p. 81–83°.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_4$: C, 48.1; H, 5.5; N, 10.2. Found: C, 47.9; H, 5.4; N, 10.1.

The infrared spectra of all three adducts were recorded. None had the band near 14.2μ which is present in norbornylene and in bicyclo(2,2,1)hept-5-ene-2,3-dicarboxylic acid and which is characteristic of the two *cis*-hydrogen atoms in the bridged six-membered ring.

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(6) The author is indebted to N. F. Chamberlain and associates for the NMR spectrum and its interpretation.

Alkaloids from *Apocynaceae*. II.[1] Ibogaline, a New Alkaloid from *Tabernanthe iboga* Baill

NORBERT NEUSS

Received July 2, 1959

As a result of our interest in the Rauwolfia alkaloids[2] we have undertaken in these laboratories a systematic study of other genera of the family *Apocynaceae*, in particular the members of the subfamily *Plumeroideae*. This subfamily contains several species which are known to be abundant in alkaloids.[3] (*e.g. Aspidosperma, Tabernaemontana, Tabernanthe, Voacanga, Rauwolfia, etc.*)

Among the genera which were examined was the African hardwood *Tabernanthe iboga* Baill. This plant has been the subject of intensive investigations by several groups.[4] More recently Taylor and co-workers have elucidated the structures of alkaloids occurring in this plant.[5]

The following alkaloids have been isolated from this plant: ibogaine,[6] tabernanthine,[6] ibogamine,[6] iboluteine,[7] iboquine,[7] desmethoxyiboluteine,[8] and hydroxyindolenine derivatives of ibogaine[8] and ibogamine,[8] voacangine,[8] gabonine,[8] kisanthine,[8] and kimvuline.[8]

Of these the hydroxyindolenine derivatives as well as iboluteine, desmethoxyiboluteine, and iboquine could also be formed by the easy autoxidation of the parent alkaloids during the process of isolation.[8]

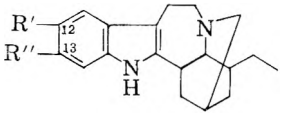
During the course of our investigation small amounts of a presumably new alkaloid,[9] ibogaline, were isolated.

The commercial bark was processed by a scheme described in detail in the Experimental section, fractionation being accomplished by taking advantage of the solubility of ibogaine and congeners in ether. Ether-soluble alkaloids were chromatographed on alumina. Elution with ether gave small amounts of ibogamine. Ether-chloroform mixtures and chloroform yielded small amounts of ibogaine followed immediately by an amorphous base which did not crystallize. The alkaloid was made into a crystalline hydrochloride salt, and the base was liberated and crystallized from aqueous methanol. This material, named ibogaline, gave analytical results compatible with a $C_{21}H_{28}N_2O_2$ formulation.

The ultraviolet spectrum of ibogaline is typical of a 2,3-dimethyl-5,6-dimethoxyindole,[10] λ_{max}^{EtOH} 227 mμ, (log a_M 4.40), 302 mμ, (log a_M 3.92).

Bands at 6.13, 6.28, 6.39, 6.74, and 11.96 μ in the infrared spectrum of ibogaline in chloroform solution occur at very nearly the same wave lengths and with about the same intensity in 2,3-dimethyl-5,6-dimethoxyindole[10] (but are absent in the spectrum of ibogamine).

The major alkaloids of *Tabernanthe iboga* are represented by structures[11] I, II, and III for ibogamine, ibogaine, and tabernanthine, respectively.



R′ = R″ = H; Ibogamine (I)
R′ = OCH_3; R″ = H; Ibogaine (II)
R′ = H; R″ = OCH_3; Tabernanthine (III)

On the basis of physical and analytical data as well as probable biogenesis of these alkaloids[12] it is reasonable to assume that ibogaline represents another congener of ibogamine with methoxyls placed at C_{12} and C_{13}.

The scarcity of the material did not allow any degradative studies to prove the tentative assignment of the structure of ibogaline as 12,13-dimethoxy ibogamine.

EXPERIMENTAL

All melting points are uncorrected. The known alkaloids were identified by m.p., infrared spectra, and x-ray diffraction patterns with those of authentic samples.

Isolation of ibogaline. The ground root of *Tabernanthe iboga* (Hugo Frey, Belgium, 7.6 kg.) were mixed with 200 g. of sodium bicarbonate and exhaustively extracted with benzene until alkaloid test with Mayer's reagent was negligible. The benzene extract was evaporated to dryness *in vacuo*, and the residue dissolved in 5% sulfuric acid. After washing with Skelly F, the bases were liberated with aqueous ammonia and filtered (194 g.). The solids were dissolved in ether, and the ether-soluble material evaporated *in vacuo* (45 g.). This was dissolved in ether, passed quickly through 350 g. of deactivated alumina (acid-washed alumina, Merck), and the filtrate evaporated to dryness (23.5 g.). Crystallization from ethanol gave 10 g. of crystalline ibogaine still containing traces of another alkaloid

(1) Alkaloids from *Apocynaceae*, I. M. Gorman, N. Neuss, and N. J. Cone, 139th National Meeting of the American Chemical Society, San Francisco, Calif., April 1958.

(2) Norbert Neuss and Harold E. Boaz, *J. Org. Chem.*, 22, 1001 (1957) and references cited therein.

(3) J. J. Willaman and B. G. Schubert, *Am. J. Pharm.*, 129, 246 (1957).

(4) M. M. Janot, R. Goutarel, and R. P. A. Sneedon, *Helv. Chim. Acta*, 34, 1205 (1951) and E. Schlittler, C. A. Burkhardt, and B. Gellert, *Helv. Chim. Acta*, 36, 1337 (1953).

(5) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, 80, 126 (1958) and references cited therein.

(6) T. A. Henry, *The Plant Alkaloids*, J. A. Churchill Ltd., London, 1949, p. 768.

(7) R. Goutarel and M. M. Janot, *Ann. pharm. franc.*, 11, 272 (1953).

(8) D. F. Dickel, C. L. Holden, R. C. Maxfield, L. E. Paszek, and W. I. Taylor, *J. Am. Chem. Soc.*, 80, 123 (1958).

(9) We should like to thank Dr. W. I. Taylor for the samples of some of the rare Iboga alkaloids for the comparison with our alkaloid.

(10) N. Neuss, H. E. Boaz, and J. W. Forbes, *J. Am. Chem. Soc.*, 76, 2463 (1954).

(11) W. I. Taylor, *J. Am. Chem. Soc.*, 79, 3298 (1957).

(12) W. I. Taylor, *Experientia*, 13, 454 (1957).

(paper chromatography). The mother liquor was evaporated to dryness to give 13.0 g. of a buff colored powder. This fraction was dissolved in 100 ml. of ether-benzene mixture (3:1) and chromatographed on 260 g. of deactivated acid-washed alumina. Elution with ether gave 350 mg. of crude ibogamine, which crystallized from methanol. When the solvent was changed to chloroform-ether mixtures, then to chloroform alone, 450 mg. of crude ibogaine were obtained. This fraction was followed by 520 mg. of a base which could not be induced to crystallize and gave a bright rose red color with Keller's reagent. The hydrochloride salt was prepared in the usual manner. After recrystallization from methanol-ether, 120 mg. of the hydrochloride were obtained, m.p. 264–266° (dec.).

Anal. Calcd. for $C_{21}H_{28}O_2N_2$.HCl: C, 66.91; H, 7.75; N, 7.43; Cl, 9.41; OCH_3(2), 16.47. Found: C, 66.58; H, 7.86; N, 7.39; Cl, 9.40; OCH_3, 16.75, 15.94.

The free base was liberated and crystallized from aqueous methanol, m.p. 141–143°. (The m.p. of the mixtures of ibogaline and ibogaine, and ibogaline and ibogamine were 112–119° and 113–123° respectively), $[\alpha]_D^{26} = -42.9°$ ($CHCl_3$, C = 1).

Anal. Calcd. for $C_{21}H_{28}O_2N_2$: C, 74.08; H, 8.29; N, 8.23; OCH_3 (2), 18.24. Found: C, 73.87, 74.30; H, 8.33, 8.48; N, 8.21, 8.23; OCH_3, 18.26. (The second analysis was obtained on material sublimed at 0.01 mm. pressure and 115°.)

The ultraviolet spectrum has the following bands: λ_{max}^{EtOH} 228 mμ (log a_M 4.43), 304 mμ (log a_M 4.01).

The infrared spectrum of ibogaline is characterized by the following prominent bands: $\lambda_{max}^{CHCl_3}$ 2.91 (indole NH), 6.13,[13] 6.28,[13] 6.39,[13] 6.74,[13] 7.65, 8.64, 8.80, 9.79, and 11.96.[13]

ADDED IN PROOF: Since the submission of this paper, U. Renner, D. A. Prins and W. G. Stoll [*Helv. Chim. Acta*, **42**, 1572 (1959)] have reported the isolation of an alkaloid, conopharyngine, from the bark of *Conopharyngia durissima* Stapf. A direct comparison of descarbomethoxy conopharyngine with our ibogaline has shown that, although the two compounds have different X-ray patterns, they are identical in all other respects (mixture m.p., optical rotation, and infrared spectrum in chloroform solution); therefore, conopharyngine is carbomethoxy ibogaline. We should like to thank Dr. Prins for the sample of descarbomethoxy conopharyngine.

Acknowledgment. The author wishes to thank Dr. H. E. Boaz for the infrared data, L. G. Howard for the ultraviolet spectra, W. L. Brown, G. M. Maciak, H. L. Hunter, and Miss G. Beckmann for microanalyses.

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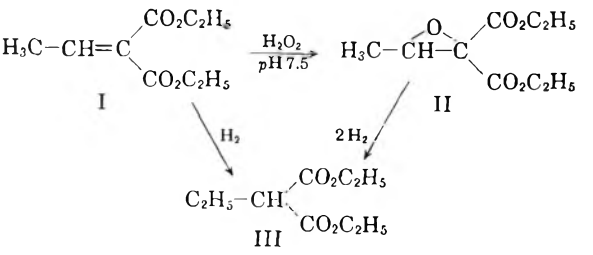
(13) These bands occur at the same wave lengths in the infrared spectrum in chloroform solution of 2,3-dimethyl-5,6-dimethoxyindole and are absent in the spectrum of ibogamine.

Epoxidation of Diethyl Ethylidenemalonate by Alkaline Hydrogen Peroxide

GEORGE B. PAYNE

Received July 6, 1959

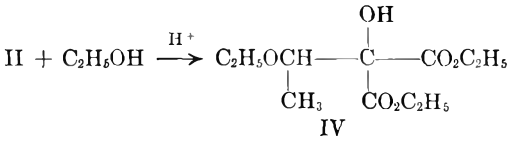
The technique recently employed for the epoxidation of acrolein to glycidaldehyde[1] has also been successfully applied to an α,β-unsaturated diester, diethyl ethylidenemalonate (I). A solution of this ester in methanol containing 1.1 mol. equiv. of



50% hydrogen peroxide was treated dropwise with 1*N* aqueous alkali to effect the reaction over a 2-hr. period at 35–40° and *p*H 7.5–8. The product, ethyl 2-carbethoxy-2,3-epoxybutyrate (II) was readily isolated in 82% yield.

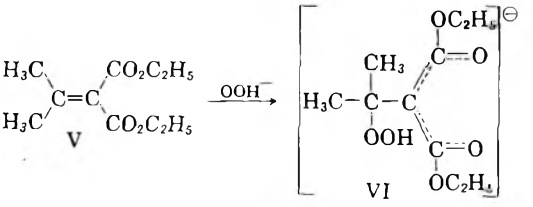
Hydrogenation of II proceeded with the absorption of 2 mol. of hydrogen to give diethyl ethylmalonate (III). The latter was also obtained from I to provide an authentic sample of ethylmalonic acid. When the hydrogenation of II was halted after 1 mol. uptake, only II and III were found.

Although II did not give the usual[2] titration for oxirane oxygen, the presence of that functional group was further indicated by reaction of II with hot acidic ethanol to give what was most likely the hydroxy ether IV, or the isomer having hydroxyl and ethoxyl groups reversed. The analysis of carefully fractionated IV was only fair; a low sapon-



ification equivalent, in particular, indicated the presence of an impurity.

The reaction of diethyl isopropylidenemalonate (V) with hydrogen peroxide proceeded to the extent of only 23% in 3 hr. at 45–50° and a higher *p*H (8–9) than used with I. Since alkali consumption was excessive during this period, the reaction was abandoned.



Failure of V to undergo epoxidation is in striking contrast to the facile reaction observed with I. This difference in reactivity is best rationalized on the basis of a steric inhibition of coplanarity

(1) G. B. Payne, *J. Am. Chem. Soc.*, **80**, 6461 (1958); **81**, 4901 (1959).

(2) J. L. Jungnickel, E. D. Peters, A. Polgar, and F. T. Weiss, *Organic Analysis*, Vol. I, Interscience Publishers, Inc., New York, N. Y., 1953, p. 135.

required for stabilization of the intermediate carbanion (VI).[3]

EXPERIMENTAL

Alkaline epoxidation of diethyl ethylidenemalonate. To a 1-l., five-neck, round-bottom flask equipped with stirrer, thermometer, *p*H electrodes and dropping funnel, were charged 400 ml. of methanol, 122 g. (0.656 mol.) of diethyl ethylidenemalonate[4] and 49 g. (0.72 mol.) of 50% hydrogen peroxide. To the dropping funnel was charged *N* sodium hydroxide.

The mixture was held at 35–40° by periodic cooling with an ice bath as alkali was added as needed to maintain a *meter* *p*H of 8.5–9.0; the true *p*H by indicator paper was about 7.5. At the end of 1 hr., 85% of the peroxide had been consumed (iodometric titration) along with 37 ml. of caustic. After an additional hour at meter *p*H 9–9.5, the reaction was essentially complete; 81 ml. of caustic had been consumed.

After dilution of the colorless reaction mixture with 1-l. of water, three 250-ml. portions of chloroform were used for extraction. The combined extract was washed, dried over anhydrous magnesium sulfate, and concentrated on the steam bath to a colorless residue. Distillation of the latter through a 0.7 × 50 cm. glass spiral packed column afforded 5 g. of pre-cut, b.p. 70–80° (1 mm.) and 99 ml., 109 g. (82% yield) of ethyl 2-carbethoxy-2,3-epoxybutyrate, b.p. 80–81° (1 mm.); n_D^{20} 1.4294.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.4; H, 7.0; O, 39.6; sapon. equiv., 101; mol. wt., 202. Found: C, 53.2; H, 6.9; O, 39.0; sapon. equiv., 100; mol. wt., 195 ± 10.

Hydrogenation of ethyl 2-carbethoxy-2,3-epoxybutyrate. To a 300-ml. capacity autoclave were charged 116 g. (0.57 mol.) of epoxy diester, 50 ml. of ethanol, and 2 teaspoons of Raney nickel catalyst. Hydrogenation was compete in 6 hr. at 100° and 300–900 lb. pressure; it was necessary to repressure three times. Exactly 2 mol. equiv. of hydrogen were consumed.

After cooling, venting, and filtration, the filtrate was distilled through the small spiral column to give 83 g. (77% yield) of diethyl ethylmalonate, b.p. 58–59° (2 mm.); n_D^{20} 1.4147 (lit.[5] b.p. 94–96° (13 mm.); n_D^{20} 1.4170).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.4; H, 8.6; sapon. equiv., 94.1. Found: C, 56.9; H, 8.5; sapon. equiv., 93.5.

Saponification of 17 g. of this ester afforded 10 g. (83% yield) of ethylmalonic acid, m.p. 109–111°. Recrystallization from benzene gave 6 g. of pure acid, m.p. 112–113°; mixed m.p. with an authentic sample[6] of ethylmalonic acid (m.p. 112–113°) was not depressed.

Anal. Calcd. for $C_5H_8O_4$: equiv. wt., 66. Found: equiv. wt., 66.

Ethanolysis of ethyl 2-carbethoxy-2,3-epoxybutyrate. A solution of 16 g. (0.08 mol.) of epoxy diester in 100 ml. of ethanol containing 2 ml. of concentrated sulfuric acid was allowed to reflux overnight. The cooled solution was treated with 10 ml. of water and 10 g. of calcium carbonate to neutralize the catalyst. After filtration and concentration, the resulting residue was taken up in warm ether and filtered to remove 4.5 g. of insoluble material. Distillation of the filtrate through a 0.7 × 50 cm. spiral packed column gave 14.9 g. of material, b.p. 85–87° (0.3 mm.), n_D^{20} 1.4323, having an analysis in substantial agreement for ethyl 2-carbethoxy-2-hydroxy-3-ethoxybutyrate or its isomer, ethyl 2-carbethoxy-2-ethoxy-3-hydroxybutyrate.

Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.2; H, 8.1; sapon. equiv., 124; hydroxyl value, 0.40 equiv./100 g. Found: C, 52.6; H, 8.0; sapon. equiv., 116; hydroxyl value, 0.42 equiv./100 g.

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(3) See H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Am. Chem. Soc.*, 81, 108 (1959) for a recent discussion of the stereochemistry of alkaline epoxidation.

(4) F. R. Goss, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, 3343 (1923).

(5) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, *J. Am. Chem. Soc.*, 63, 2056 (1941).

(6) From diethyl ethylidenemalonate by hydrogenation followed by saponification.

Phosphonic Acids and Esters. I. Radical Initiated Addition of Phosphorous Acid to Olefins

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The generation of carbon-phosphorus bonds by addition to olefins of radicals produced by homolysis of phosphorus-hydrogen bonds has been investigated by a number of workers during the past decade. The following phosphorus compounds have been utilized: phosphine and alkyl phosphines, hypophosphorus acid, dialkyl phosphonates, alkyl and aryl phosphinates.[1,2] In conjunction with studies in progress on phosphonic acids containing acid labile groupings, it became important to investigate methods which would lead to the direct synthesis of free phosphonic acids, avoiding the hydrolytic step necessary in conventional synthetic methods. Toward this end, the reaction of phosphorous acid (I) with olefins was investigated. In analogy with previously investigated systems, it was expected that homolysis of the phosphorus-hydrogen bond in I would lead to a chain reaction with the over-all result:

$$RCH{=}CH_2 + HP(O)(OH)_2 \longrightarrow RCH_2CH_2P(O)(OH)_2$$

This expectation is borne out by the experimental results; however, the reaction does not constitute a practical approach to alkylphosphonic acids because of the meager yields obtained.

The reactions of three representative olefins (1-octene, cyclohexene, and indene) with I were investigated; in the absence of peroxides, no reaction occurred at reflux temperature in either aqueous dioxane or acetic acid. When the reactions were conducted in the presence of either dibenzoyl peroxide or di-*t*-butyl peroxide at 90° or ultraviolet irradiation at room temperature, the expected products were obtained. Reactant ratios, reaction conditions, and yields of the purified products are presented in Table I.

(1) P. C. Crofts, *Quarterly Revs.*, 12, 363 (1958).

(2) L. A. Hamilton, paper presented at the 134th meeting of the American Chemical Society, Chicago, Ill., September 11, 1958; Abstracts, p. 69P.

TABLE I

REACTION OF PHOSPHOROUS ACID WITH OLEFINS

Olefin[a]	Initiator[b]	Temp., °C.	Time, Hr.	Product Phosphonic Acid	Yield,[c] %
1-Octene					
(0.33)	DBP	90	6	*n*-Octyl	23
(1.0)	DBP	90	6		18
(3.0)	DBP	90	6		8
(0.33)	DTBP	90	6		28
(0.33)	UV	25	18		18
Cyclohexene					
(0.33)	DBP	90	6	Cyclohexyl	26
(1.0)	DBP	90	6		20
(0.5)[d]	DBP	90	6		25
(0.5)[e]	DBP	90	6		14
(0.33)	DTBP	90	7		24
(0.33)	UV	25	18		20
Indene					
(0.30)	DBP	90	5	2-Indanyl	23
(0.30)	DTBP	90	4		20
(0.30)	UV	25	18		18

[a] Mol. olefin/mol. phosphorous acid in parentheses. [b] DBP = dibenzoyl peroxide, DTBP = di-*t*-butyl peroxide (5 mol. % based on phosphorous acid); UV = ultraviolet irradiation (Hanova ultraviolet lamp). [c] Based on minor component of reaction mixture. [d] 0.5 mol. cyclohexane/mol. phosphorous acid added. [e] 0.5 mol. cumene/mol. phosphorous acid added.

An excess of phosphorous acid was generally employed in order to minimize telomerization and obtain a maximum yield of the 1:1 adduct. The following phosphonic acids were obtained in yields of 18–28%: *n*-octylphosphonic acid, cyclohexylphosphonic acid and 2-indanylphosphonic acid. In no case was an appreciable amount of olefin recovered; the major reaction product in each experiment was an intractable oil of high molecular weight. In reactions with 1-octene, basic extraction of the oil and ion exchange chromatography of the extract led to the isolation of a fraction which analysis indicated to be the 2:1 adduct, 2-hexyldecylphosphonic acid.[3] Fractionation of the oil from the indene reaction led to the isolation of 3-isochromanone and 2 - (1 - indanyl) - indene. The former substance has been demonstrated to be a degradation product of the polymeric peroxide formed on autooxidation of indene[4,5] and the latter has been shown to arise from acid catalyzed reactions of indene.[6] When the addition to indene was performed in the absence of oxygen, no 3-isochromanone could be detected.

The results of this study parallel those of other investigators in the field.[7,8] The diminished yields effected by increases in olefin concentration indicate an inhibition by the olefin itself as observed in the addition of dialkyl phosphonates to olefins.[7] Abstraction of an allylic hydrogen from the olefin would give a relatively unreactive allyl radical which effectively interrupts the chain reaction. This inhibition by allylic abstraction was substantiated by the experiments with cyclohexene indicated in Table I: Dilution with cyclohexane led to increased phosphonic acid yield, while the addition of cumene produced a marked lowering of yield. The tendency toward formation of telomers and polymers derived from the monomer olefin indicates the kinetic chain length for the reaction to be quite low. By comparison of 1:1 adduct yields with both phosphine and dialkyl phosphonate additions, it is to be concluded that the transfer constant for phosphorous acid is quite low and dimerization, telomerization, and allylic abstraction become dominant processes.

EXPERIMENTAL

The experimental procedure was comparatively simple. The reactants were dissolved in either 50% aqueous dioxane or 50% aqueous acetic acid; because of better solubility characteristics, aqueous dioxane was preferred. Peroxide was added and the solution heated at the desired temperature; irradiation experiments were conducted at room temperature in quartz flasks employing a Hanovia quartz ultraviolet lamp (140 watts) as radiation source. Upon completion of reaction, all volatiles were stripped off at 50°/1 mm.; the residual dark oil was treated as below to yield the products. Normally 0.12 mol. of phosphorous acid was employed; the ratio of olefin to acid is given in Table I.

1-Octene reactions. The dark oil from a typical run was repeatedly extracted with ligroin. Vacuum evaporation of the extracts gave a semicrystalline mass which was recrystallized from *n*-hexane to yield *n*-octylphosphonic acid, m.p. 99–100° (reported[9] m.p. 99.5–100.5°). A mixture melting point of this material with an authentic sample was not depressed.

The ligroin-insoluble material was extracted with 10% aqueous potassium hydroxide; the basic extract was washed with ether and chromatographed on a 30-cm. column of Amberlite IRA-400 (chloride form). Fractions (10 ml.) were eluted with 0.1*M* hydrochloric acid. Unreacted phosphorous acid was eluted in fractions 3–11; identity was established by reduction of potassium iodate to iodine. Fractions 17–25 were collected and evaporated to dryness to yield a colorless crystalline material. Recrystallization from ligroin gave *2-hexyldecylphosphonic acid* (10–14%), m.p. 100.5–101.5°. A mixture melting point of this material with an authentic sample[3] was not depressed.

Anal. Calcd. for $C_{16}H_{35}O_3P$: C, 62.71; H, 11.51; P, 10.11; mol. wt., 306; neut. equiv., 153.2. Found: C, 62.48; H, 11.40; P, 9.80; mol. wt. (Rast), 321; neut. equiv., 152.7.

Cyclohexene reactions. The dark oil from a typical run was extracted with 0.1*N* sodium hydroxide. The basic extract was acidified with sulfuric acid and thoroughly extracted with ether. Evaporation of the ethereal solution gave a crystalline mass which was recrystallized from water to yield *cyclohexylphosphonic acid,* m.p. 166–167° (reported m.p.

(3) 2-Hexyldecylphosphonic acid has been synthesized independently and has been shown to be identical to the material isolated in this study. Experimental results will be reported elsewhere.

(4) H. Hock, S. Lang, and G. Knauel, *Chem. Ber.*, **83**, 227 (1950).

(5) G. A. Russell, *J. Am. Chem. Soc.*, **78**, 1035 (1956).

(6) H. Stobbe and E. Farber, *Ber.*, **57**, 1838 (1924).

(7) A. R. Stiles, W. E. Vaughan, and F. F. Rust, *J. Am. Chem. Soc.*, **80**, 714 (1958).

(8) A. R. Stiles, F. F. Rust, and W. E. Vaughan, *J. Am. Chem. Soc.*, **74**, 3282 (1952).

(9) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **67**, 1180 (1945).

166–167°,[10] 167–168°[11]). A mixture melting point of this material with an authentic sample was not depressed.

Indene reactions. The dark oil from a typical run was extracted with hot glacial acetic acid; upon cooling a colorless crystalline material separated from the acetic acid solution. The solid was washed with a mixture of acetic acid and methanol and recrystallized from glacial acetic acid to yield *2-indanylphosphonic acid*, m.p. 195–196° (reported[12] m.p. 196°). The infrared spectrum (Nujol mull) of this material was identical to that of an authentic sample of 2-indanylphosphonic acid.

The dark material remaining after acetic acid extraction was further extracted with ether. Evaporation of the ethereal solution yielded a solid which was recrystallized from ether to yield *2-(1-indanyl)-indene* (14–31%), m.p. 56–57° (reported[5] m.p. 57–58°). The identity of this material was confirmed by comparison of infrared spectra and lack of mixture melting point depression with an authentic sample of 2-(1-indanyl)-indene.

The ether insoluble material remaining after the isolation of 2-(1-indanyl)-indene was extracted with 20% aqueous potassium hydroxide. The basic extract was acidified with sulfuric acid and filtered (60°); upon cooling, a crystalline material precipitated. Recrystallization of this material from a mixture of benzene and petroleum ether gave *3-isochromanone* (8–21%), m.p. 81–83° (reported m.p. 81–83°,[4] 83°[3]). The identity of this product was confirmed by infrared and mixture melting point methods. No 3-isochromanone was detected when an indene/phosphorous acid reaction was conducted in a nitrogen atmosphere.

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(10) J. O. Clayton and W. L. Jensen, *J. Am. Chem. Soc.*, 70, 3880 (1948).
(11) R. Graf, *Chem. Ber.*, 85, 9 (1952).
(12) E. Bergmann and A. Bondi, *Ber.*, 63, 1158 (1930).

4-Fluoro- and 3,4-Difluorobenzoic Acids: An Isomorphic Pair

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We recently had occasion to prepare 3,4-difluorotoluene (I). As a proof of structure, the material was oxidized to the known 3,4-difluorobenzoic acid (II). We should like to record our observations with this acid and 4-fluorobenzoic (III).

The product obtained on oxidation of I, when crystallized from toluene, melted at 184–185°.[1] The melting point of III is 184–186°. The melting point of a mixture of the oxidation product with an authentic sample of III was 183–184°. The neutral equivalent of the oxidation product was determined to be 158 (theory for II, 158). The neutral equivalent of the authentic sample of III was determined to be 142.8 (theory, 140). A fluorine analysis of the oxidation product gave a value consistent with its formulation as 3,4-difluorobenzoic acid. These data suggested an isomorphic relationship between II and III.

J. W. Turley of Dow's Spectroscopy Laboratory obtained single-crystal x-ray diffraction photographs of the two acids and indicated them to be isomorphic crystals with the following unit cell constants:

4-Fluorobenzoic	3,4-Difluorobenzoic
a = 26.64 Å	a = 26.96 Å
b = 6.421 Å	b = 6.529 Å
c = 3.835 Å	c = 3.795 Å
B = 109.9°	B = 101.5°
Space group Pz/N	Space group Pz/N

EXPERIMENTAL

2-Fluoro-5-methylaniline. 3-Bromo-4-fluorotoluene (75.6 g.), ammonium hydroxide (220 g., 27.5% NH_3) and cuprous oxide (6.5 g.) were charged to a stainless steel bomb. The bomb was agitated by rocking and heated at 175–180° for a period of 5 hr. The cooled reaction mixture was filtered through a supercel filter pad to remove catalyst and sludge. The sludge was washed with ether and the filtrate extracted with ether. The combined ether layers were extracted with dilute hydrochloric acid until no more color went into the aqueous phase. Unreacted 3-bromo-4-fluorotoluene was recovered from the ether. The aqueous phase was made alkaline with 20% sodium hydroxide. The dark oil which separated was taken up in ether and the aqueous phase was extracted with ether several times. The combined ether extracts was dried over anhydrous magnesium sulfate overnight. The solvent was removed by distillation and the residual liquid was distilled under reduced pressure. The fraction boiling 80–86°/11 was collected. This amounted to 30.9 g. or 61.8% of the theoretical. The literature reports a b.p. of 88–90/17 mm.[2]

2-Fluoro-5-methylbenzenediazonium fluoborate. 2-Fluoro-5-methylaniline (37.1 g.) was dissolved in a mixture of 100 ml. of fluoboric acid (48–50%) and 100 g. of ice. With stirring and while maintaining the temperature below 10°, a solution of 21.0 g. of sodium nitrite in 35 ml. of water was added slowly. A precipitate formed as the reaction proceeded. The mixture was stirred at 0° for 0.5 hr. after the nitrite solution had been added. The salt was collected by filtration, washed with 50 ml. of 5% fluoboric acid, 50 ml. of ice-cold absolute methanol and then with several portions of anhydrous ether. The product was air dried for several hours and finally kept in a vacuum desiccator over calcium chloride overnight. There was obtained 60.0 g. of pale tan solid, decomposing at 140–145° (vigorous evolution of gas). Yield, 90.2%.

3,4-Difluorotoluene. 2-Fluoro-5-methylbenzenediazonium fluoborate (60.0 g.) was placed in a 500 ml. three necked flask, fitted with a thermocouple, stirrer, and air condenser. The air condenser was connected downward to a cold water condenser by means of an adapter carrying a thermometer. 1,2,4-Trichlorobenzene (250 ml.) was added to the reaction flask and, with vigorous stirring, heating was begun. A white gas began to evolve at 100°. As this initial reaction subsided, the temperature was again raised slowly and evolution of gas was again apparent at 140°. The temperature was slowly raised as the reaction proceeded until the temperature at the top of the air condenser had reached 195°. The reaction was stopped by cooling. The material which had collected in the receiver connected to the cold water condenser was dried over calcium chloride overnight and distilled through a short Vigreaux column. The fraction

(1) J. T. Minor and C. A. Vanderwerf, *J. Org. Chem.*, 17, 1429 (1952) report a m.p. of 119.2–120.1 for the hydrate of this compound (0.5 H_2O).

(2) Ng. Ph. Buu-Hoï and Ng. D. Xuong, *J. Chem. Soc.*, 386 (1953).

boiling at 100–120° was redistilled through an 8-inch vacuum jacketed glass helices packed column and the fractions boiling at 110–112° (I), and 112–113° (II) were collected. Fraction I had n_D^{24} 1.4475, while Fraction II gave n_D^{24} 1.4473. Yield, 18.7 g. (41.9%).

Anal. Calcd. for $C_7H_6F_2$: C, 65.63; H, 4.72; F, 29.66. Found: C, 65.89; H, 4.22; F, 30.21.

3,4-Difluorobenzoic acid. 3,4-Difluorotoluene (0.9 g.) was oxidized to the corresponding acid according to procedure 32B in "Identification of Organic Compounds," 2nd edition, Shriner and Fuson, John Wiley & Sons, p. 164. The product, recrystallized from toluene, melted at 184–185° and had a neutral equivalent of 158 (theory, 158).

Anal. Calcd. for $C_7H_4F_2O_2$: F, 24.03. Found: F, 23.72.

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Addition of Silicon Hydrides to Olefinic Double Bonds. IV. The Addition to Styrene and α-Methylstyrene

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Styrene with methyldichlorosilane in the presence of platinized carbon has recently[1] been described as giving only (2-phenylethyl)methyldichlorosilane. Careful experiments repeated several times now indicate two isomeric products form with either platinized carbon or chloroplatinic acid. The two products are the 1- and the 2-phenylethylmethyldichlorosilane in a ratio of approximately 33 to 53. The mixture has physical properties very nearly coinciding with those previously reported[1] as those of 2-phenylethylmethyldichlorosilane.

Careful distillation separated the isomers which were methylated to form obviously different derivatives (see Table I).

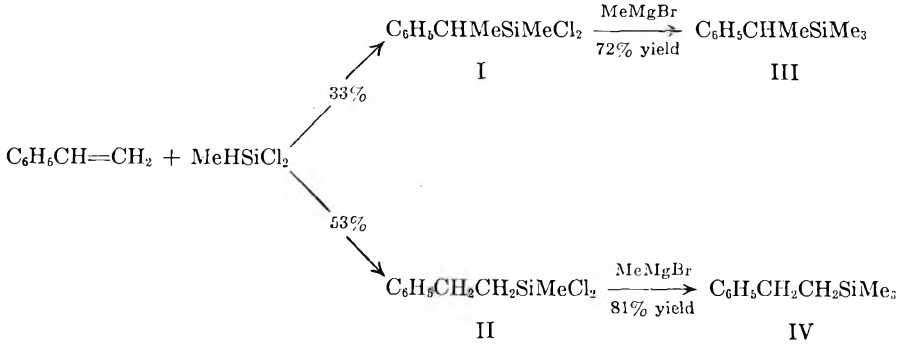
The NMR proton spectra of I, II, III, and IV were consistent with the structures assigned.[3]

From these data we conclude that styrene forms two adducts. However, experiments indicated that only one product formed with α-methylstyrene under the same conditions. Only one product (V) was detected by distillation. This product was methylated to form apparently pure VI (2-phenylpropyl)trimethylsilane as judged by distillation, gas liquid phase chromatography and by a NMR proton spectrum. The spectrum clearly showed the presence of phenyl, $SiCH_3$, $—CH_2—$, and $—CHCH_3—$ groups.

Methylcyclosiloxanes $(MeHSiO)_n$ react very well with α-methylstyrene in the presence of chloroplatinic acid to form nearly quantitative yields of (2 - phenylpropyl)methylcyclosiloxanes. The structure of these was established by the NMR proton spectra and also in one case by converting the adduct to VI by way of (2-phenylpropyl)methyldifluorosilane and methylmagnesium bromide.

Hydrolysis of (2-phenylpropyl)methyldichlorosilane gave a polysiloxane mixture from which was isolated a cyclic trimer (VII). The trimer (VII) was also isolated as the most volatile product formed in the alkaline depolymerization of the adduct obtained with 1,3,5,7,9-pentamethylcyclopentasiloxane.

sym-Tetramethyldisiloxane gave an 81% yield of 1,3-bis(2-phenylpropyl)tetramethyldisiloxane (IX) and trichlorosilane gave 67% (2-phenylpropyl)trichlorosilane (X). These products were assigned their structures largely on the basis of their NMR proton spectra. All of the adducts had spectra clearly indicative of (2-phenylpropyl) structures free of any detectable impurities.



The structure of IV was confirmed by the agreement of its physical properties with those of an authentic sample prepared from trimethylchlorosilane and 2-phenylethylmagnesium bromide.[1,2]

EXPERIMENTAL

Styrene and methyldichlorosilane. Styrene (921 g., 8.85 mol.), *t*-butylcatechol (0.1 g.) and 8×10^{-5} mol. of chloroplatinic acid (added as a 0.06*M* solution in dioxane ethanol) was heated to 90° in a 3-l., three necked flask equipped with an addition funnel, reflux condenser, and thermometer Methyldichlorosilane (1120 g., 9.73 mol.) was added during 2 hr. so that the heat of reaction maintained the mixture between 90 and 130°. Distillation then gave: (I), 642 g.,

(1) Part II of this series; J. L. Speier, J. A. Webster, and G. H. Barnes, *J. Am. Chem. Soc.*, 79, 974 (1957).

(2) H. Gilman and F. J. Marshal, *J. Am. Chem. Soc.*, **71**, 2066 (1949).

(3) All NMR spectra and their interpretation were obtained by P. C. Lauterbur, Mellon Institute, Pittsburgh, Pa.

TABLE I

No.	Structure	B.P.	Mm. Hg	n_D^{25}	D_4^{25}	R_D Found	R_D Calcd.[a]	% Si Found	% Si Calcd.	Neut. Equiv. Found	Neut. Equiv. Calcd.
I	$C_6H_5MeCHSiMeCl_2$	121–122	25	1.5197	1.1321	0.2684	0.2650	12.6	12.8	109.8	109.6
II	$C_6H_5CH_2CH_2SiMeCl_2$	137–138	30	1.5107	1.1216	0.2669	0.2650	12.7	12.8	109.9	109.6
III	$C_6H_5MeCHSiMe_3$	111.3	38	1.4959	0.8738	0.3345	0.3307	15.4	15.7		
IV	$C_6H_5CH_2CH_2SiMe_3$[b]	117	40	1.4840	0.8582	0.3329	0.3307	15.6	15.7		
V	$C_6H_5MeCHCH_2SiMeCl_2$	148–149	42	1.5082	1.100	0.2708	0.2690	12.0	11.8	117.2	116.6
VI	$C_6H_5MeCHCH_2SiMe_3$	217	750	1.4841	0.8619	0.3320	0.3308	14.3	14.6		
VII	$(C_6H_5MeCHCH_2SiMeO)_3$	228[c]	1	1.5220	1.041	0.2926	0.2924	16.0	15.8	Viscosity 88–91 cs. at 25°	
VIII	$(C_6H_5MeCHCH_2SiMeO)_4$	270[c]	1	1.5262	1.051	0.2923	0.2924	16.0	15.8	Viscosity 198–202 cs. at 25°	
IX	$(C_6H_5MeCHCH_2SiMe_2)_2O$	162	1	1.5043	0.9487	0.3123	0.3124	15.2	15.1		
X	$C_6H_5MeCHCH_2SiCl_3$	141	30	1.5140	1.218	0.2471	0.2457	11.3	11.1	83.6	83.6

[a] Calculated according to the bond values of A. I. Vogel, W. T. Cresswell, G. H. Jeffrey, and J. Leicester, *J. Chem. Soc.*, 514 (1952); A. I. Vogel, W. T. Cresswell, and J. Leicester, *J. Phys. Chem.*, **58**, 174 (1954). [b] Ref. 1 cites for an authentic sample, b.p. 101° at 20 mm., n_D^{25} 1.4842, D_4^{25} 0.8591. [c] Ebulliometric boiling points. The other boiling points are condensation temperatures taken during distillation.

33% yield with the properties given in Table I, and (II), 1019 g., 53% yield. A viscous polymer (128 g.) remained as residue.

2-Phenylpropylmethyldichlorosilane (V). α-Methylstyrene (354 g., 3.0 mol.) and methyldichlorosilane (380 g., 3.3 mol.) with 2×10^{-5} mol. of chloroplatinic acid were treated as above, and kept overnight at about 140°. Careful fractionation gave 38 g. boiling between the excess methyldichlorosilane and a constant boiling plateau described as V in Table I, 631 g., 90% yield.

2-Phenylpropyltrimethylsilane (VI). Excess methylmagnesium bromide in ether with V formed VI in 85% yield.

(2-Phenylpropyl)methylpolysiloxanes. Hydrolysis of V (700 g., 3.0 mol.) in 2500 ml. of toluene with 1 l. of water was followed by a thorough washing with dilute sodium carbonate and then with water. Distillation at 1 mm. gave 190 g., 36% of the cyclotrisiloxane (VII) n_D^{25} 1.5220–1.5222, viscosity, 88–91 cs. at 25°.

α-Methylstyrene (1182 g., 10.0 mol.) with 2×10^{-4} mol. of chloroplatinic acid was heated to 110° and 1,3,5,7,9-pentamethylcyclopentasiloxane (601 g., 10.0 equivalents) was added slowly. The mixture was kept at 110° overnight and then distilled rapidly from 1 g. of potassium hydroxide at 1 mm. The distillate (1704 g., 96% yield) was a mixture of cyclosiloxanes, n_D^{25} 1.5242, viscosity, 216 cs. at 25°.

On redistillation of a portion of this material the trisiloxane (VII) was again isolated, n_D^{25} 1.5220, D_4^{25} 1.041, viscosity 88 cs. at 25° (45% yield). After recovering an intermediate portion, presumably a mixture of cyclic trimer and tetramer, there was recovered the cyclotetrasiloxane (VIII), n_D^{25} 1.5262, D_4^{25} 1.051, viscosity 200 cs. at 25° (18% yield). The condensation temperatures recorded during the low pressure distillations were variable and unreliable. The progress of the distillation was followed chiefly by the index of refraction and viscosity of each fraction.

A second portion of this adduct (50 g., 0.28 mol.) was dissolved in 200 ml. of cold concentrated sulfuric acid and saturated with hydrogen fluoride. The upper layer which was assumed to be (2-phenylpropyl)methyldifluorosilane was added to excess methylmagnesium bromide in ether. In the usual way, 2-phenylpropyltrimethylsilane (VI) was isolated in 34% yield. By vapor-liquid phase chromatography this product was judged to be not less than 99% the same as VI, made by methylation of V.

α-Methylstyrene (1040 g., 8.8 mol.), chloroplatinic acid (9×10^{-5} mol.) and 1,3,5,7-tetramethylcyclotetrasiloxane (481 g., 8 equiv.) were heated at 110° overnight. The excess α-methylstyrene was removed at 1 mm. up to a temperature of 315°. The residue then had a viscosity of 211 cs. at 25°. Distillation without the potassium hydroxide gave 1355 g., 95% of a distillate boiling at a flask temperature of 315–320° at 1 mm., n_D^{25} 1.5258–1.5267, viscosity 184–203 cs. at 25°. Most of the distillate had n_D^{25} 1.5263–1.5266, viscosity 193–203 cs. at 25°.

1,3-Bis(2-phenylpropyl)tetramethyldisiloxane (IX). α-Methylstyrene (591 g., 5.0 mol.) and chloroplatinic acid (1 ml. of 0.06*M* solution in dioxane ethanol) were heated to 110° and *sym*-tetramethyldisiloxane (336 g., 2.5 mol.) was added in 50 ml. portions. The reaction proceeded slowly. The mixture was maintained at 110° overnight and distilled through a 1-inch by 3-inch vacuum-jacketed column containing no packing to yield a low boiling fraction (37 g.), b.p. 80° at 1 mm., which gave a positive test for Si-H. This material presumably is 1-(2-phenylpropyl)-1,1,3,3-tetramethyldisiloxane. On continued distillation there was recovered 1,3-bis(2-phenylpropyl)tetramethyldisiloxane (747 g., 81% yield) having the properties given in Table I.

2-Phenylpropyltrichlorosilane (X). α-Methylstyrene (354 g., 3.0 mol.) containing 6×10^{-5} mol. H_2PtCl_6 was kept at 100–110° in a flask equipped with a reflux condenser and a dropping funnel as trichlorosilane (330 ml., 3.3 mol.) was added during 6 hr. The mixture was then maintained at 110° overnight.

Fractionation of the mixture gave 2-phenylpropyltrichlorosilane (505 g., 67% yield) of X.

The residue from the above fractionation (137 g.) contained little hydrolyzable chloride, indicating that it was principally a polymer of α-methylstyrene.

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Action of Trifluoroacetic Acid on Peptide Bonds

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In view of the utility of anhydrous trifluoroacetic acid as a protein solvent, a report on its reactivity toward peptide bonds may be of interest. Simple amides such as *N*-acetyl-β-phenylethylamine and acetanilide can be recovered unchanged

after prolonged heating in this solvent, but *N*-acyl amino acids and polypeptides undergo extensive trifluoroacetolysis. For example, during 20 hr. at reflux (71°) *N*-acetyl-L-leucine in 0.03 *M* solution was converted to a mixture of partially racemized leucine, *N*-trifluoroacetyl-L-leucine and acetyl-DL-leucine. After similar treatment of *N*-acetyl-DL-phenylalanine, phenylalanine and *N*-trifluoroacetyl phenylalanine were isolated; hippuric acid was converted to benzoic acid, *N*-trifluoroacetyl glycine and glycine. From L-leucine itself after 24 hours' heating with trifluoroacetic acid only traces of trifluoroacetyl L-leucine were isolated.[1]

Several amino acid polymers were treated with refluxing trifluoroacetic acid. Each was converted to a mixture of *N*-trifluoroacetyl amino acid plus trifluoroacetylated peptides, but complete degradation was not achieved.

Although the conditions under which trifluoroacetolysis occurs are relatively severe, these observations indicate a necessity for caution in using trifluoroacetic acid as a solvent for peptides and proteins, even when specifically acid labile residues such as serine[2] and tryptophane[3] are lacking.

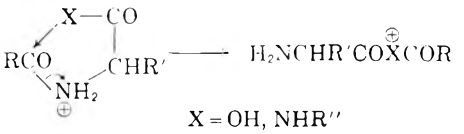
The trifluoroacetolysis reaction, which is probably similar to the hydrogen chloride catalyzed acetolysis of insulin reported by Vadja,[4] is apparently an equilibrium; experiments with hippuric acid indicate that the conversion to benzoic acid increases with increasing dilution. Catalytic quantities (0.1 mol. equiv.) of triethylamine, sulfuric acid, or trifluoroacetic anhydride did not affect the conversion after 24 hours' heating. The following reactions are probably involved.[5]

$$RCONHR' + CF_3COOH \rightleftharpoons RC\overset{\oplus}{O}NH_2R' + CF_3COO^{\ominus} \quad (1)$$

$$RC\overset{\oplus}{O}NH_2R' + CF_3COO^{\ominus} \rightleftharpoons RCOOCOCF_3 + (R'NH_2) \rightleftharpoons RCOO^{\ominus} + CF_3C\overset{\oplus}{O}NH_2R' \quad (2)$$

$$RCOOCOCF_3 + CF_3COOH \rightleftharpoons RCOOH + (CF_3CO)_2 \quad (3)$$

Racemized products are formed by the usual interaction of α-acylamino acids and the anhydrides present in the medium.[6] The reactivity of α-acylamino acids and peptides is not explained by reactions (1) and (2) but might be accounted for by participation of the carboxyl or carboxamide group as in Equation 4.[7]



(4)

Weygand and co-workers have reported the cleavage of peptides by trifluoroacetic anhydride in trifluoroacetic acid.[8] In the presence of the anhydride cleavage occurs more rapidly than under the conditions reported here. The direct *N*-acylation of amide groups suggested for reaction with the anhydride[8] seems less likely in pure trifluoroacetic acid, however.

EXPERIMENTAL

Reaction of hippuric acid with trifluoroacetic acid. Hippuric acid, m.p. 187–188°, (2.0 g.) was dissolved in commercially obtained anhydrous trifluoroacetic acid and the solution, protected from atmospheric moisture, was heated to reflux for 24 hr. Solvent was then removed by distillation at room temperature. The resulting oil was poured into 50 ml. of water and stored several hours at room temperature. A crystalline precipitate of benzoic acid, m.p. 122°, was collected and dried. The mother liquors were concentrated to 15 ml. and stored at 0–5° before a second crop of crystals, crude hippuric acid, m.p. 172–180° was collected. Extraction of these mother liquors with ether allowed isolation of crude trifluoroacetyl glycine, m.p. 95–106°, which could be recrystallized from benzene to m.p. 114°.[9]

When 40 ml. of trifluoroacetic acid solvent was used, the yield of benzoic acid was 50%, of trifluoroacetyl glycine 32%, and of recovered hippuric acid, 33%. When 250 ml. of solvent was used 92% of benzoic acid was isolated. Prolonged heating did not affect these yields.

Reaction of N-acetyl L-leucine with trifluoroacetic acid. N-Acetyl L-leucine, m.p. 196–198°[10] (1.0 g.) was treated as above with 200 ml. of trifluoroacetic acid. The oily reaction product was extracted three times with boiling benzene and the benzene extracts were concentrated to yield, after crystallization from ethyl acetate, 110 mg. of *N*-acetyl leucine, m.p. 154–165° (reported 157–158°),[11] $[\alpha]_D^{25}$ = 0.0°. The residue from the benzene extraction was taken up in ethyl acetate and filtered free of insoluble, ninhydrin positive material, 145 mg. (19%) which proved to be partially racemized L-leucine, m.p. 273–279° d., $[\alpha]_D^{25}$ = +8.5° (c = 2.02 in 6*N* hydrochloric acid, pure enantiomer +15.1°).[12] The material extracted into ethyl acetate was a mixture of acetyl and trifluoroacetyl leucine which exhibited carboxyl and trifluoroacetamido infrared absorption at 1730 cm.$^{-1}$, acetamido absorption at 1640 cm.$^{-1}$, and C—F absorption at 1160, 1185, and 1210 cm.$^{-1}$ Vacuum distillation afforded about 50 mg. of trifluoroacetyl-

(1) Similar treatment of L-leucine with acetic acid leads to acetyl-DL-leucine in 75% yield. E. A. Bell, *J. Chem. Soc.*, 2423 (1958).

(2) D. F. Elliot, *Biochem. J.*, **50**, 542 (1954).

(3) R. A. Uphaus, L. I. Grossweiner, J. J. Katz, and K. D. Kopple, *Science*, **129**, 641 (1959).

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(7) For a similar case see M. Bender, *J. Am. Chem. Soc.*, **80**, 5380 (1958).

(8) F. Weygand, R. Geiger, and U. Glöckler, *Chem. Ber.*, **89**, 1543 (1956).

(9) E. E. Schallenberg and M. Calvin, *J. Am. Chem. Soc.*, **77**, 2780 (1955).

(10) M. Bergmann and J. Tietzman, *J. Biol. Chem.*, **155**, 535 (1944), report m.p. 189–190°.

(11) E. Fischer, *Ber.*, **34**, 444 (1901); a partially racemized acetyl-L-leucine, m.p. 155–167° is reported by A. Karrer, K. Escher, and R. Widmer, *Helv. Chim. Acta*, **9**, 322 (1926).

(12) M. S. Dunn and G. Courtney, cited in "Handbook of Chemistry and Physics," 40th edition, Chemical Rubber Publishing Co., Cleveland, Ohio, 1958, p. 1753.

L-leucine, m.p. 68°[13] and about 200 mg. of crude acetyl leucine, characterized by its infrared spectrum.

Reaction of Poly-L-leucine with trifluoroacetic acid. Poly-L-leucine (2.0 g.) was dissolved in 250 ml. of trifluoroacetic acid and treated as above. The reaction product was digested with ether and the material extracted by ether was distilled at 70–100° and 0.1 mm. pressure. The distillation yielded 0.4 g. of trifluoroacetyl-L-leucine, $[\alpha]_D^{25} = -35.2°$ (c = 1.0 in water, reported −39.4°[13]) (11%) and a non-volatile residue (0.64 g.) with the infrared spectrum of polyleucine. The ether insoluble residue, washed with aqueous sodium bicarbonate and with water, weighed 0.90 g. and exhibited infrared absorption due to CF_3— groups at 1160, 1185 and 1210 cm.$^{-1}$, in addition to the bands of the polyleucine spectrum.

Other trifluoroacetolyses. From 2.0 g. (0.01 mol.) of *acetyl-DL-phenylalanine* was obtained, after 36 hr. at reflux in 60 ml. of trifluoroacetic acid, 0.95 g. of *N*-trifluoroacetyl phenylalanine, m.p. 130°[9] after recrystallization from water, plus an undetermined amount of phenylalanine.

Acetanilide and *acetyl-β-phenylethylamine* were both recovered quantitatively after 24 hr. at reflux in 5% solutions.

Polyglycine and a *copolymer of DL-alanine and L-glutamic acid* were also treated with excess trifluoroacetic acid and the reaction product extracted with organic solvents. From these extracts were isolated *N*-trifluoroacetyl glycine and *N*-trifluoroacetyl-DL-alanine, respectively.

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(13) F. Weygand and R. Geiger, *Chem. Ber.*, 89, 647 (1956).

β-Arylglutaconic Acids. II.[1] Imides of Certain β-Arylglutaconic and Glutaric Acids

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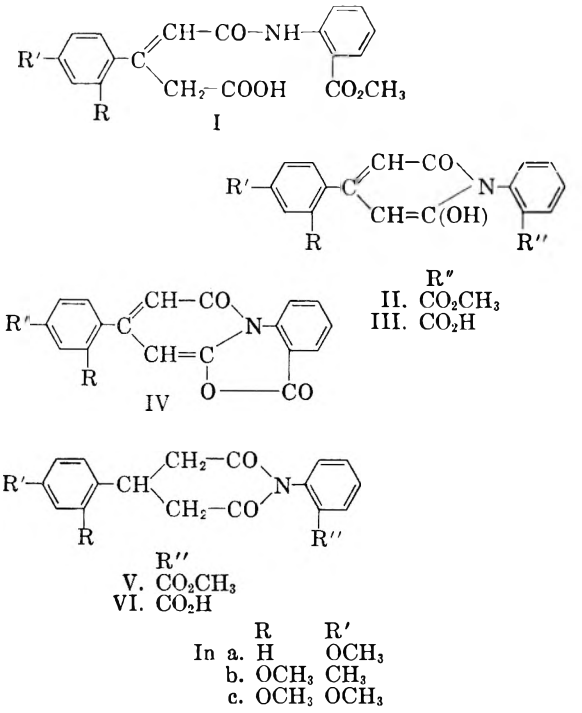
The anhydrides of β-arylglutaconic acids on treatment with equimolar quantities of methyl anthranilate in refluxing benzene solution give rise to the corresponding *cis*-semianilides (I).[1] In the present studies, the *cis*-semianilides were found to undergo dehydration when heated above 170–180° to give the corresponding imides (II) in 75–80% yield and a small quantity (5%) of a neutral substance which was later characterized as the *trans*-decarboxylation product.[3] The yield of the imides (II) was increased to 90–92% by heating at reflux temperature the β-arylglutaconic anhydrides with an excess of methyl anthranilate. The β-arylglutaconic anhydrides are in part enolic in nature, as indicated through production of a purple color with alcoholic ferric chloride solution and by the fact that they can be titrated as monobasic acids with standard alkali. The imides (II) should therefore exist partially in the enolic form. This fact was confirmed by a positive ferric chloride test and by titration with standard alkali. From the resulting alkaline solution the imides could be recovered by acidification in the cold.



Since we were interested in studying the chemical properties of these weakly acidic compounds, imides IIa, b, and c were synthesized from (a) β-(4-methoxyphenyl)glutaconic acid,[4] (b) β-(2-methoxy-4-methylphenyl)glutaconic acid,[5] and (c) β-(2,4-dimethoxyphenyl)glutaconic acid.[6]

When the carbomethoxy substituted hydroxyimides (IIa, b, and c, respectively) were boiled with strong sodium hydroxide solution (12.5*N*), they were hydrolyzed to the corresponding carboxyimides (IIIa, b, and c, respectively). Unlike the carbomethoxyimides (IIa, b, and c), these acids did not give any coloration with ferric chloride solution but did titrate as dibasic acids with standard alkali, indicating the presence of an enol group. This was further confirmed by treating the carboxyimides with acetic anhydride at reflux temperature. From the reaction mixture, neutral substances (40 to 50% yields) were isolated and after purification were characterized as the lactones (IVa, b, and c, respectively). When they were dissolved in dilute sodium hydroxide solution and the alkaline solution was neutralized, the starting carboxyimides (IIIa, b, and c, respectively) were recovered. This behavior confirms the

(1) Prior publication, *J. Org. Chem.*, 24, 520 (1959).

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(3) S. S. Karmarkar and V. M. Bhave, *J. Ind. Chem. Soc.*, **31**, 455 (1954).

(4) D. B. Limaye and V. M. Bhave, *J. Ind. Chem. Soc.*, **8**, 139 (1931).

(5) D. B. Limaye and G. R. Gogte, *J. Univ. Bombay*, **3**, 135 (1934).

(6) G. R. Gogte, *Proc. Indian Acad. Sci.*, **1A**, 48 (1934).

enolic nature of the carboxyimides, and therefore allows lactonic oxazine ring formation.

In further studies, the carboxyimides of β-(2-methoxy-4-methylphenyl)glutaric acid and β-(2,4-dimethoxyphenyl)glutaric acid (VIb and c) were prepared and treated with acetic anhydride. The carboxyimides were recovered unchanged indicating the absence of enolization in the case of glutaric acid imides.

EXPERIMENTAL

1-(2-Carbomethoxyphenyl)-4-(4-methoxyphenyl)-6-hydroxy-2-pyridone (IIa). A mixture of 2.2 g. (0.01 mol.) of β-(4-methoxyphenyl)glutaconic anhydride[4] and 5 ml. of methyl anthranilate was heated at reflux temperature in an oil bath for 10 min. After cooling, the red gummy solid was treated with concentrated hydrochloric acid. The solid was collected on a filter and after it had been washed with several portions of cold water, it was air dried. Two recrystallizations from 50% acetic acid gave 3.2 g. (92% yield) of IIa, m.p. 126–130°. An analytical sample was prepared by further recrystallization from ethanol, m.p. 131–132°. It was insoluble in dilute sodium bicarbonate but soluble in dilute sodium hydroxide. The pyridone was recovered from the alkaline solution by acidification with dilute hydrochloric acid.

Anal. Calcd. for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.63; H, 5.19; N, 4.10.

1-(2-Carboxyphenyl)-4-(4-methoxyphenyl)-6-hydroxy-2-pyridone (IIIa). The acid (IIIa) was obtained in 63% yield by hydrolysis of the ester (IIa) with ethanolic sodium hydroxide solution. Recrystallization from ethanol gave pure IIIa, m.p. 194–195° (dec.).

Anal. Calcd. for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; neut. equiv., 168.7. Found: C, 67.33; H, 4.75; neut. equiv., 171.0.

1-(2-Carboxyphenyl)-4-(4-methoxyphenyl)-6-hydroxy-2-pyridone lactone (IVa). A mixture of 6.7 g. (0.02 mol.) of IIIa and 20 ml. acetic anhydride was refluxed for 1 hr. The contents of the reaction flask was stirred into an excess of cold water (*ca.* 50 ml.) and the solid that separated was collected on a filter. It was washed with water, 5%-sodium bicarbonate solution, and again with water. The dry solid was recrystallized three times from alcohol to afford 2.6 g. (42% yield) of IVa as white needles, m.p. 85–86.5°.

Anal. Calcd. for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10. Found: C, 71.11; H, 4.45.

1-(2-Carbomethoxyphenyl)-4-(2-methoxy-4-methylphenyl)-6-hydroxy-2-pyridone (IIb). The procedure used in making this compound was the same described for IIa. From 5.8 g. (0.025 mol.) of β-(2-methoxy-4-methylphenyl)glutaconic anhydride,[5] 8.2 g. (90% yield) of IIb was obtained as dull white crystals, m.p. 175–176°.

Anal. Calcd. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.34; H, 5.12; N, 4.02.

1-(2-Carboxyphenyl)-4-(2-methoxy-4-methylphenyl)-6-hydroxy-2-pyridone (IIIb). This acid was prepared by alkaline hydrolysis of IIb. From 3.6 g. (0.01 mol.) of IIb, 1.9 g. (54% yield) of the acid (IIIb) was obtained, m.p. 214–216° (dec.).

Anal. Calcd. for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; neut. equiv., 175.6. Found: C, 68.18; H, 5.01; neut. equiv., 172.4.

1-(2-Carboxyphenyl)-4-(2-methoxy-4-methylphenyl)-6-hydroxy-2-pyridone lactone (IVb). Treatment of IIIb with acetic anhydride by the procedure outlined for IVa, gave IVb in 47% yield, m.p. 163–164.5°.

Anal. Calcd. for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54. Found: C, 72.19; H, 4.52.

1-(2-Carbomethoxyphenyl)-4-(2,4-dimethoxyphenyl)-6-hydroxy-2-pyridone (IIc). This ester was prepared from β-(2,4-dimethoxyphenyl)glutaconic anhydride[6] by the procedure used for IIa. The yield of IIc was 93%, m.p. 118–118.5°.

Anal. Calcd. for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02. Found: C, 65.96; H, 4.76.

1-(2-Carboxyphenyl)-4-(2,4-dimethoxyphenyl)-6-2-hydroxy-pyridone (IIIc). Alkaline hydrolysis of the ester (IIc) gave IIIc in 87% yield, m.p. 170–171° (dec.).

Anal. Calcd. for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; neut. equiv., 188.65. Found: C, 65.25; H, 4.50; neut. equiv., 185.20.

1-(2-Carboxyphenyl)-4-(2,4-dimethoxyphenyl)-6-hydroxy-2-pyridone lactone (IVc). This lactone was made from IIIc by treatment with acetic anhydride following the procedure used for IVa. From 3.7 g. (0.01 mol.) of the acid (IIIc), 1.7 g. (48% yield) of IVc was obtained, m.p. 152–153.5°.

Anal. Calcd. for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33. Found: C, 68.60; H, 4.19.

1-(2-Carbomethoxyphenyl)-4-(2-methoxy-4-methylphenyl)-piperidine-2,6-dione (Vb). A mixture of 2.5 g. (0.01 mol.) of β-(2-methoxy-4-methylphenyl)glutaric acid[7] and 7.5 ml. of methyl anthranilate was heated at reflux temperature for 15 min. The resulting product after processing as in the preparation of IIa, gave 3.2 g. (87% yield) of Vb, m.p. 120–121°.

Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76. Found: C, 68.44; H, 5.40.

It was found completely insoluble in dilute sodium bicarbonate and dilute sodium hydroxide solution and gave a negative test with ferric chloride.

1-(2-Carboxyphenyl)-4-(2-methoxy-4-methylphenyl)-piperidine-2,6-dione (VIb). This acid was prepared in 57% yield by the alkaline hydrolysis of Vb, m.p. 152–152.5°. It dissolved in dilute sodium bicarbonate solution with effervescence.

Anal. Calcd. for $C_{20}H_{19}NO_5$: neut. equiv., 353.61. Found: neut. equiv., 352.80.

1-(2-Carbomethoxyphenyl)-4-(2,4-dimethoxyphenyl)-piperidine-2,6-dione (Vc). This substance was prepared from β-(2,4-dimethoxyphenyl)glutaric acid[1] and methyl anthranilate by the procedure adopted for making IIa. The yield of Vc was 88%, m.p. 145–145.5°.

Anal. Calcd. for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52. Found: C, 65.52; H, 5.20.

1-(2-Carboxyphenyl)-4-(2,4-dimethoxyphenyl)-piperidine-2,6-dione (VIc). Alkaline hydrolysis of Vc gave VIc in 46% yield, m.p. 134–136°.

Anal. Calcd. for $C_{20}H_{19}NO_6$: neut. equiv., 369.4. Found: neut. equiv., 368.0.

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(7) D. B. Limaye and R. G. Chitre, *J. Univ. Bombay*, **4**, 101 (1935).

Some 2- and 4-Substituted Estrone 3-Methyl Ethers[1a,b]

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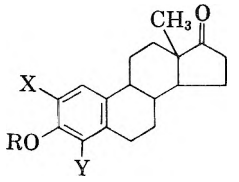
This communication describes the syntheses of several 2- and 4-substituted 1,3,5(10)-estratriene-17-one (estrone) 3-methyl ethers which were required for a biological study of the effect of substi-

tution at these sites on the estrogenic potency of estrone 3-methyl ether.

The positional assignment of substituents in 2-nitroestrone (IIIa) and 4-nitroestrone (IVa) have recently been established from two independent studies.[2–4] Unfortunately, a description of the preparative method failed to include the relative yields of the isomeric mononitroestrones and 2,4-dinitroestrone (Va) from I. Moreover, repetition of this procedure[3] indicated that the mechanical difficulties inherent in the chromatographic separation of IIIa, IVa, and Va would be increased in an extension of the method to the needs of the present study.



I. X = Y = R = H
II. X = Y = H; R = CH_3
IIIa. X = NO_2, Y = R = H
b. X = NO_2, Y = H, R = CH_3
c. X = NH_2, Y = H, R = CH_3
d. X = Cl, Y = H, R = CH_3
e. X = Br, Y = H, R = CH_3
f. X = I, Y = H, R = CH_3
IVa. X = R = H, Y = NO_2
b. X = H, Y = NO_2, R = CH_3
c. X = H, Y = NH_2, R = CH_3
d. X = H, Y = Cl, R = CH_3
e. X = H, Y = Br, R = CH_3
f. X = H, Y = I, R = CH_3
Va. X = Y = NO_2, R = H
b. X = Y = NO_2, R = CH_3
c. X = NH_2, Y = NO_2, R = CH_3

A reinvestigation of this reaction showed, in accord with previous observations[2] that the majority of IVa is deposited from the nitrating medium following the completion of the reaction. However, the use of one equivalent of concentrated nitric acid reduces the formation of the dinitro derivative (Va) to less than 1%.[5] Removal of Va from IIIa and the remaining IVa was accomplished by washing the mixture with aqueous sodium bicarbonate. Fractional crystallization of the residue effected a separation of IIIa from a small quantity of IVa. The mononitroestrones, IIIa and IVa, were, thus, obtained in 38% and 44% yield, respectively.

Methylation of IIIa and IVa, followed by catalytic reduction of the corresponding methyl ethers IIIb and IVb, gave 2-amino- (IIIc) and 4-aminoestrone 3-methyl ether (IVc).[6] The dinitroestrone (Va) was converted to a 2,4-dinitroestrone 3-methyl ether (Vb) in 65% yield with methyl iodide and potassium carbonate in acetone. Partial reduction of Vb with one equivalent of stannous chloride gave 2-amino-4-nitroestrone 3-methyl ether (Vc). The identity of the latter was established by successive diazotization and reduction which yielded a product identical with IVb.

The isomeric aminoestrone 3-methyl ethers (IIIc and IVc) were converted to the corresponding haloestrone 3-methyl ethers [Cl (IIId and IVd), Br (IIIe and IVe), and I (IIIf and IVf)] by conventional Sandmeyer reactions.

EXPERIMENTAL[7]

Nitration of estrone (I). To a solution of 17.28 g. of estrone (0.064 mol.) in 900 ml. of glacial acetic acid at 70–75° was added, all at once with stirring, a solution of 4 ml. of concentrated nitric acid, sp. g. 1.42, in 100 ml. of glacial acetic acid. The clear solution was allowed to cool to room temperature and then stand for 18 hr. during which time 4-nitroestrone (IVa) was deposited, wt. 8.13 g., m.p. 273–276° dec. (lit.[2] 270–280° dec.). The filtrate was evaporated to dryness *in vacuo*, the residue dissolved in 300 ml. of benzene and stirred for 5–6 hr. with 200 ml. of 2% sodium bicarbonate. The aqueous layer was then drawn off and acidified with concentrated hydrochloric acid. The 2,4-dinitroestrone (Va) was then collected, wt. 0.2 g. (yield 1%), m.p. 179–184°. Recrystallization from 95% ethanol gave light yellow plates, m.p. 183–184° (lit.[2] 185–187°).

The benzene fraction was dried over magnesium sulfate and concentrated to a volume of approximately 50 ml. which afforded an additional crop, 0.75 g. of IVa, m.p. 273–276° dec. (total yield 8.88 g., 44%). The filtrate was finally evaporated to dryness *in vacuo* and the residue crystallized from 95% ethanol to give 7.75 g. (38%) yield of 2-nitroestrone (IIIa), m.p. 174–176° (lit.[2] 183.5–184°). A pure sample of IIIa, m.p. 185–186° was obtained in the form of transparent irregular plates by slow crystallization from 95% ethanol. However, the material, m.p. 174–176°, is sufficiently pure to proceed with the methylation step.

4-Nitroestrone 3-methyl ether (IVb). To a solution of 1.58 g. of IVa (0.005 mol.) in 20 ml. of 10% sodium hydroxide, diluted with water to a volume of *ca.* 300 ml. was added portionwise with stirring, along with additional 10% sodium hydroxide, 30 ml. of dimethyl sulfate. The mixture was stirred for 2 hr. at room temperature and then heated to 75° for 0.5 hr. The mixture was cooled and the product collected, wt. 125 g. (75% yield), m.p. 258–259°, $[\alpha]_D^{26}$ +209° (lit.[6] 261°, $[\alpha]_D^{30}$ +212°).

(1) (a) This work was supported in part by an institutional grant to the Detroit Institute of Cancer Research from the American Cancer Society, Southeastern Michigan Division, and in part by research grants p-IR-17J from the American Cancer Society, Inc., and CY-2903 from the National Cancer Institute, Public Health Service. (b) Presented before the Division of Medicinal Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958.

(2) H. Werbin and C. Holloway, *J. Biol. Chem.*, **223**, 651 (1956).

(3) R. A. Pickering and H. Werbin, *J. Am. Chem. Soc.*, **80**, 680 (1958).

(4) S. Kraychy and T. F. Gallagher, *J. Am. Chem. Soc.*, **79**, 754 (1957).

(5) The original procedure employs, approximately, two equivalents of nitric acid and leads to considerable Va.

(6) After the present study had been completed, S. Kraychy, *J. Am. Chem. Soc.*, **81**, 1702 (1959), reported the conversion of 2-nitro- and 4-nitroestrone to IIIc and IVc by similar methods. The precursory nitroestrones, IIIa and IVa, however, were obtained according to the procedure of Werbin and Holloway.

(7) All melting points are uncorrected. Rotations were determined in a 1-dcm. tube and chloroform was the solvent. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

2-Nitroestrone 3-methyl ether (IIIb). A mixture of 3.15 g. of IIIa (0.01 mol.), 100 g. of anhydrous potassium carbonate and 50 ml. of methyl iodide in 200 ml. of acetone was stirred under reflux for 30 hr. The inorganic salts were removed by filtration and the filtrate was evaporated to dryness *in vacuo* to give 3.12 g. (94% yield) of product, m.p. 148–150°. Two recrystallizations from 95% ethanol gave light yellow needles, m.p. 161–162°, $[\alpha]_D^{28}$ +146°. A double melting point, 147° and 157.5–159.5° ($[\alpha]_D^{24}$ +146°) has been recorded for IIIb.[6]

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.27; H, 7.04. Found: C, 68.94; H, 6.91.

2,4-Dinitroestrone 3-methyl ether (Vb). A mixture of 3.60 g. of Va[8] (0.01 mol.), m.p. 184–185°, 100 g. of anhydrous potassium carbonate, and 50 ml. of methyl iodide in 500 ml. of acetone was stirred under reflux for 36 hr. An additional 50 ml. of methyl iodide was added and the mixture refluxed with stirring for another period of 36 hr. The inorganic salts were separated by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was collected, washed with water, and recrystallized from a mixture of acetone, methanol, and water to give 2.45 g. (65% yield) of yellow plates, m.p. 116–117°. Three recrystallizations from ethanol provided an analytical sample, m.p. 119–120°, $[\alpha]_D^{26}$ +179°.

Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.94; H, 5.92. Found: C, 60.99; H, 6.09.

2-Aminoestrone 3-methyl ether (IIIc). A solution of 3.2 g. of IIIb (0.0097 mol.) in 150 ml. of 95% ethanol was shaken with (1 teaspoonful) W-2 Raney nickel[9] under 15 lb. of hydrogen for *ca.* 15 min. The catalyst was separated by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was washed into a filter funnel with petroleum ether (65–110°) and sucked dry, wt. 2.36 g. (81% yield), m.p. 160–163°. An analytical sample was obtained in the form of colorless needles on recrystallization from a mixture of ether and petroleum ether (65–110°), m.p. 164–165°, $[\alpha]_D^{26}$ +153° (lit.[6] 160.5–162.5° and 172.5–174.5°, $[\alpha]_D^{28.5}$ +155°).

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.21; H, 8.42. Found: C, 76.50; H, 8.56.

4-Aminoestrone 3-methyl ether (IVc). Application of this same method to IVb gave IVc in 62% yield, m.p. 187–189°. The analytical sample, m.p. 190–191°, $[\alpha]_D^{27}$ +140° (lit.[6] 190.5–191.5°, $[\alpha]_D^{28}$ +149°) was obtained in the form of colorless needles from a mixture of benzene and petroleum ether (65–110°).

Anal. Found: C, 75.68; H, 8.32.

2-Amino-4-nitroestrone 3-methyl ether (Vc). To a solution of 3.74 g. of Vb (0.01 mol.) in 150 ml. of glacial acetic acid at 50° was added all at once with stirring a solution of 6.75 g. of stannous chloride dihydrate (0.03 mol.) in 20 ml. of concentrated hydrochloric acid. The mixture was stirred at room temperature for 3 hr., warmed to 75° for 0.5 hr., then concentrated *in vacuo* to *ca.* one third the original volume. The reaction mixture was made basic with excess 10% sodium hydroxide, the product was, then, collected, and washed with generous quantities of water. The product crystallized from ethanol in the form of yellow plates, wt. 2.51 g. (73% yield), m.p. 200–202°. An analytical sample was obtained by recrystallization from a mixture of ether and petroleum ether (60–110°), m.p. 203–204°, $[\alpha]_D^{26}$ +210°.

Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.25; H, 7.02. Found: C, 66.21; H, 7.02.

To a solution of 0.5 g. of sodium nitrite (0.007 mol.) in a mixture of 2 ml. of concentrated sulfuric acid and 25 ml. of hypophosphorous acid (50%), cooled to 0°, was added, all at once, a solution of 0.344 g. of Vc (0.001 mol.) in 10 ml. of glacial acetic acid. The temperature of the reaction mixture was maintained at 5 to 10° for 2 hr., then 100 ml. of ice water was added and the vessel refrigerated (5°) for 2 days. The product, which was deposited during this period, was collected, washed with water, and sucked dry, wt. 0.198 g. (60% yield), m.p. 248–250°. Recrystallization from ethanol gave yellow plates, m.p. 258–259°, alone or admixed with an authentic sample of IVb.

2-Chloroestrone 3-methyl ether (IIId). A solution of 299 mg. of IIIc (1 mmol.) in 12 ml. of 2*N* hydrochloric acid was diazotized at 5–10° with a solution of 80 mg. of sodium nitrite (1.15 mmol.) dissolved in 5 ml. of water. The solution was stirred for 0.5 hr. followed by the dropwise addition of 500 mg. of cuprous chloride dissolved in 25 ml. of 0.5*N* hydrochloric acid. The mixture was stirred magnetically at, approximately, room temperature for 24 hr. and the product collected, wt. 200 mg. (63% yield), m.p. 186–190°. Three recrystallizations from a mixture of ether and petroleum ether (30–60°) provided analytical and biological samples in the form of slightly yellow colored needles, m.p. 191–192°, $[\alpha]_D^{26}$ +146°.

Anal. Calcd. for $C_{19}H_{23}ClO_2$: C, 71.57; H, 7.27. Found: C, 71.47; H, 7.17.

4-Chloroestrone 3-methyl ether (IVd). The conversion of 1.0 mmol. of IVc to IVd was carried out with the same quantities of reagents and under the same conditions as those described above; yield 220 mg. (69%), m.p. 190–198°. Several recrystallizations from 95% ethanol provided the analytical and biological samples in the form of needles, m.p. 196–197°, $[\alpha]_D^{26}$ +143°.

Anal. Found: C, 71.72; H, 7.40.

2-Bromoestrone 3-methyl ether (IIIe). A solution of 299 mg. (1 mmol.) in 11 ml. of 5% hydrobromic acid was diazotized at 5–10° with a solution of 80 mg. (1.15 mmol.) of sodium nitrite in 5 ml. of water. The solution was stirred for 0.5 hr., followed by the addition of 1.0 g. of cuprous bromide in 32 ml. of 3% hydrobromic acid. The mixture was then stirred at room temperature for 20 hr. and the product collected, wt. 220 mg. (61% yield), m.p. 188–190°. Several recrystallizations from 95% ethanol provided the analytical and biological samples, m.p. 197–198°, $[\alpha]_D^{26}$ +149°.

Anal. Calcd. for $C_{19}H_{23}BrO_2$: C, 62.81; H, 6.38. Found: C, 62.77; H, 6.41.

4-Bromoestrone 3-methyl ether (IVe). The same procedure applied to IVc (1.0 mmol.) gave 200 mg. (55% yield) of IVe, m.p. 183–185°. Several recrystallizations from 95% ethanol provided analytical and biological samples in the form of colorless plates, m.p. 187–188°, $[\alpha]_D^{27}$ +124°.

Anal. Found: C, 63.09; H, 6.47.

2-Iodoestrone 3-methyl ether (IIIf). A solution of 299 mg. of IIIc (1.0 mmol.) in 21 ml. of 0.6*N* hydrochloric acid was diazotized in the usual manner with 80 mg. of sodium nitrite (1.15 mmol.) in 5 ml. of water. The ice cold solution, added dropwise with stirring to a solution of 1.0 g. of potassium iodide (6.0 mmol.) in 30 ml. of water, gave an immediate precipitate. After stirring for 20 hr. at room temperature, the product was collected, wt. 180 mg. (44% yield), m.p. 160–162°. Several recrystallizations from 95% ethanol provided both the analytical and biological samples in the form of colorless needles, m.p. 164–165°, $[\alpha]_D^{27}$ +141°.

Anal. Calcd. for $C_{19}H_{23}IO_2$: C, 55.61; H, 5.65. Found: C, 55.56; H, 5.65.

4-Iodoestrone 3-methyl ether (IVf). The same procedure applied to IVc (1.0 mmol.) gave 220 mg. (54% yield) of IVf, m.p. 210–215°. Recrystallization from acetone provided both the analytical and biological samples in the form of colorless plates, m.p. 219–220°, $[\alpha]_D^{27}$ +102°.

Anal. Found: C, 55.56; H, 5.66.

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(8) The dinitration of I was effected in 66% yield according to the method of Werbin and Holloway (see ref. 2).

(9) E. C. Horning, *Org. Syntheses*, **Coll. Vol. III**, 181 (1955).

Structures of the "Isomers" of 2,3,6,7-Dibenzo-1-thia-4,5-diazacyclohepta-2,4,6-triene-1,1-dioxide[1]

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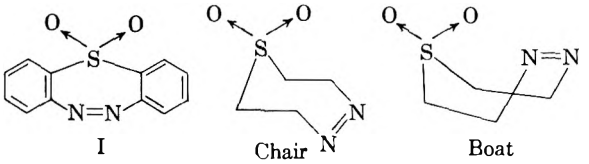
Szmant and Chow[3] originally reported the isolation of three isomers of 2,3,6,7-dibenzo-1-thia-4,5-diazacyclohepta-2,4,6-triene-1,1-dioxide (I). Shortly thereafter one of the compounds was actually found to be the corresponding hydrazo



compound.[4] The two remaining isomers (IA and IB) were assigned structures which differed in the conformation of the center ring, one being a chair and the other a boat form. The more stable isomer was assigned the chair structure.

It can be argued *a priori* that the chair structure represents an exceedingly improbable situation. There is no authentic case known in which both of a pair of conformers such as these can be isolated as separate stable individual substances. The energy barrier for the interconversion of boat and chair forms is estimated to be only about 10 kcal. for cyclohexane,[5] and since the angular deformation necessary to attain planarity appears to be less with a seven-membered ring, the corresponding barrier should be even smaller here. There is still, however, a more serious objection to the chair structure. In the regular chair form illustrated the dihedral angles between either nitrogen and the sulfur are 93°. Since there are benzene rings fused onto positions 2 and 3, and also 6 and 7, these benzene rings would have to be twisted from planarity to an improbable degree. While such a structure might conceivably exist it would certainly not be expected to be more stable than the boat form and yet the isomerization of IB to IA was reported.[3]

An examination of the experimental data reported by Szmant and Chow showed a surprising similarity between the substances IA and IB. The two compounds did not give a mixture melting point depression. The azo compounds IA and IB were reported to oxidize to the corresponding azoxy compounds IIA and IIB, respectively, and the latter pair likewise showed no mixture melting point depression. The isomerization of IB to IA and the various reactions in which IB was converted to derivatives of IA appeared to suggest that IA and IB were actually the same compound and merely samples of different purity.

The chair structure postulated for IA was sufficiently unusual, and the data upon which the structure was based were sufficiently indecisive that the work of Szmant and Chow was repeated. The materials designated by them as IA and IB were isolated without undue difficulty following a modification of their procedure. Compound IA, m.p. 173°, appeared to be a pure substance. Their compound IB, m.p. 126–130°, which did not appear upon close examination of the crystals to be a single substance, was separated by chromatography on alumina into two compounds, IA and the diamine (III) from which I had been prepared, m.p. 148.5°. Szmant and Chow reported[3] that it gave only one band when chromatographed on alumina. This observation was repeated and confirmed. The amine, being colorless, was not visible on the column, and only the azo compound was seen. The other extensive observations of Szmant and Chow on "isomerizations" can be better interpreted as purification. The rapid oxidation of IB relative to IA is not surprising, since the amine would oxidize very easily. Since IB contains about 50% amine, a large amount of oxidant would be consumed, and the rate was apparently not followed far enough to observe a break in the curve. It is clear therefore that only one isomer of I has in fact been previously isolated, that which corresponds in physical properties to the compound labeled IA by the earlier workers. Only the boat form is regarded by the present authors as a reasonable structure for this compound. It follows that the corresponding azoxy compounds IIA and IIB must also be regarded as identical, and possessing the boat structure.

EXPERIMENTAL

2,3,6,7-Dibenzo-1-thia-4,5-diazacyclohepta-2,4,6-triene-1,1-dioxide (I). The preparation was similar to that reported by Szmant and Chow.[3] 2,2′-Diaminodiphenyl disulfide was prepared[5] from benzothiazole, and converted to 2-nitro-2′-aminodiphenyl sulfide,[7] which was acetylated[8] and oxidized[8] to the sulfone. This compound was in turn reduced and hydrolyzed to the diamino sulfone III.[9] 2,2′-Diaminodiphenyl sulfone (III), 4.0 g., phenyliodoso acetate,[10] 4.65 g., and 400 ml. of dry toluene were mixed and allowed to stand at room temperature for 5 days with occasional shaking. The mixture was filtered and the brown precipitate

(1) Supported in part by a research grant from the National Science Foundation.

(2) National Science Foundation Predoctoral Fellow 1956–59.

(3) H. H. Szmant and Y. L. Chow, *J. Am. Chem. Soc.*, **79**, 4382 (1957).

(4) H. H. Szmant and Y. L. Chow, *J. Am. Chem. Soc.*, **79**, 5583 (1957).

(5) C. W. Shoppee, *J. Chem. Soc.*, 1138 (1946).

(6) J. A. Gardner, British Patent 558,887 (1944); *Chem. Abstr.*, **40**, 7237 (1946).

(7) A. Levi, L. A. Warren, and S. Smiles, *J. Chem. Soc.*, 1490 (1933).

(8) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935).

(9) B. R. Baker, A. F. Kadish, and M. V. Querry, *J. Org. Chem.*, **15**, 400 (1950).

(10) K. H. Pausacker, *J. Chem. Soc.*, 107 (1953).

was washed with benzene. The filtrate and washings were combined and the solvent was removed under diminished pressure to yield a dark red oil. Crystallization of the oil from methanol as described was attempted, but was unsuccessful. The solution was therefore diluted with water and extracted with ether. The ether layer was washed and dried, and the solvent was evaporated. The residue was a red oil which partially solidified. This material was triturated with 20 ml. of benzene. The insoluble solid (IB) was removed by filtration.

The benzene filtrate was poured onto a column of 200 g. of activated alumina. The column was eluted with 2:8 hexane:ether, and then with ether. The early fractions yielded orange crystals which were combined and recrystallized from methylene chloride–hexane, m.p. 148–149°, wt. 0.27 g. (7%). The mixture melting point with authentic III was undepressed.

A small portion of the benzene-insoluble solid (IB) was recrystallized from methanol, m.p. 127–131° (lit.[3] m.p. 131.5°). The remainder of the crude IB was chromatographed on alumina with gradually increasing concentrations of methylene chloride in hexane, followed by pure ether. From the 4:6 hexane:methylene chloride fractions there was obtained a solid which was crystallized to yield IA as orange needles, m.p. 172.5–173.5°, wt. 0.20 g. From the ether fractions there was obtained material which after recrystallization gave III as colorless plates, m.p. 147–148.5°. The mixed melting point with authentic III was undepressed.

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Synthesis of the *gem*-Dimethylcyclopentenes

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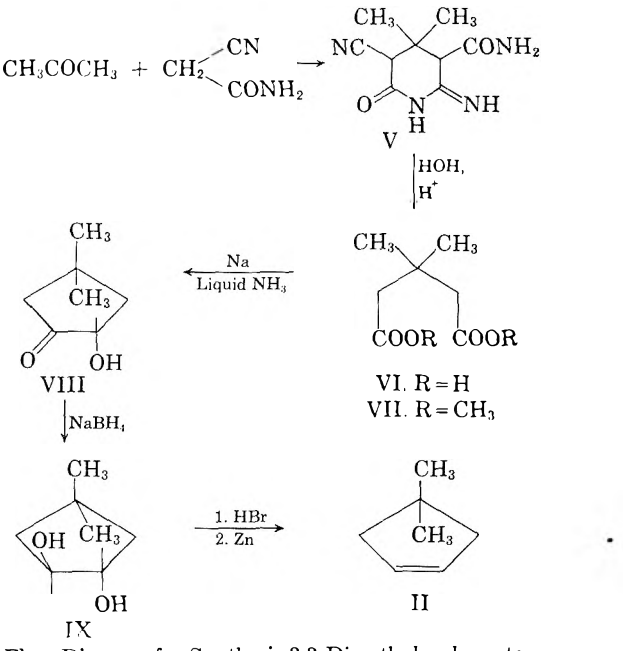
The two isomeric *gem*-dimethylcyclopentenes were required for an investigation in progress in these laboratories. A method of preparation of 2,2-dimethylcyclopentane (I) has been reported,[2] but apparently the conditions employed for obtaining a significant yield were very exacting. Kizhner[2] has described the formation of (I) by dehydrobromination of 1-bromo-2,2-dimethylcyclopentane, (III), which, as he indicated, resulted from a Demjanov type of rearrangement[3] of cyclobutyldimethyl carbinol (IV) on boiling with fuming hydrobromic acid. When we used 48% aqueous hydrobromic acid instead in the procedure of the Russian author, we obtained chiefly 1,2 dimethylcyclopentene and none of the desired bromo compound (III). Subsequently we found, however, that stirring (IV) with 48% hydrobromic acid at 20–30° (without heating) produced a good yield of (III). Furthermore, upon increasing the reaction time given by Kizhner[2] for the dehydrobromination of (III) we were able to raise the yield of (I) from 42 to 74%



Flow Diagram for Synthesis 3,3-Dimethylcyclopentene

The synthesis of the other isomer, 3,3-dimethylcyclopentene (II), has not been reported. This has now been achieved according to the reactions illustrated in the flow diagram.

The starting material, 5-carbamyl-3-cyano-4,4-dimethyl-6-imino-2-piperidone, (V), was made by condensation of acetone and cyanoacetamide.[4] (V) was hydrolyzed to 3,3-dimethylglutaric acid (VI) by a procedure analogous to that given by Thole and Thorpe.[5] Cyclization of the methyl ester[6] (VII) to 3,3 dimethylglutaroin (VIII) was effected by means of sodium in liquid ammonia. The structure of (VIII) was confirmed by the identity of its osazone with that from 1,1-dimethyl-3,4-cyclopentanedione.[7]

Reduction of (VIII) with sodium borohydride gave 1,1-dimethyl-*trans*-3,4-cyclopentanediol (IX). The trans structure was confirmed by the failure of (IX) to form a cyclic ketal with *p*-nitrobenzaldehyde[8] and the absence of any infrared evidence[9] for intramolecular hydrogen bonding.

(1) Abstracted from the doctorate thesis of John A. Ford, Jr., submitted to the University of Delaware in partial fulfillment of the requirements of the Ph.D. degree, June, 1958; present address, Eastman Kodak Co., Rochester 4, N. Y.

(2) N. Kizhner, *J. Russ. Phys. Chem. Soc.*, **40**, 999 (1908); *Chem. Abstr.*, **3**, 533 (1909).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 486 *et. seq.*, Cornell University Press, Ithaca, N. Y. (1953).

(4) F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, **99**, 430 (1911).

(5) F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, **99**, 434 (1911).

(6) G. Kommpa, *Ber.*, **32**, 1423 (1899).

(7) G. L. Blanc and J. F. Thorpe, *J. Chem. Soc.*, **99**, 2012 (1911).

(8) H. M. Walborsky and D. F. Loncrini, *J. Am. Chem. Soc.*, **76**, 5399 (1954).

(9) See for examples, L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952); **76**, 4323 (1954) and H. Kwart and G. C. Gatos, *J. Am. Chem. Soc.*, **80**, 881 (1958).

Treatment of (IX) with hydrogen bromide in glacial acetic acid gave 1,2-dibromo-4,4-dimethylcyclopentane (X), which was reacted with zinc dust to give (II). The structure of (II) was confirmed by ozonization and peroxidation to (VI).[10]

EXPERIMENTAL[11]

1-Bromo-2,2-dimethylcyclopentane (III). A mixture of 400 ml. of 48% aqueous hydrobromic acid and 100 g. (0.877 mol.) of cyclobutyldimethylcarbinol was stirred 3 hr. at 20–30° and the organic layer separated and boiled 1 hr. with a solution of 100 g. of potassium hydroxide in 250 ml. of water. The mixture was steam distilled. A volume of 600 ml. of distillate was collected and diluted with a liter of water. The organic layer was separated, dried with anhydrous calcium chloride, and distilled, giving 100 g. of pale yellow liquid, b.p. 157–164°, n_D^{20} 1.4792 (65%).

2,2-Dimethylcyclopentene (I). A solution of 94.0 g. (0.531 mol.) of (III), 140 g. of potassium hydroxide, and 850 ml. of absolute ethanol was refluxed 24 hr. and then diluted with a liter of water prior to steam distillation. A 600 ml. volume of distillate was collected, diluted with a liter of water and the organic layer separated, dried with anhydrous calcium chloride, and distilled to give 38 g. of colorless liquid (74%), b.p. 78–80°, n_D^{25} 1.4151.

5-Carbamyl-3-cyano-6-imino-4,4-dimethyl-2-piperidone (V). A mixture of 250 g. (2.97 mol.) of cyanoacetamide, 125 g. (2.15 mol.) of acetone, 50 ml. of piperidine, and 1 l. of water was allowed to stand with occasional shaking for 24 hr. The white solid was filtered, washed with cold water and dried at room temperature giving 261 g. of product (84%).

3,3-Dimethylglutaroin (VIII). In a flask previously flamed dry for 15 min. and swept with dry oxygen-free nitrogen for 0.5 hr. was placed 5 l. of anhydrous ether. A 5 l. volume of liquid ammonia was collected in the flask, a dry ice-acetone trap being used as the condenser. With vigorous stirring 67 g. (2.91 g. at.) of sodium was added in small pieces under nitrogen during a 20 min. period. To the deep blue solution was added dropwise over a 4 hr. period a solution of 125 g. (0.665 mol.) of (VII) in 500 ml. of anhydrous ether. The mixture was stirred an additional 2 hr. at −33°, and the ammonia was allowed to evaporate gradually overnight. To the resulting yellow suspension was added dropwise a solution of 250 ml. of methanol in 500 ml. of ether. The mixture was acidified with 3*N* hydrochloric acid. At this point the nitrogen flow was stopped. The ether layer was separated, the aqueous layer was extracted four times with a total of 800 ml. of ether, and the combined ether solutions were dried overnight with anhydrous calcium sulfate. After removal of the ether on a steam bath distillation of the residue gave 68 g. of colorless liquid, b.p. 68–70° (2 mm.) (80%); phenylosazone, orange needles from methanol, m.p. 167–169°.[7]

1,1-Dimethyl-trans-3,4-cyclopentanediol (IX). A solution of 58 g. (0.45 mol.) of (VIII) in 50 ml. of absolute ethanol was added slowly with stirring to a solution of 15 g. (0.40 mol.) of sodium borohydride in 400 ml. of absolute ethanol. The solution was refluxed 2 hr., cooled, poured into 500 ml. of 6*N* sulfuric acid, the alcohol removed by steam distillation, and the residue extracted for 24 hr. with ether in a continuous liquid-liquid extractor. After drying with anhydrous potassium carbonate the ethereal solution was concentrated on a steam bath and the residue distilled at 93–96° (0.7 mm.). The white solid distillate was recrystallized from benzene to give 28 g. of (IX), m.p. 96–97° (48%).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.57; H, 10.83. Found: C, 64.36; H, 10.78.

An attempt to prepare a cyclic ketal with *p*-nitrobenzaldehyde[8] gave back only starting material. The infrared spectrum showed only one hydroxyl band[9] which occurred at 3620 cm.$^{-1}$

1,2-Dibromo-4,4-dimethylcyclopentane (X). A solution of 40.0 g. (0.308 mol.) of (IX), 2 ml. on conc. sulfuric acid, 200 g. of glacial acetic acid and 900 g. of 30–32% hydrogen bromide in glacial acetic acid (Eastman Kodak white label) was allowed to stand 8 hr. at room temperature and then heated 4 hr. at 100°. An additional 100 g. of the hydrogen bromide–glacial acetic acid reagent was added and the mixture heated another 4 hr. at 100°. The solution was cooled and poured into ice water. The organic layer was separated and the aqueous layer extracted three times with a total of 600 ml. of petroleum ether, b.p. 30–60°. The combined organic solutions were washed with saturated bicarbonate solution until effervescence ceased and then dried overnight with anhydrous sodium sulfate. The solvent was removed on a steam bath and the residue distilled to give 69.0 g. of colorless liquid, b.p. 65–67° (1 mm.) (88%), n_D^{20} 1.5053.

Anal. Calcd. for $C_7H_{12}Br_2$: C, 32.84; H, 4.69; Br, 62.4. Found: C, 32.78; H, 4.64; Br, 59.6.

3,3-Dimethylcyclopentene (II). To 130 g. of zinc dust in 600 ml. of boiling ethanol was added with stirring 130 g. (0.508 mol.) of (X) during 1.5 hr. The mixture was refluxed overnight, diluted with an equal volume of water and steam distilled. A volume of 800 ml. of distillate was collected, saturated with salt, and the organic layer separated and dried with anhydrous calcium chloride. Distillation gave 42.4 g. of (II) (87%), b.p. 74–75°, n_D^{22} 1.4160.

Anal. Calcd. for C_7H_{12}: C, 87.42; H, 12.58. Found: C, 86.09; H, 12.34.

Ozonization of (II). A solution of 3.14 g. (0.0326 mol.) of (II) in 100 ml. of purified carbon tetrachloride[12] was ozonized at 0–5° and then the solution concentrated to 20 ml. under water pump vacuum. After dilution to 100 ml. with glacial acetic acid the solution was added dropwise with stirring during 15 min. to a solution of 25 g. of 30% hydrogen peroxide, 1 ml. of conc. sulfuric acid, and 70 ml. of water. The mixture was refluxed 4 hr. and evaporated to 10 ml. under water pump vacuum. The residual solution was diluted with 50 ml. of water, extracted with ether, and the ether solution decolorized with norite and dried with anhydrous sodium sulfate. Evaporation and recrystallization from benzene gave 1.47 g. (28%) of (VI), m.p. 98–100°. A second recrystallization from benzene gave 1.35 g., m.p. and m.m.p. with (VI) 100–102°.

Acknowledgment. We are indebted to Mr. E. Sarasohn for translation of the Russian literature pertinent to this work and to the E. I. duPont de Nemours and Co., Inc. for a fellowship to one of us (J. A. F.) during the course of this research. We are also obliged to Mr. M. Hackett for valuable assistance in carrying out several procedures.

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(10) The infrared and Raman spectra of both (I) and (II) on samples we have synthesized by the above procedures have been extensively studied by H. C. Beachell and W. Jones in these laboratories. The as yet unpublished results of their work and the spectral assignments they ascertained appear to be quite consistent with the structures we have assumed for (I) and (II).

(11) All melting point and boiling points given are uncorrected.

(12) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Second Edition, Longmans, Green and Co., New York, N. Y., 1951, p. 174.

ϵ-Imido Esters. I. The Course of the Reaction between Phthalic Anhydride and Caprolactam

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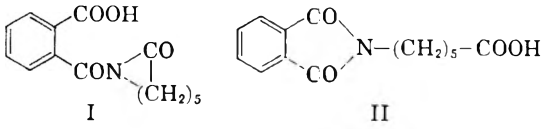
In the course of an investigation of the reaction of anhydrides with caprolactam we had occasion to condense the latter compound with phthalic anhydride. According to Benson and Cairns,[1] the compound formed by this reaction is *N*-phthaloyl-ϵ-caprolactam (I). However, G. M. van der Want[2] repeated this work and found the material to be ϵ-phthalimidocaproic acid (II). His proof of structure was based on the comparison of the latter's ultraviolet absorption curve with spectra from analagous compounds of known structure.



We have found by chemical means and by unequivocal syntheses of the possible structures, that the product formed by reaction of caprolactam with phthalic anhydride is the corresponding phthalimidocaproic acid (II) rather than the substituted *N*-acyl-ϵ-caprolactam (I).

This was accomplished by condensing caprolactam with phthalic anhydride at 180° to yield a substituted monocarboxylic acid which in turn was esterified with methyl alcohol. The product after distillation, solidified and had a melting point of 43.5–44.0°. Phthalic anhydride was then treated with methyl-6-isocyanatocaproate at 125° following the procedure of Hurd and Prapas[3] to yield methyl-ϵ-phthalimidocaproate which also solidified and melted at 43.5–44.0°. There was no depression of the melting point when the compounds prepared *via* the two methods were mixed. The infrared and ultraviolet absorption curves were identical for both compounds.

To elucidate further the course of the reaction between phthalic anhydride and caprolactam, the methyl ester of *N*-phthaloyl-ϵ-caprolactam (I) was prepared by an unequivocal synthesis. Thus, phthalic anhydride was esterified with methyl alcohol to yield methyl hydrogen phthalate which in turn was converted to the acid chloride with thionyl chloride. Finally, the acid chloride was condensed with caprolactam in the presence of triethylamine to give *N*-(*o*-carbomethoxybenzoyl)-ϵ-caprolactam which melted at 68–70°. The infrared and ultraviolet absorption curves were different from those of the phthalimido ester. This is conclusive evidence that the structure proposed by van der Want is correct.

(1) R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, **70**, 2115 (1948).

(2) G. M. van der Want, *Rec. Trav. Chim.*, **71**, 1012 (1952).

(3) C. D. Hurd and A. G. Prapas, *J. Org. Chem.*, **24**, 388 (1959).

EXPERIMENTAL

ϵ-Phthalimidocaproic acid. The compound was prepared following the procedure of Benson and Cairns.[1] Thus, a mixture of 113 g. (1.0 mol.) of caprolactam and 148 g. (1.0 mol.) of phthalic anhydride was heated to 180° and held there for 18 hr. Unreacted starting materials were removed by distillation and the residue was fractionally distilled to yield 169 g. (65%) of ϵ-phthalimidocaproic acid; b.p. 239–240°/3 mm.; m.p. 107–108°.

Methyl-ϵ-phthalimidocaproate. A. *From ϵ-phthalimidocaproic acid and methanol.* A mixture of 51 g. (0.20 mol.) of ϵ-phthalimidocaproic acid, 40 ml. of methanol, 100 ml. of benzene and 0.4 g. of *p*-toluenesulfonic acid was refluxed for 18 hr. The excess alcohol and the water formed during the esterification were removed by distillation following which the resultant benzene solution was washed with water, 5% aqueous sodium carbonate, again with water and finally dried over anhydrous sodium sulfate. The solvent was distilled off atmospherically and the residue was distilled in vacuo to yield 54 g. (84%) of methyl-ϵ-phthalimidocaproate; b.p. 182–183°/0.7 mm.; m.p. 43.5–44.0°.

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.5; H, 6.2; N, 5.1. Found: C, 66.0; H, 6.4; N, 5.0.

B. *From phthalic anhydride and methyl-6-isocyanatocaproate.* A mixture of 37 g. (0.25 mol.) of phthalic anhydride and 34.2 g. (0.20 mol.) of methyl-6-isocyanatocaproate was heated to 125° and held there for 18 hr. While on temperature evolution of carbon dioxide was apparent. The excess phthalic anhydride was distilled off following which the residue was distilled under vacuum to yield 48 g. (87%) of methyl-ϵ-phthalimidocaproate; b.p. 187°/0.9 mm.; m.p. 43.5–44.0°.

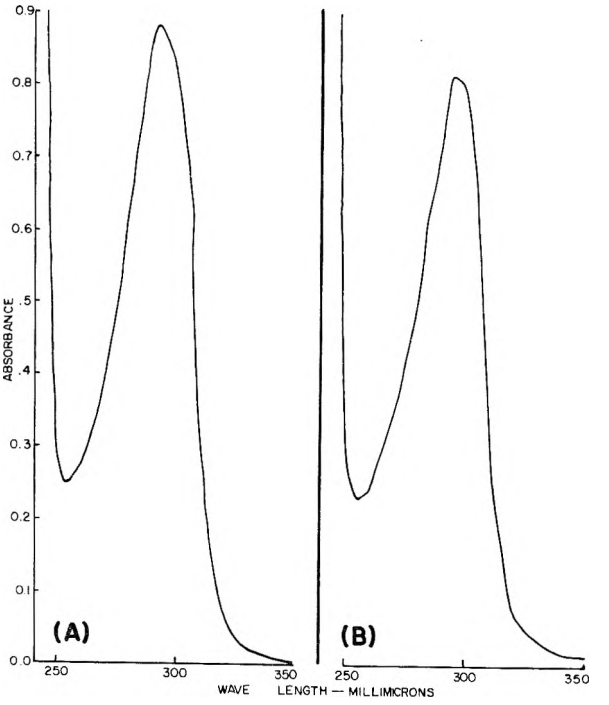


Fig. 1. Ultraviolet absorption curves for methyl-ϵ-phthalimidocaproate: (A) prepared by procedure A; (B) prepared by procedure B

Anal. Calcd. for $C_{15}H_{17}NO_4$: N, 5.09. Found: N, 4.93.

The compound when mixed with the material from procedure A failed to show any depression in the melting point. The ultraviolet absorption curves for both compounds were identical, exhibiting a maximum at 293 mμ (Fig. 1, A and B). The infrared absorption curves for both compounds were also identical (Fig. 2, A and B).

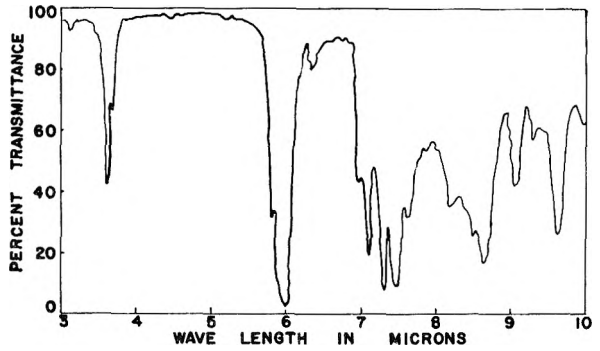


Fig. 2(A). Infrared absorption curve for methyl-ε-phthalimidocaproate prepared by procedure A

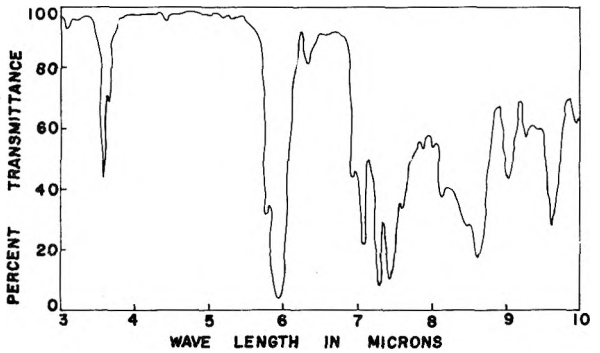


Fig. 2(B). Infrared absorption curve for methyl-ε-phthalimidocaproate prepared by procedure B

Methyl hydrogen phthalate. Methyl hydrogen phthalate was prepared following the procedure of Eliel and Burgstahler.[4] Thus, 74 g. (0.50 mol.) of phthalic anhydride and 50 ml. of methanol were refluxed for 2 hr. The excess methanol was distilled off, 25 ml. of benzene was added and the distillation continued to insure the complete removal of the excess alcohol. The residual oil was dissolved in 200 ml. of benzene following which 300 ml. of Skellysolve B was added. Upon cooling in an ice-salt bath, the product crystallized following which it was filtered, washed with more Skellysolve B and finally dried in vacuo. There was obtained 80 g. (89%) of methyl hydrogen phthalate; m.p. 80–82°; lit. val. 82°.[4]

o-Carbomethoxybenzoyl chloride. A mixture of 36 g. (0.2 mol.) of methyl hydrogen phthalate and 100 ml. of thionyl chloride was refluxed for 1 hr. on a steam bath. The excess thionyl chloride was removed under reduced pressure following which dry benzene (two 50-ml. portions) was added and distilled away from the acid chloride *in vacuo* two times, to complete the removal of unreacted thionyl chloride. The acid chloride, a pale yellow oily liquid was used as such in the following experiment without any further purification.

N-(o-Carbomethoxybenzoyl)-ε-caprolactam. Into a flask equipped with an agitator, thermometer, dropping funnel and reflux condenser was placed a solution of 22.6 g. (0.20 mol.) of caprolactam in 100 ml. of dry dioxane. While stirring, a solution of the *o*-carbomethoxybenzoyl chloride (from the previous experiment) in 100 ml. of dioxane was added dropwise over a period of 30 min. The mixture was next cooled to 10° and a solution of 20.2 g. (0.20 mol.) of triethylamine in 200 ml. of dioxane was added dropwise, maintaining the temperature below 20°. After the addition was complete, the mixture was refluxed for 3 hr., cooled to room temperature and filtered to remove the triethylamine hydrochloride.

The salt was washed with two 50-ml. portions of fresh dioxane following which the combined filtrates were subjected to a vacuum distillation to remove the dioxane. The residue was distilled at reduced pressures to yield 31 g. (57%) of *N*-(*o*-carbomethoxybenzoyl)-ε-caprolactam; b.p. 190–194°/0.8 mm. The compound crystallized on standing. After recrystallizing from Skellysolve B, the compound melted at 68–70°.

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.46; H, 6.18; N, 5.09. Found: C, 65.39; H, 5.51; N, 4.97.

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(4) E. L. Eliel and A. W. Burgstahler, *J. Am. Chem. Soc.*, **71**, 2251 (1949).

Benzyllithium from Triphenylbenzyltin and Phenyllithium

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Received July 22, 1959

In a recent communication to this journal procedures were described for the direct preparation of benzyllithium by cleavage reactions.[1] An attempt was made to list all types of procedures that had been described for the synthesis of benzyllithium. However, a method involving a metal-metal interconversion or exchange was not included.[2] This involves the following reaction:

$$(C_6H_5)_3SnCH_2C_6H_5 + C_6H_5Li \longrightarrow C_6H_5CH_2Li + (C_6H_5)_4Sn$$

The yield of phenylacetic acid obtained subsequent to carbonation was 39%; and the yield of tetraphenyltin was as high as 91.8%. This exchange reaction between organotin and organolithium compounds is one which has been employed broadly for some time,[3] and a particularly effective use of it was described recently by Seyferth and Weiner[4] for a neat preparation of vinyllithium from tetravinyltin and phenyllithium.

(1) H. Gilman, H. A. McNinch, and D. Wittenberg, *J. Org. Chem.*, **23**, 2044 (1958).

(2) S. D. Rosenberg, Doctoral Dissertation, Iowa State College, 1952.

(3) H. Gilman, F. W. Moore, and R. G. Jones, *J. Am. Chem. Soc.*, **63**, 2482 (1941). See, also, R. G. Jones and H. Gilman, *Chem. Revs.*, **54**, 835 (1954) on the preparation of organometallic compounds.

(4) D. Seyferth and M. A. Weiner, *Chem. & Ind.* (*London*), 402 (1959).

EXPERIMENTAL

To 5.0 g. (0.0113 mol.) of triphenylbenzyltin in 150 ml. of ether cooled to −35° (by a Dry Ice–acetone bath) was added 0.012 mol. of phenyllithium in 10 ml. of ether. The solution turned bright yellow immediately and then tetraphenyltin precipitated from the solution a few minutes later. After 1 hr. of stirring the mixture was allowed to stand a few minutes while the solid settled. The supernatant solution was decanted onto a Dry Ice–ether slurry with vigorous stirring, and the yellow color of benzyllithium was discharged. On working up the mixture by conventional procedures involving alkaline liquid–liquid extraction, acid liquid–liquid extraction, and crystallization there was obtained 0.6 g. (39%) of phenylacetic acid melting at 73–74° (mixed melting point). From this experiment, the yield of tetraphenyltin was 4.1 g. (88%). In two other experiments the yields of tetraphenyltin were 91.8% and 89%, respectively.

It might be mentioned that, under corresponding conditions, from reaction between triphenylethyltin and phenyllithium there was obtained a 9.4% yield of tetraphenyltin in addition to a 52.6% recovery of triphenylethyltin.

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Studies on Synthetic Estrogens. I

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Received March 30, 1959

Following the observation that oxygen heterocyclic compounds such as coumarins,[1] isoflavens, isoflavones,[2] etc. have estrogenic activity, Buu-Hoï and co-workers[3] synthesized a number of benzofuran derivatives and some of these compounds showed estrogenic activity. In view of the physiological properties of the benzofuran derivatives[4] it was of considerable interest to synthesize additional derivatives.

2-*p*-Anisoylbenzofurans were prepared by refluxing an alcoholic solution of the potassium salt of *o*-hydroxyketones with *p*-methoxyphenacylbromide[5] according to Buu-Hoï.[3b] They have been characterized through their oximes.

The details of the *in vivo* biological activity of these compounds will be reported later.

EXPERIMENTAL[6]

o-Hydroxyketones were prepared by the method of Fries.[7]

2-p-Anisoyl-3,5-dimethylbenzofuran. A solution of 5-methyl-2-hydroxyacetophenone (0.1 mole) dissolved in caustic potash (0.125 mole) was added to *p*-methoxyphenacylbromide (0.1 mole) in ethanol. It was refluxed for 2 hr. on a water bath. The 2-*p*-anisoyl-3,5-dimethylbenzofuran formed was isolated and recrystallized from an acetic acid ethanol mixture. Similarly other benzofurans were prepared. The data concerning the new compounds are listed in Table I.

Acknowledgment. The authors wish to express their gratitude to Dr. S. S. Joshi, Principal, Meerut College, Meerut (India) for his kind interest in this work.

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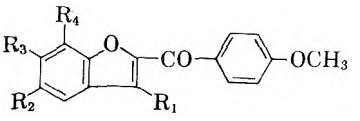
MEERUT, INDIA

TABLE I

2-*p*-ANISOYLBENZOFURANS



Sl. No.	R_1	R_2	R_3	R_4	Formula	Solvent for Recrystn.	M.P., °C.	Analysis	Calcd.	Found	Oxime M.P., °C.	Oxime Analysis	Calcd.	Found
1.	CH_3	CH_3	H	H	$C_{18}H_{16}O_3$	AcOH-EtOH	118	C:	77.14	76.7	169	C:	73.23	72.9
								H:	5.71	5 55		H:	5.76	5.61
2.	CH_3	Cl	H	H	$C_{17}H_{13}O_3Cl$	AcOH-EtOH	165	Cl:	11.81	11.6	110	Cl:	11.26	10.8
3.	CH_3	Br	H	H	$C_{17}H_{13}O_3Br$	AcOH-EtOH	154	Br:	23.19	22.6	189	Br:	22.22	22.1
4.	CH_3	CH_3	H	Br	$C_{18}H_{15}O_3Br$	AcOH-EtOH	190	Br:	22.28	21.9				
5.	CH_3	Cl	Cl	H	$C_{17}H_{12}O_3Cl_2$	AcOH-EtOH	155	Cl:	21.19	20.8				
6.	C_2H_5	CH_3	H	H	$C_{19}H_{18}O_3$	EtOH	148	C:	77.56	77.1	213	C:	73.77	73.4
								H:	6.12	5.71		H:	6.15	5 92
7.	C_2H_5	Cl	H	H	$C_{18}H_{15}O_3Cl$	EtOH	103	Cl:	11.29	11.1	144	Cl:	10.77	10.5
8.	C_2H_5	Br	H	H	$C_{18}H_{15}O_3Br$	EtOH	93	Br:	22.28	21.8	215	Br:	21.39	20.9

(1) (a) P. Gley and C. Mentzer, *Compt. rend. soc. biol.*, **139**, 1055 (1945); (b) C. Mentzer, P. Gley, D. Molho, and D. Billet, *Bull. soc. chim.*, 271 (1946).

(2) (a) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 3447 (1951); 871 (1953); (b) G. S. Pope, P. V. Elcoate, S. A. Simpson, and D. G. Andrews, *Chem. & Ind. (London)*, 1092 (1953); (c) G. S. Pope and H. G. Wright, *Chem. & Ind. (London)*, 1019 (1954); (d) J. L. Bose and K. Chandran, *J. Sci. Ind. Research (India)*, 13B, 888 (1954).

(3) (a) M. Bisagni, N. P. Buu-Hoï, and R. Royer, *J. Chem. Soc.*, 3688 (1955); (b) 3693 (1955); (c) N. P. Buu-Hoï, E. Bisagni, R. Royer, and C. Routier, *J. Chem. Soc.*, 625 (1957).

(4) (a) A. Burger, *Medicinal Chemistry*, Interscience, New York, 1951, Vol. I, p. 238; (b) A. Schonberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 1611 (1950); (c) J. C. Ghosh, *Pharm. J.*, **121**, 54 (1928).

(5) J. B. Rather and E. M. Reid, *J. Am. Chem. Soc.*, **41**, 75 (1919).

(6) All melting points given are uncorrected.

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A New Synthesis of Porphin

STEFAN KROL[1]

Received April 8, 1957

Porphin was synthesized by Fischer and Gleim[2] by prolonged boiling of pyrrole α-aldehyde with formic acid. It was also obtained by Rothemund[3] by heating pyrrole and formaldehyde in the presence of methanol in a sealed tube. Yields were below 0.1%

As porphobilinogen, 5-(aminomethyl)-4-(carboxymethyl)-3-pyrrolepropionic acid, can be readily transformed into uroporphyrins by boiling with dilute acid (Cookson and Rimington[4]) and ready formation of aetioporphyrins from hydroxymethylpyrroles (later shown to be acetoxymethyl derivatives[5]) has been demonstrated (Siedel and Winkler[6]), it seemed possible that either 2-aminomethylpyrrole or 2-hydroxymethylpyrrole might be similarly convertible into porphin.

Eisner and Linstead[7] have reported the synthesis of chlorin in 3.9% yield from 2-dimethylaminomethylpyrrole and its conversion to porphin.[8] They were unable to prepare porphin or any other macrocyclic pigment from 2-hydroxymethylpyrrole.

In this laboratory, porphin has been obtained in a one-step synthesis in yields of up to 5% by treating dilute solutions of 2-hydroxymethylpyrrole with potassium persulfate or a similar peroxidizing agent in glacial acetic acid. Porphin has also been obtained directly from 2-dimethylaminomethylpyrrole by treatment in ethereal solution with magnesium and methyl iodide in the presence of air.

In preliminary experiments, 2-dimethylaminomethylpyrrole methiodide was refluxed with sodium ethoxide and small quantities of porphin were obtained. Treatment of the solution at 50–60° with potassium persulfate resulted in a large increase of fluorescence. Of other oxidizing agents investigated, benzoyl peroxide proved equally effective, but hydrogen peroxide and Caro's acid were much less efficient. The presence of magnesium in the reaction mixture increased the yield of porphin (Eisner and Linstead[8]).

These experiments indicated that 2-hydroxymethylpyrrole might be implicated and further investigations were conducted with this substance. Porphin was produced with either water or benzene as solvent and best yields were obtained when the 2-hydroxymethylpyrrole was present in high dilution (*ca.* 0.01*M*). Other conditions favoring porphin production were slow addition of the 2-hydroxymethylpyrrole to a stirred solution of the oxidizing agent and magnesium dissolved in glacial acetic acid at 50° (Table I). The porphin was purified chromatographically and was characterized by analysis and spectrophotometry. Light absorption data is summarized in Table II. (See also Rimington, Mason, and Kennard[10]).

Conclusion: The synthesis of porphin described in this paper constitutes the best preparative method yet recorded. Yields much in excess of 5% would seem unlikely in a reaction of this type in which polymerization of macromolecules and cyclization in 4-ring units are equally possible.

TABLE I

YIELDS OF PORPHIN

	Without Mg Acetate			With Mg Acetate			
Time taken to add R·OH′ soln. (minutes)	5	10	15	5	10	15	25
μg R·OH	157	314	471	157	314	471	785
μg Porphin	0.79	1.20	1.71	4.25	11.77	19.85	33.86
Per cent yield	0.63	0.47	0.45	3.35	4.64	5.22	5.33

TABLE II

LIGHT ABSORPTION DATA FOR PORPHIN IN BENZENE

This Preparation		Eisner and Linstead[8]		Stern, Wenderlein and Molvig[9]	
λ_{max} (mμ)	$\epsilon \times 10^{-3}$	γ_{max} (mμ)	$\epsilon \times 10^{-3}$	λ_{max} (mμ)	$\epsilon \times 10^{-3}$
616.5	0.853	616	0.89	634	0.16
569	4.170	568.5	4.40	615	0.80
563.5	4.978	563	5.20		
519.5	2.640	520	3.00	562	4.74
489.5	15.750	489.5	16.00	519	2.55
396.5	264.000	395	261.00	489	14.80

(1) Present address: Ethicon Ltd., Ethicon Research Unit, Buckston Browne Farm, Downe, Kent, England.

(2) H. Fischer and W. Gleim, *Liebig's Ann.*, **521**, 157 (1936).

(3) P. Rothemund, *J. Am. Chem. Soc.*, **58**, 625 (1936).

(4) G. H. Cookson and C. Rimington, *Biochem. J.*, **57**, 476 (1954).

(5) E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958).

(6) W. Siedel and F. Winkler, *Liebig's Ann.*, **554**, 162 (1943).

(7) U. Eisner and R. P. Linstead, *J. Chem. Soc.*, 3742 (1955).

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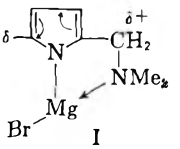
(9) A. Stern, H. Wenderlein, and H. Molvig, *Z. physik. Chem.*, **A177**, 40 (1936).

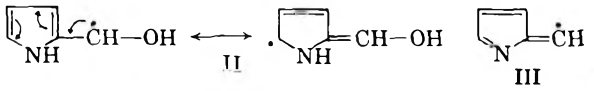
(10) C. Rimington, S. F. Mason, and O. Kennard, *Spectrochim. Acta*, **12**, 65 (1958).

The essential feature of many of the reactions described above is that there is no possibility of I,



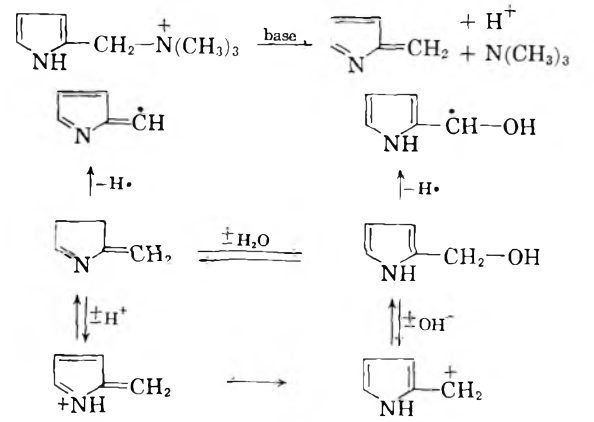
I

postulated by Eisner and Linstead,[7] being formed, as the synthesis involves the use of preformed 2-hydroxymethylpyrrole and it can proceed in the absence of magnesium. The present experimental evidence points either to the ionic mechanism postulated by Cookson and Rimington[4] or to the



II III

free radical mechanism involving secondary radicals such as II and III. Both these radicals or the ionic species of Cookson and Rimington can be derived either from 2-hydroxymethylpyrrole or from the pyrrole-Mannich base as in the following



scheme: This postulate not only accounts for the known lack of alcoholic properties of 2-hydroxymethylpyrrole (*cf.* Silverstein *et al.*[11]) but also brings under one general scheme the apparently diverse conditions capable of resulting in porphin production.

EXPERIMENTAL

2-Dimethylaminomethylpyrrole methiodide. 2-Dimethylaminomethylpyrrole was prepared by the method of Herz, Dittmer, and Cristol.[12] It was converted to the methiodide by adding a slight excess (1.5 g.) of methyl iodide to the Mannich base (1.14 g.) in ethanol (25.0 ml.). The precipitated methiodide was filtered and crystallized from water.

2-Hydroxymethylpyrrole. This was prepared by the method of Silverstein, Ryskiewicz, Willard, and Koehler.[11]

Spontaneous formation of porphin. When 2m*M* ethereal solutions of the methiodide of pyrrole-Mannich base were left standing in the absence of strong sunlight but in contact with air for three weeks at room temperature or at 0°, several red-fluorescing substances were formed. These were separated by extracting the ethereal solutions successively with 5%, 10%, 15%, 20%, and 25% w/v HCl. Porphin was found in the 5% HCl extract.

Experiments with 2-dimethylaminomethylpyrrole in the presence of methyl iodide and magnesium. Magnesium (0.01 mole), 2-dimethylaminomethylpyrrole (0.01 mole), and methyl iodide (0.012 mole) plus a trace of iodine were mixed in ether (100 ml.) and left standing in contact with air at room temperature with occasional shaking. No precautions were taken to exclude moisture. Trimethylamine was evolved and an intense green fluorescence developed within 10–15 min.; in a short time this changed to orange and eventually to strong red. After 90 min. the reaction mixture was extracted with 5% w/v HCl (6 × 5 ml.). The acid extracts were combined, neutralized to Congo red by addition of solid sodium acetate, and extracted with benzene (3 × 40 ml.). The benzene solution was distilled to dryness under reduced pressure, and the residue was redissolved in hot benzene (50 ml.) and applied to a column of MgO (20 × 2 cm.) prepared according to Nicholas.[13] Development of the chromatogram with a benzene–chloroform–methanol mixture (85:10:5) eluted two small bands in advance of the main porphin band. This was collected and concentrated to small bulk. On cooling 3.4 mg. of porphin crystals were obtained.

A green band followed the porphin band. It had an absorption spectrum similar to that of chlorin with maxima at 481, 489, 534, 582, 602.5 and 631 mμ in benzene solution and at 399.5 (Soret band) 515 and 620 mμ in 20% HCl.

Similar experiments were carried out in which the methiodide was refluxed with ethanolic sodium ethoxide or with aqueous sodium hydroxide followed by acidification and oxidation. Porphin was obtained in each case although in small yield.

Experiments with 2-hydroxymethylpyrrole. 0.1 Gm. (approx. 0.001 mole) of hydroxymethylpyrrole and 2.2 gm. (0.01 mole) of benzoyl peroxide were each dissolved in 50 ml. benzene and transferred to burettes discharging into a 500 ml. conical flask containing 150 ml. benzene and immersed in a water bath at 60°. The solutions from the burettes were added simultaneously drop by drop to the vigorously stirred benzene, the rate of addition being approx. 25 ml. per hour per burette. The solution was then transferred to a separating funnel and the porphin extracted as described above. Yield 5%.

The experiment was repeated with addition of magnesium acetate (0.05 ml. saturated Mg acetate in glacial acetic acid per ml. oxidizing solution) to the benzoyl peroxide solution. Yield 5.3%.

Products with higher and lower acid numbers than that of porphin were also present in both reaction mixtures, but no attempt was made to identify them (Rimington, Mason, and Kennard[10]).

A number of similar experiments were carried out except that benzene solutions of 2-hydroxymethylpyrrole were added to a solution of potassium persulphate in acetic acid at 60°. The addition of magnesium acetate again increased the yield of porphin. A series of experiments was performed using varying quantities of 2-hydroxymethylpyrrole in order to determine the best conditions for porphin formation (see Table I).

Final synthesis of porphin. Ninety-seven mg. of 2-hydroxymethylpyrrole dissolved in 40 ml. water was added slowly over 25 minutes to 200 ml. glacial acetic acid containing 0.2% magnesium acetate, 10 ml. saturated potassium persulphate solution, and maintained at 59–60°. The mixture was then filtered from black amorphous material, 250 ml. water was added and the porphin was extracted into benzene (3 × 150 ml.), the benzene layer was washed twice with 0.35% HCl (50 ml.) and then extracted with 20 ml. portions of 5% w/v HCl until the aqueous layer was almost non-fluorescent. Excess

(11) R. M. Silverstein, E. E. Ryskiewicz, C. Willard, and R. Koehler, *J. Org. Chem.*, **20**, 668 (1955).

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(13) R. E. H. Nicholas, *Biochem. J.*, 48, 309 (1951).

sodium acetate was added and the porphin was re-extracted into benzene (3 × 200 ml.). The benzene solution was distilled to dryness under reduced pressure, the residue redissolved in hot benzene (50 ml.) and purified as previously described.

Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.5; H, 4.5; N, 18.1. Found: C, 77.5; H, 4.7; N, 18.3.

Acknowledgment. I wish to thank Professor C. Rimington for suggesting this problem and for his interest and encouragement.

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Substituted Aminobenzacridines

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Received May 13, 1959

The preparation of a number of substituted 7-aminobenz[*c*]acridines as potential amoebicides has been reported by Elslager and co-workers[1,2] and by Short and co-workers.[3] The present communication deals with the preparation of a number of substituted 7-aminobenz[*c*]acridines and 12-aminobenz[*a*]acridines for trials against *Entamoeba histolytica in vitro*.

The compounds were prepared by the interaction of 7-chlorobenz[*c*]acridine and 12-chlorobenz[*a*]acridine with a slight excess of the appropriate amine in phenol at 120° for 2 hours and isolated as the salicylate as described in an earlier communication by Chatterjee.[4] The compounds were purified by crystallization from 90% ethanol and are shown in Table I.

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(1) E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, 79, 4699 (1957).

(2) E. F. Elslager, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, 80, 451 (1958).

(3) F. W. Short, E. F. Elslager, A. M. Moore, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, 80, 223 (1958).

(4) A. K. Chatterjee, *J. Org. Chem.*, 24, 856 (1959).

Attempted Preparation of Benzpinacol Carbonate

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In an endeavor to synthetize benzpinacol carbonate, needed for a kinetic study, two different methods have been attempted: 1) a base-catalyzed ester-interchange between benzpinacol (I) and diethyl carbonate, and 2) the reaction of phosgene with I in presence of antipyrine, according to the method of Ludwig and Piech.[1] Both methods failed to produce the desired cyclic carbonate. Instead, the first method gave a mixture consisting of benzophenone (II), ethyl benzhydryl, and dibenzhydryl carbonates (III and IV), whereas the sec-

(1) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, 73, 5779 (1951).

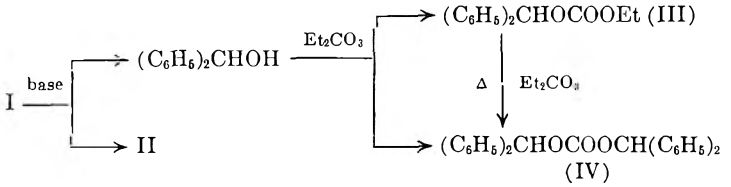
TABLE I[a]

Serial No.	Base	Salt	M.p. of Salt, °C.	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	7-benzylaminobenz[*c*]acridine	1.5 $C_7H_6O_3$[b]	202	76.52	76.81	4.99	4.98	5.18	5.10
2	12-benzylaminobenz[*a*]acridine	1.5 $C_7H_6O_3$	216	76.52	76.49	4.99	4.80	5.18	5.15
3	7-(2-phenylethyl)aminobenz[*c*]-acridine	1.5 $C_7H_6O_3$	204	76.76	76.55	5.23	4.92	5.05	4.90
4	12-(2-phenylethyl)aminobenz[*a*]-acridine	1.5 $C_7H_6O_3$	203	76.76	76.91	5.23	4.80	5.05	5.15
5	7-(3-phenylpropyl)aminobenz-[*c*] acridine	1.5 $C_7H_6O_3$	187	76.98	77.21	5.45	5.53	4.92	4.75
6	12-(3-phenylpropyl)aminobenz-[*a*]acridine	1.5 $C_7H_6O_3$	194	76.98	77.15	5.45	5.55	4.92	4.70
7	7-(4-phenoxybutyl)aminobenz-[c] acridine	$C_7H_6O_3$	174	76.98	77.00	5.66	5.87	5.28	5.19
8	12-(4-phenoxybutyl)aminobenz-[*a*] acridine	$C_7H_6O_3$	172	76.98	76.75	5.66	5.82	5.28	5.20
9	7-*p*-dimethylaminoanilinobenz-[*c*]acridine	1.5 $C_7H_6O_3$	200	74.74	74.50	5.26	5.00	7.37	7.26
10	12-*p*-dimethylaminoanilinobenz-[*a*] acridine	1.5 $C_7H_6O_3$	196	74.74	74.53	5.26	5.13	7.37	7.42

[a] All melting points are uncorrected. [b] $C_7H_6O_3$, salicylic acid.

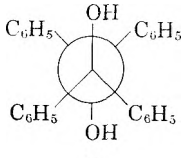
ond one yielded, again, a mixture composed of equimolar quantities of benzpinacolone (V) and tetraphenylethylene oxide (VI) as the only identifiable products.

The reactions involved in the formation of II, III, and IV may be formulated as below:



Accordingly, I first undergoes a base-catalyzed disproportionation into II and benzhydrol, and then the latter produces III and/or IV by ester-interchange with diethyl carbonate.[2] The first stage, involving C—C bond fission, actually represent a reversal of the benzpinacole formation.[3]

The transformation of I into V and VI, is presumably an acid-catalyzed process, which probably proceeds by way suggested by Gebhart and Adams.[4] The above demonstrated ability of phosgene-antipyrine system to cause in I a 1.2-nucleophilic molecular rearrangement paralells that of acetyl chloride–pyridine system,[5] but unlike the former the latter leads only to the formation of V. The action of thionyl chloride-antipyrine on I resembles that of acetyl chloride–pyridine (see experimental). It is worthy to note that unlike the acyl halides, similar treatment of I with acetic anhydride–pyridine resulted only in its cleavage into II and benzhydrol. From the above it is evident that because of the tendency of benzpinacole to undergo easily either molecular rearrangement or a reaction involving C—C bond cleavage, the methods herein described are certainly not applicable for the formation of benzpinacole carbonate. These failures could conceivably be related to conformational factors, as due to the repulsion between the phenyl groups, I most probably tends to exist as the rotational isomer Ia, having the OH groups farther apart, and therefore would not favor the formation of the presumably strained cyclic ester.



Ia

EXPERIMENTAL

Benzpinacol, m.p. 194–195° (from ligroin-benzene) was prepared in 90% yield by the method of Bachmann.[6]

The reaction of benzpinacol with phosgene. A solution containing a mixture of benzpinacol (18.5 g., 0.05 mole) and antipyrine (18 g., 0.1 mole) in dry chloroform (600 ml.) was treated with a 10% solution of phosgene (50 ml.) in toluene in a fashion as described. The reaction mixture was filtered, and from the precipitate 5 g. of crystalline benzpinacolone melting at 172° was obtained, after being thoroughly washed with water. Two recrystallizations, first from chloroform-ethanol, and then from benzene-ligroin, raised the m.p. to 184°. It gave no depression of melting point upon admixture with an authentic sample, prepared according to the method of Bachmann.[7] From the filtrate, 11 g. of residue were obtained after removal of solvents by distillation at reduced pressure. From this residue three identifiable products were isolated upon ether treatment. Two products were obtained from the ether extracted by means of fractional crystallization: (1) 1 g. of benzpinacolone, m.p. 184° (benzene-ligroin), and (2) 1.2 g. of benzpinacole, m.p. 194–195° (benzene-ligroin). From the ether-insoluble residue, 8 g. (46%) of tetraphenylethylene-oxide, a third reaction products, were obtained as colorless needles, melting at 209° (reported[8] m.p. 208°) upon several recrystallizations from ethanol. The yield of analytically pure product was 4 g. (23%).

Anal. Calcd. for $C_{26}H_{20}O$: C, 89.66; H, 5.75. Found: C, 90.11; H, 6.13.

Isolation of ethyl benzhydryl and of dibenzhydryl carbonates (III and IV). In the treatment of benzpinacol (37 g., 0.1 mole) with diethyl carbonate (12 g., 0.1 mole) in the presence of 2 mole % of sodium methoxide, 7 g. (76%) of ethanol, boiling at 78–81°, were liberated after 4 hr. of heating (pot temperature 130°). After removal of unreacted starting materials in the usual way, the residue (42 g.) was subjected to fractional distillation at reduced pressure, whereupon two cuts were obtained: (i) b.p. 112–124° (1 mm.), (20 g.) and (ii) 4 g. of a product boiling at 135–140° (1 mm.), leaving behind 8 g. of a residue (iii) in the distilling flask. Refractionation of fraction (i) gave 12 g. (67%) of benzophenone, b.p. 117° at 1 mm., which solidified upon cooling. Recrystallization from ether gave a crystalline product melting at 47–48°. The infrared spectrum shows bands at 1656 cm.$^{-1}$ (carbonyl), 1631 cm.$^{-1}$, 1580 cm.$^{-1}$

The 2.4 dinitrophenyl hydrazone was crystallized from acetic acid, orange-yellow needles, m.p. 238° (lit.[9] m.p. 238–239°). It gave no depression in mixed melting point with an authentic material. Fraction (ii) was combined with the residue remaining in the distilling flask after redistillation of (i) and the whole was again refractionated. The cut boiling at 140° (1 mm.) was collected yielding on cooling

(2) Since disproportionation of unsummetrical carbonates into symmetrical ones is a possible process [see J. L. R. Williams, D. D. Reynolds, K. R. Dunham, and J. F. Tinker, *J. Org. Chem.*, **24**, 64 (1959)] IV could have well been originated from III by a similar way.

(3) For leading references see, G. W. Wheland "Advanced Organic Chemistry," John Wiley & Sons, Inc., New York, 1949, p. 716–720.

(4) H. J. Gebhart and K. H. Adams, *J. Am. Chem. Soc.*, **76**, 3925 (1954).

(5) W. Thörner and T. Zincke, *Ber.*, **10**, 1475 (1877); see also S. Winstein and R. B. Henderson in Elderfield's "Heterocyclic Compounds," Vol. I, John Wiley & Sons, Inc., New York, 1950, p. 19–20.

(6) W. E. Bachmann, *Org. Syntheses*, **Coll. Vol. II**, 71 (1941).

(7) W. E. Bachmann, *Org. Syntheses*, **Coll. Vol. II**, 73 (1941).

(8) J. F. Norris, R. Thomas and B. M. Brown, *Ber.*, **43**, 2954 (1910).

(9) N. R. Campbell, *Analyst*, **61**, 393 (1936).

4 g. of a solid ethyl benzhydryl carbonate (III). Recrystallization of the latter from ethanol gave white crystals of m.p. 52°. The yield of pure product amounts to 16% of conversion.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.0; H, 6.25; saponif. equiv. 256. Found: C, 74.7; H. 5.8; Sapon. equiv., 260. Infrared: (C=O) 1739 cm.$^{-1}$, (C—H) 1376 cm.$^{-1}$, 1460 cm.$^{-1}$, 3030 cm.$^{-1}$, 1587 cm.$^{-1}$ (phenyl).

Identification of IV. For the purpose of identification, fraction (ii) was subjected to alkaline hydrolysis. Thus, 0.81 g. of (ii) were dissolved in 20 ml. of 0.5*N* ethanolic potassium hydroxide and the resulted solution was refluxed for 2 hr. From the cooled acidified solution, crystalline benzhydrol (0.41 g., m.p. 68–68.5°) was recovered by ether extraction and crystallization from aqueous ethanol. No depression in melting point was observed for a mixture with an authentic sample of benzhydrol (reported[10] m.p. 68°).

Fraction (iii) was purified by its crystallization from ethanol giving colorless crystals of melting point 127°. The yield of this product amounted to 41% of conversion.

Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.2; H, 5.6; mol. wt., 394. Found: C, 82.7; H, 5.5; mol. wt., 380 (Rast).

The infrared spectrum shows bands (cm.$^{-1}$) at 3096, 3067, 3053 (C—H aromatic), 1739 (carbonyl), 1591, 1504, 1460, 1370, 1274.

Identification of (iii). Alkaline hydrolysis of this fraction in a fashion described above again afforded, in 80% yield, colorless needles of benzhydrol (from aqueous ethanol) melting at 68°.

Experiments aimed at converting benzpinacole into tetraphenylethylene oxide by means of a variety of reagents failed. Thus, when benzpinacole was treated with thionyl chloride–antipyrine, phosphor pentoxide in benzene, and polyphosphoric acid (for 1–2 min.), benzpinacoline has invariably been recovered as the only identifiable reaction product.

(10) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," J. Wiley & Sons, Inc., New York, N. Y., 1941.

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Communications TO THE EDITOR

Occurrence of 1-Nitro-2-phenylethane in *Ocotea pretiosa* and *Aniba canelilla*[1]

Sir:

The present communication is concerned with the isolation and identification of the compound responsible for the cinnamon odor of the Brazilian trees *Ocotea pretiosa* (Nees) Mez[2] and *Aniba canelilla* (H.B.K.) Mez[3] (family *Lauraceae*). In both cases the light petroleum ether soluble portion of the benzene extract of the plant material, submitted to chromatography on alumina (activity I) and eluted with benzene, furnished at first fractions rich in methyleugenol and later on fractions with a strong cinnamon-like odor. These, or (in an alternative procedure) the essential oil obtained from vapor distillation of the plant material, were dissolved in light petroleum ether. The solution was extracted exhaustively with 3% aqueous sodium hydroxide. Continuous percolation of chloroform through the alkaline layer removed an oil which was rectified by vacuum distillation.

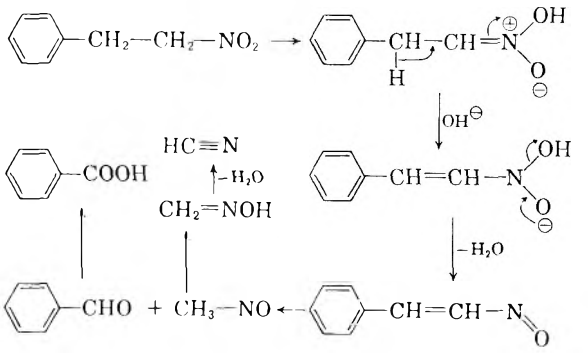
Ocotea pretiosa wood (yield 0.1%) and bark, as well as *Aniba canelilla* wood (yield 0.7%) and bark (yield 0.6%) furnished the same compound when processed in this way; a colorless oil, D_{25}^{25} 1.122, n_D^{25} 1.527, b.p. 130–135° (14 mm.). Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27; O, 21.17. Found: C, 64.04; H, 6.22; N, 8.88; O, 20.69. C—CH_3, N—CH_3, and O—CH_3 groups were absent. The infrared spectrum showed two strong peaks at 6.45 and 7.25μ (primary nitro group[4]), two peaks of medium intensity at 13.30 and 14.30μ (monosubstituted benzene nucleus), and feeble absorption maxima at 8.50, 9.25, 9.72, 11.60μ *inter al.*

Oxidation with hot alkaline potassium permanganate afforded benzoic acid in 60% yield. Hydrogenation at atmospheric pressure, over 10% palladium on charcoal catalyst, resulted in the uptake of 3 mol. of hydrogen and led to β-phenylethylamine (infrared bands at 3.1, 6.28, 13.33, 14.30μ); m.p. of picrate, undepressed by admixture of an authentic specimen, 170–171° (lit. 171°[5]).

Alkaline degradation (30 min. boiling with 3% sodium hydroxide solution or 60 min. boiling with *N* alcoholic potassium hydroxide) yielded benzoic acid (about 15% of the quantity theoretically available from $C_8H_9NO_2$) and hydrocyanic acid (about 20% of the quantity theoretically available from the N of $C_8H_9NO_2$).

The evidence allows the substance to be formulated as 1-nitro-2-phenylethane. This compound is known by synthesis[6] and direct comparison of the natural isolate with a synthetic specimen by physical, organoleptic, and spectral criteria proved their identity. Surprisingly, the authors of the synthesis[6] do not mention the quite obvious cinnamon odor and flavor of the compound.

The products of alkaline degradation, subsequently obtained also from synthetic 1-nitro-2-phenylethane, were at first difficult to explain. However, their formation may be rationalized by alkali catalyzed transformation of the nitro compound into ω-nitrosostyrene[7] which by reverse aldol condensation would give benzaldehyde (and subsequently benzoic acid) and nitrosomethane. It is known that the latter isomerizes readily into formaldoxime[8] and this we have shown to decompose into hydrocyanic acid under the conditions of our alkaline degradation.



1-Nitro-2-phenylethane is the first organic compound to be isolated from plants which possesses as the sole function a nitro group. Very few other natural nitro derivatives have been described. In higher plants apparently only β-nitropropionic acid (as the glucoside)[9] and the aristolochia acids I[10] and II[11] were found.

(1) The authors wish to thank Dr. B. Gilbert, Dr. Roderick A. Barnes, and Dr. Walter B. Mors for useful discussion and the Conselho Nacional de Pesquisas, Brazil, for financial aid.

(2) W. B. Mors, M. Taveira Magalhães, and O. R. Gottlieb, *Perf. Essent. Oil Record*, **50**, 26 (1959).

(3) See E. Gildemeister and F. Hoffmann, *The Volatile Oils*, 2nd ed., Vol. II, p. 500, John Wiley & Sons, New York (1916).

(4) N. Kornblum, H. E. Ungnade, and R. A. Smiley, *J. Org. Chem.*, **21**, 377 (1956).

(5) H. Decker and W. Kropp, *Ber.* **42**, 2078 (1909).

(6) W. Borsche and F. Sinn, *Ann.*, **553**, 260 (1942).

(7) This transformation is essentially an intramolecular oxidation-reduction involving the nitro group and the possibility for an intramolecular equivalent cannot be eliminated by the present data.

(8) K. H. Mueller, *J. Am. Chem. Soc.*, **77**, 3459 (1955).

(9) C. L. Carter and W. J. McChesney, *Nature* **164**, 576 (1949).

(10) M. Pailer, L. Belohlav, and E. Simonitsch, *Monatsh* **87**, 249 (1956).

Full details of the work on the two species mentioned will be reported later.

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Received October 26, 1959

(11) M. Pailer and A. Schleppnik, *Monatsh.*, **88**, 367 (1957).

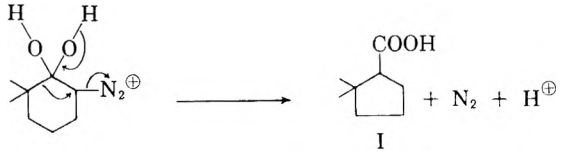
Deamination of α-Aminoketones

Sir:

Observation that nitrous acid deamination of a primary aminoketone derived from the alkaloid lycoctonine[1] gave an acid led us to consider the possibility that aliphatic α-aminoketones would give acids by Favorskii-type rearrangement on deamination.

We have now shown that 2-aminocyclohexanone hydrochloride[2] (prepared by stannous chloride reduction of 2-oximinocyclohexanone) gives up to 57% yields of carboxylic acid when treated with aqueous nitrous acid. This proved to be mainly cyclopentanecarboxylic acid (amide m.p. 179°; anilide, m.p. 165°, showing no melting point depression with authentic derivatives). Similarly, 2-amino-6,6-dimethylcyclohexanone (hydrochloride m.p. 182°, *Anal.*, Calcd. for $C_8H_{16}ONCl$: C, 54.08; H, 9.07; N, 7.82. Found: C, 53.47; H, 9.00; N, 7.92) gave a 25% yield of acid. This was mainly a saturated monocyclic acid $C_8H_{14}O_2$ (anilide, m.p. 125°, *Anal.*, Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.49; H, 8.57; N, 6.44) which on mechanistic grounds and by analogy to the product from 2-aminocyclohexanone should be 2,2-dimethylcyclopentanecarboxylic acid (I). This assignment was supported by its infrared spectrum, which had the pair of peaks characteristic of a *gem*-dimethyl group (ν_{max} 1370 and 1385 cm.$^{-1}$, liquid film), and by the NMR spectrum of its methyl ester, which had two unsplit methyl signals at 186 and 199 c.p.s. (60 Mc, water reference). In addition, the spectrum contained signals due to a single hydrogen with a large chemical shift flanked by one methylene (triplet with J = 6.5 c.p.s. centered about +118 c.p.s.).

We suggest that the positive charge on the amine salt and diazonium ion aid hydration of the carbonyl, and that I is formed by the following mechanism:



I

(1) Unpublished work by O.E.E.

(2) H. E. Baumgarten and F. A. Bower, *J. Am. Chem. Soc.*, **76**, 4561 (1954).

Close analogs are found in the deamination of cyclic α-aminoalcohols[3] and the silver ion initiated rearrangement of α-bromoketones.[4]

Attempts to prepare I by vigorous alkaline treatment of 2-chloro-6,6-dimethylcyclohexanone (m.p. 62°, ν_{max} 1720 cm.$^{-1}$ as Nujol mull. *Anal.*, Calcd. for $C_6H_{13}OCl$: C, 59.81; H, 8.15; Cl, 22.07. Found: C, 59.65; H, 8.09; Cl, 22.33) and by the action of silver nitrate in aqueous alcohol[4] on 2-bromo-6,6-dimethylcyclohexanone (m.p. 58°. *Anal.*, Calcd. for $C_6H_{13}OCl$: C, 46.84; H, 6.38. Found: C, 47.05; H, 6.26) failed to yield more than traces of carboxylic acid. Hence the above deamination may prove a useful alternative to the Favorskii reaction when one carbon alpha to the carbonyl is quaternary.[5] The neutral products of the reaction are under investigation.

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Received November 16, 1959

(3) G. E. McCasland, *J. Am. Chem. Soc.*, **73**, 2293 (1951); D. Y. Curtin and S. Schmukler, *J. Am. Chem. Soc.*, **77**, 1105 (1955).

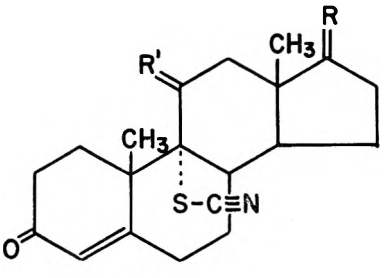
(4) A. C. Cope and E. S. Graham, *J. Am. Chem. Soc.*, **73**, 4702 (1951).

(5) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

Synthesis of 9α- and 11β-Thiocyano Steroid Analogs

Sir:

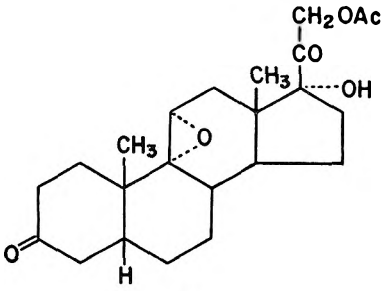
With the intention of finding antimetabolites of steroidal hormones, some thiocyano derivatives of corticoids and androgens (Ia–f and IIIa–b) have been synthesized.



I

(a) R = α-OH, -CO—CH_2OH
R′ = β-OH, -H
(b) R = α-OH, -CO—CH_2OAc
R′ = β-OH, -H
(c) R = =O
R′ = β-OH, -H
(d) R = α-OH, -CO—CH_2OH
R′ = =O
(e) R = α-OH, -CO—CH_2OAc
R′ = =O
(f) R = =O
R′ = =O

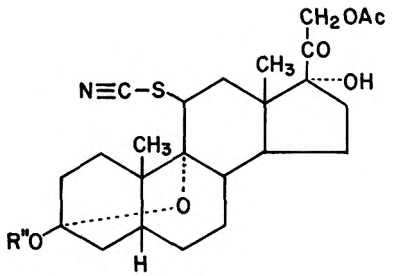
9β,11β-Oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione, its 21-acetate and 9β,11β-oxido-Δ⁴-androstene-3,17-dione with hydrogen thiocyanide solution in acetic acid gave, respectively, 9α-thiocyano-Δ⁴-pregnene 11β,17α,21-triol-3,20-dione (Ia) (yield *ca.* 28%), m.p. 174–175° (dec.), $[\alpha]_D^{20}$ +283.3° (dioxane), λ_{max}^{EtOH} 243 mμ (ε, 13,430), λ_{max}^{Nujol} 4.64μ (S—C≡N) (*Anal.* Calcd. for $C_{22}H_{29}O_5NS$: C, 62.98; H, 6.97; N, 3.34; S, 7.64. Found: C, 63.21; H, 7.16; N, 3.41; S, 7.65), its 21-acetate (Ib) (yield *ca.* 55%), m.p. 149–153° (dec.), $[\alpha]_D^{20}$ +224.9° (dioxane), λ_{max}^{EtOH} 243 mμ (ε, 14,000), λ_{max}^{Nujol} 4.66μ (S—C≡N) (*Anal.* Calcd. for $C_{24}H_{31}O_6NS$: C, 62.45; H, 6.77; N, 3.04; S, 6.95. Found: C, 62.43; H, 6.84; N, 3.25; S, 6.72) and 9α-thiocyano-Δ⁴-androstene-11β-ol-3,17-dione (Ic) (yield *ca.* 35%), m.p. 160–162° (dec.), $[\alpha]_D^{20}$ +248.1° (dioxane), λ_{max}^{EtOH} 242 mμ (ε, 14,200), λ_{max}^{Nujol} 4.67μ (S—C≡N) (*Anal.* Calcd. for $C_{20}H_{25}O_3NS$: C, 66.82; H, 7.01; N, 3.90; S, 8.92. Found: C, 66.72; H, 7.16; N, 4.03; S, 8.44).



II

The chromic acid oxidation of Ib and Ic gave the corresponding 11-oxo compounds, 9α-thiocyano-Δ⁴-pregnene-17α,21-diol-3,11,20-trione 21-acetate (Ie) (with one mol. of methanol of crystallization) (yield *ca.* 64%), m.p. 218–219° (dec.), $[\alpha]_D^{20}$ +333.7° (chloroform), +322.8° (dioxane), λ_{max}^{EtOH} 238 mμ (ε, 16,310), λ_{max}^{Nujol} 4.64μ (S—C≡N) (*Anal.* Calcd. for $C_{24}H_{29}O_6NS \cdot CH_3OH$: C, 61.08; H, 6.77; N, 2.85; S, 6.52; OCH_3, 6.31. Found: C, 61.22; H, 6.84; N, 2.87; S, 6.55; OCH_3, 6.12), and 9α-thiocyano-Δ⁴-androstene-3,11,17-trione (If) (yield *ca.* 76%), m.p. 214–216° (dec.), $[\alpha]_D^{20}$ +453.6° (dioxane), λ_{max}^{EtOH} 236 mμ (ε, 14,270), λ_{max}^{Nujol} 4.64μ (S—C≡N) (*Anal.* Calcd. for $C_{20}H_{23}O_3NS$: C, 67.20; H, 6.49; N, 3.92; S, 8.97. Found: C, 66.97; H, 6.38; N, 4.28; S, 9.00). 9α-Thiocyano-Δ⁴-pregnene-17α,21-diol-3,11,20-trione (Id), m.p. 245–246° (dec.), $[\alpha]_D^{20}$ +337.2° (dioxane), λ_{max}^{EtOH} 238 mμ (ε, 16,200), λ_{max}^{Nujol} 4.63μ (S—C≡N) (*Anal.* Calcd. for $C_{22}H_{27}O_5NS$: C, 63.29; H, 6.52; N, 3.36; S, 7.68. Found: C, 63.37; H, 6.53; N, 3.38; S, 7.62), was obtained in *ca.* 58% yield by hydrolysis of the 21-acetate (Ie) with hydrogen chloride in chloroform and methanol.

The reaction product of 9α,11α-oxido-5β-pregnane-17α,21-diol-3,20-dione 21-acetate (II),[1] m.p. 231–234°, $[\alpha]_D^{20}$ +30.0° (chloroform) (*Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.56; H, 8.13), with hydrogen thiocyanide solution when crystallized from acetone-hexane gave 3α,9α-oxido-11β-thiocyano-5β-pregnane-3β,17α,21-triol-20-one 21-acetate (IIIa) (yield *ca.* 65%), m.p. 155–156° (dec.), $[\alpha]_D^{20}$ +144.4° (chloroform), λ_{max}^{Nujol} 4.62μ (S—C≡N) (*Anal.* Calcd. for $C_{24}H_{33}O_6NS$: C, 62.18; H, 7.18; N, 3.02; S, 6.92. Found: C, 62.07; H, 7.19; N, 3.03; S, 6.96), when the reaction product was crystallized from methanol the 3-methyl-ether (IIIb)[2] resulted (yield *ca.* 36%), m.p. 181–182°, $[\alpha]_D^{20}$ +120.1° (chloroform), λ_{max}^{Nujol} 4.63μ (S—C≡N) (*Anal.* Calcd. for $C_{25}H_{35}O_6NS$: C, 62.87; H, 7.39; N, 2.93; S, 6.71; OCH_3, 6.50. Found: C, 62.85; H, 7.54; N, 3.11; S, 6.58; OCH_3, 6.79).



III
(a) R″ = H
(b) R″ = CH_3

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(1) Prepared by catalytic reduction of the corresponding Δ⁴-compound, J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957). See also A. J. Lemin and C. Djerassi, *J. Am. Chem. Soc.*, **76**, 5672 (1954).

(2) *Cf.* H. Heymann and L. F. Fieser, *J. Am. Chem. Soc.*, **73**, 5252 (1951).

(3) Visiting Scientist (1957–59), National Institutes of Health.

Additions and Corrections

VOL. 19, 1954

A. C. Anderson, Jr. and Shih Yi Wang: An Attempted Synthesis of 1,10-Cyclopentenoheptalene. 1,8-Tetramethyleneazulene.

Page 280. Correct the value of ϵ on the ordinate of the graph in Fig. 2 to read 100, 200, and 300.

Page 282. Correct the λ_{max}, ϵ values for the visible spectrum of 1,8-tetramethyleneazulene to read: 586, ϵ 300; 605, ϵ 350; 630, ϵ 320; 660, ϵ 310; and 730, ϵ 130. ARTHUR G. ANDERSON, JR., MARCH 13, 1959.

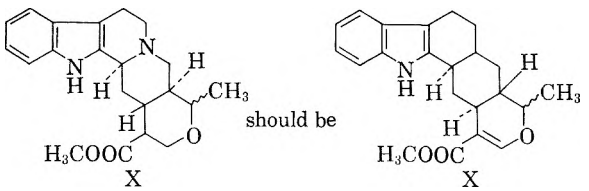
VOL. 22, 1957

E. Campaigne and S. W. Osborn: Improved Procedure for Preparation of Aromatic Thiols.

Page 561. Under Experimental, in col. 2, paragraph 1, lines 4–5, for "60 g. (0375 mole) of technical potassium ethyl xanthate" read "120 g. (0.75 mole) of technical potassium ethyl xanthate." E. CAMPAIGNE, JULY 22, 1959.

Norbert Neuss and H. E. Boaz: Rauwolfia Alkaloids. V. Stereochemical Correlation of Some Indole Alkaloids from the Infrared Spectra.

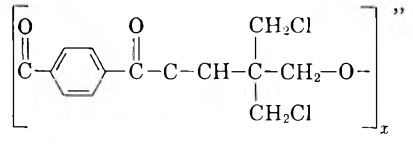
Page 1006. In col. 1, line 8 and line 14, for "the C/D ring" read "the D/E ring." In col. 2,



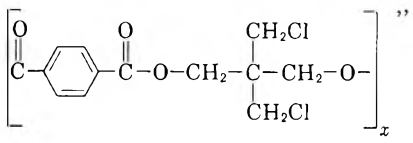
NORBERT NEUSS, JULY 7, 1959.

Tod W. Campbell: Some Reactions of 3,3-Bis(chloromethyl)oxetane.

Page 1032. Col. 1, paragraph 4: for "Thus terephthaloyl chloride and 3,3-bis(chloromethyl)oxetane gave a polymer presumed to be



please read "Thus terephthaloyl chloride and 2,6-dioxaspiroheptane gave a polymer presumed to be



TOD W. CAMPBELL, JULY 28, 1959.

M. S. Kharasch, Robert Malec, and N. C. Yang: Bromination of Octene-1 with *N*-Bromosuccinimide.

Page 1443. The authors failed to acknowledge that a similar article had appeared in the literature by L. Bateman and J. I. Cunneen, *J. Chem. Soc.*, 941 (1950). We sincerely apologize to Drs. Bateman and Cunneen for our negligence. N. C. YANG, NOVEMBER 5, 1958.

VOL. 23, 1958

J. H. Looker and Loren L. Braun: Isomeric 2-Phenoxycyclopropanecarboxylic Acids.

Page 930. We have received a recent communication from Professor Marc Julia directing our attention to a paper which he and G. Tchernoff published in May, 1958 [*Compt. rend.*, **246**, 2897 (1958)]. This article, which describes the characterization of both stereoisomeric 2-phenoxycyclopropanecarboxylic acids, was not available at the time our manuscript was submitted. However, it is obvious that our statement that *cis*-2-phenoxycyclopropanecarboxylic acid apparently was not obtained by Julia and Tchernoff is incorrect and is hereby retracted. As noted by Professor Julia in his communication to us, the chemical procedure employed in his laboratory for assigning configuration and the infrared spectral method we used are in agreement. The article of Julia and Tchernoff cites the study of L. Canonica and A. Fiechi [*Gazz. chim. ital.*, **86**, 710 (1956)], who also obtained the stereoisomeric 2-phenoxycyclopropanecarboxylic acids. We inadvertently overlooked the work of Canonica and Fiechi in the Italian original, the abstract of which appeared after our manuscript had been submitted [*Chem. Abstr.*, **52**, 311 (1958)]. J. H. LOOKER, JANUARY 6, 1959.

N. J. Leonard and C. W. Schimelpfenig: Synthesis of Medium- and Large-Ring Ketones *via* the Dieckmann Condensation.

Page 1708. Add a footnote to Table I, referring to the yield (48%)[+] of II, $n = 15$, as follows: [+]M. Stoll, in a review article [*Chimia*, **2**, 217 (1948)], has mentioned obtaining Exaltone in 20% yield when sodium magnesium ethylate was employed under special conditions. NELSON J. LEONARD, JANUARY 9, 1959.

V. Q. Yen, N. P. Buu-Hoï, and N. D. Xuong: Fluorinated Isatins and Some of Their Heterocyclic Derivatives.

Page 1858. 5-Fluoroisatin was reported as a new compound, the work of Sadler [*J. Org. Chem.*, **21**, 169 (1956)], O'Sullivan and Sadler [*J. Chem. Soc.*, 2202 (1956)], and Holt and Sadler [*Proc. Roy. Soc.*, **B148**, 481 (1958)] on this compound and some of its derivatives having been overlooked as, at the time our work was done, their publications had not yet been indexed in *Chemical Abstracts Tables*. The omission to quote these Authors is much regretted. N. P. BUU-HOÏ, MAY 26, 1959.

Ernest L. Eliel and Ralph G. Haber: The Boiling Points of the Methylcyclohexanols. An Exception to the Conformational Rule.

Page 2041. In col. 2, 5th line above Table, for "smaller" read "larger." ERNEST L. ELIEL, OCTOBER 16, 1959.

VOL. 24, 1959

Ernest L. Eliel and Ralph G. Haber: Conformational Analysis. V. The Reaction of *cis*- and *trans*-4-*t*-Butylcyclohexanol and *trans*-4-Methylcyclohexanol with Phosphorus Pentabromide. Synthesis of Alkylcyclohexyl Bromides.

Page 146. In Table I, after "Cyclohexyl Bromide," for "685" read "658" and for "709" read "687." ERNEST L. ELIEL, OCTOBER 16, 1959.

Alexis A. Oswald: Organic Sulfur Compounds. I. Hydroperoxide Intermediates in the Co-Oxidation of Mercaptans and Olefins.

Page 443. Paragraph 1, next to last line, for "70%" read "77%"

Page 444. Line 1 and line 7, for "$C_{19}H_{16}O_2S$," read "$C_{19}H_{16}O_2S$". Paragraph 2, line 4, for "(m. p., 10°" read "(M. p. −10°." ALEXIS A. OSWALD, APRIL 8, 1959.

Samuel Schalit and Royal A. Cutler: New Dihydrotriazines of Chemotherapeutic Interest.

Page 574. Table I, last entry under "Cryst. Form," add "platelets" to read "white platelets."

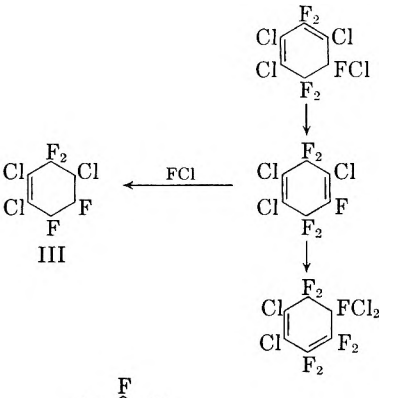
Page 576. Paragraph 3, line 2, for "(0.121 mole)" read "(0.0121 mole)." S. SCHALIT, JULY 9, 1959.

George R. Pettit and Evan G. Thomas: Formylation of Aromatic Amines with Dimethylformamide.

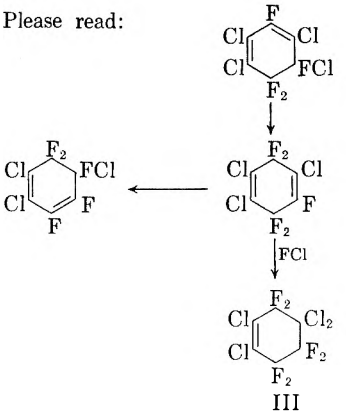
Page 895. Paragraph 3, line 8, for "dimethylformamine," read "dimethylamine." GEORGE R. PETTIT, OCTOBER 7, 1959.

A. J. Leffler: Fluorination of Hexachlorobenzene with Antimony Pentafluoride.

Page 1133. Col. 1, for



Please read:



A. J. LEFFLER, SEPTEMBER 23, 1959.

Everette L. May and J. Harrison Ager: Structures Related to Morphine. XI.

Page 1433. Col. 1, line 19, substitute *O*-demethylate for *O*-methylate.

Page 1435. Col. 2, line 1, add 331 after 316. EVERETTE L. MAY, DECEMBER 14, 1959.

Author Index 1959 VOLUME 24

Subject Index 1959 VOLUME 24