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Preparation and Reactions of *o*-Dilithiobenzene

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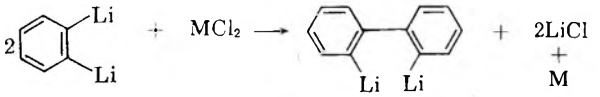
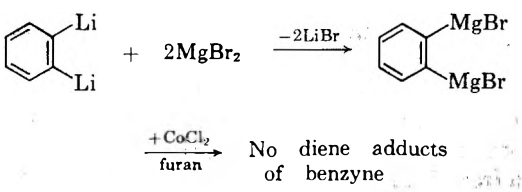
The preparation of *o*-dilithiobenzene from *o*-phenylenemercury is reported. The reactions of *o*-dilithiobenzene with chlorides of the first transition metal series leads to the formation of closed-chained *o*-phenylene compounds (diphenylene, triphenylene, tetraphenylene, etc.) and open-chained ones (diphenyl, *o*-terphenyl, *o*-quarterphenyl, etc.). The yields of these hydrocarbons vary with the transition metal used. Some characteristic properties of *o*-dilithiobenzene distinguish it from other aryllithium compounds.

The preparation of *o*-dilithiobenzene was first reported by G. Wittig and F. Bickelhaupt.[1] The reactions of *o*-dilithiobenzene with various compounds indicated that this valuable new organometallic compound contained two lithium cations bonded to the *o*-phenylene dianion, in itself remarkable since it contains two neighboring anionic carbon atoms. The compound in ether solution has a deep red color and could not be caused to crystallize from ether, but deposited red crystals from a mixed ether–tetrahydrofuran solvent. A number of transition metal chlorides were allowed to react with the new reagent and the resulting hydrocarbons separated and identified.

In the present study the remaining transition metal halides were brought to react with *o*-dilithiobenzene under comparable conditions. The possibility that *o*-dilithiobenzene in these reactions initially coupled to form 2,2′-dilithiobiphenyl could be excluded on basis of the very different yields of hydrocarbons obtained from the reactions of preprepared 2,2′-dilithiobiphenyl and the same transition metal halides.[2]



The intermediacy of dehydrobenzene tentatively was excluded because of the failure to isolate any dehydrobenzene adducts with the commonly used dienes[3] in closely related reactions.[1]

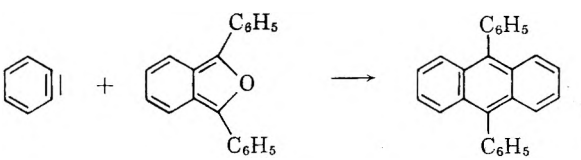


(1) F. Bickelhaupt, Ph.D. thesis, University of Tübingen; G. Wittig and F. Bickelhaupt, *Chem. Ber.*, **91**, 883 (1958).

(2) G. Wittig and G. Lehmann, *ibid.*, **90**, 875 (1957).

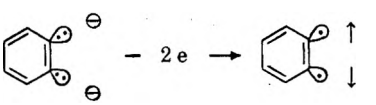
(3) G. Wittig and L. Pohmer, *ibid.*, **89**, 1334 (1956).

In the present work it was shown implicitly that free dehydrobenzene[4] can be excluded as a free intermediate in the reaction of *o*-dilithiobenzene with copper(I) and -(II) chlorides in the presence of 2,5-dimethylfuran or 1,3-diphenylisobenzofuran both of which have proved to be very effective dienes for capturing dehydrobenzene as intermediate. Both of these dienes are not readily



metalated by *o*-dilithiobenzene in contrast to either furan or cyclopentadiene. Copper salts were chosen for this study since only in these cases was there any isolated diphenylene.

That a diradical analog to dehydrobenzene with different properties from dehydrobenzene could be formed in the oxidation process is less likely since the transition metal cations are being reduced by filling their 4*s* orbitals with electrons of different spin, thus leaving a hypothetical nonexcited entity with paired electrons (benzyne).



The complete series of transition metal chlorides were allowed to react with *o*-dilithiobenzene in ether under comparable conditions. The reaction is stoichiometrically a redox process in which the transition metal cation acts as an oxidizing agent for the *o*-phenylene dianion.

The results of these studies are shown in Table I.

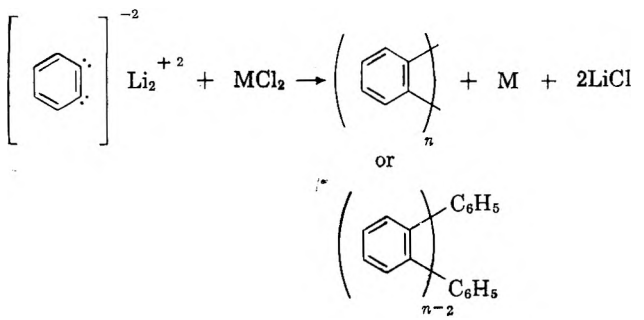
(4) Dehydrobenzene, C_6H_4, also commonly called "benzyne."

TABLE I

REACTIONS OF *o*-DILITHIOBENZENE WITH METAL CHLORIDES

Product[a]	Yields, %											
	Ti^{+4}	Ti^{+2} (1)	V^{+2}	Cr^{+3}	Mn^{+2}	Fe^{+2} (1)	Co^{+2}	Ni^{+2} (1)	Cu^{+2}	Ag^{+1} (1)	Pd^{+2}	Cu^{+1}
C_6H_6[b]	7		5		9		5		6	3	2	2
$C_6H_5C_6H_5$	8	4	15	18	13	26	7	18	2	4	14	22
$(C_6H_5)_2(o\text{-}C_6H_4)$				2		+	+[c]		4	5		7
$(C_6H_5)_2(o\text{-}C_6H_4)_2$		2	8	3		+	+		2	+		
$(C_6H_5)_2(o\text{-}C_6H_4)_4$					9	+				+		+
$(C_6H_5)_2(o\text{-}C_6H_4)_6$						+						
$(o\text{-}C_6H_4)_2$									3			
$(o\text{-}C_6H_4)_3$	18	14	2	14	15	10	26	3	24	15		12
$(o\text{-}C_6H_4)_4$			5				+	11	7	+	9	9
$(o\text{-}C_6H_4)_6$										+		+
$(o\text{-}C_6H_4)_8$							+	18		+		

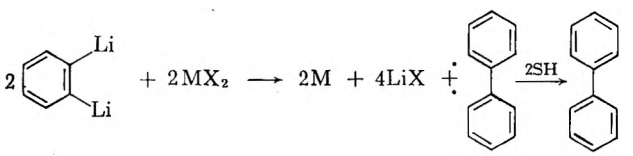
[a] Molar ratios of $n/2$, *o*-dithiobenzene to metal chloride, were used throughout unless otherwise noted (n is oxidation state of metal). [b] Benzene was not sought in all reactions; entries labeled (1) were taken over from ref. 1. [c] A yield of less than 1% is represented by +.



The following observations relative to the information contained therein were judged significant.

1. The yields of the various hydrocarbons appear to depend on the metal cation and the dependence is different from that observed from the same reactions of 2,2′-dilithiobiphenyl.[2]

2. Open-chained *o*-substituted polyphenyls containing the phenyl end groups resulted from the reactions previous to hydrolysis of corresponding organolithium reagents since the color test[5] was negative in all cases before hydrolysis was performed. This appears to be evidence for abstraction of hydrogen atoms from the solvent of an intermediate 2,2′-diphenyl diradical.



Biphenyl may partly have been the direct product from the reaction of phenyllithium, a possible impurity in the *o*-dilithiobenzene.[6] It is necessary, however, to consider the possibility that intermediate organometallic compounds, incapable of giving a positive color test, could have been formed and that these on hydrolysis give the open-chained hydrocarbons.

3. Cyclic *o*-phenylene compounds were formed in varying yields, the following being especially significant: Tetraphenylene was found in significant amounts from reactions with $NiCl_2$, $PdCl_2$, and CuCl whereas octaphenylene was the major product from the reaction with $NiCl_2$ only. Particularly high yields of biphenyl were found in reaction with $FeCl_2$ (also from 2,2′-dilithiobiphenyl). Diphenylene was detected only in the reaction with copper salts. If the relative yields of biphenyl and triphenylene are plotted for the metals Mn^{+2} ($3d^5$), Fe^{+2} ($3d^6$), Co^{+2} ($3d^7$), Ni^{+2} ($3d^8$), Cu^{+2} ($3d^9$), Cu^{+1} ($3d^{10}$), an alternating relationship appears to have been found between the number of electrons in the 3*d* level and the yields of these two hydrocarbons. However, such a relationship does not appear to hold throughout the series studied.

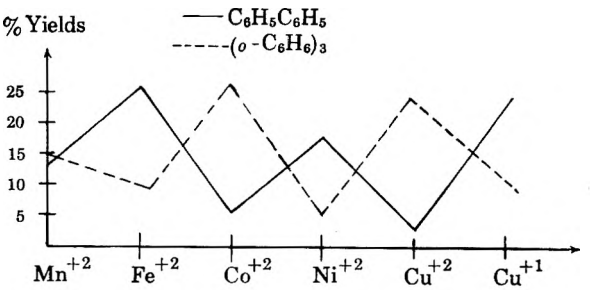


CHART 1

V^{+2} ($3d^3$) and Cr^{+3} ($3d^3$), Ni^{+2} ($3d^8$) and Pd^{+2} ($4d^8$), Cu^{+1} ($3d^{10}$) and Ag^{+1} ($4d^{10}$) show different yields, pairwise, although the number of *d*-electrons are alike in each pair. Hence the electronic configuration does not suffice to explain these observations. (See Chart 1.)

The formation of complexes of the ferrocene or the bisbenzene chromium type[7] was anticipated in the early study. It appears reasonable that not all the ten available electrons of the *o*-phenylene anion nor the eight electrons from the oxidized intermediate (six in the aromatic π-system and four or two in the sp^2-hybridization orbitals of the neighboring carbon atoms) can be accommodated readily in a stable sandwich compound. Counting sixteen electrons back from krypton one arrives at calcium, the chloride of which did not react with *o*-dilithiobenzene.[1] The nodal plane of the four electrons in thr sp^2-system is perpendicular to that of the aromatic system. A possible bis-*o*-phenylene anion metal complex would be difficult to visualize since the orbitals available for ligand bonding are fixed by the geometry of the benzene nucleus and not removed by two atoms, the general requirement for the formation of a chelate with a transition metal.

If a free diradical were the intermediate in these reactions, one would expect very similar results for the var-

(5) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(6) M. S. Kharasch, D. W. Lewis, and W. B. Reynolds, *ibid.*, **65**, 498 (1943).

(7) See Chap. 7 and 8 in H. Zeiss, "Organometallic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1960.

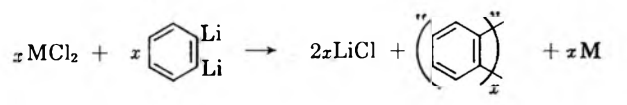
ious transition metals if it is assumed that the same steady state concentration of this intermediate is attained in these reactions. If phenyl radicals were formed to any considerable extent, then the major product would be benzene.[8] Neither of these possibilities are substantiated by the experiments.

An interpretation of these reactions is further complicated by the heterogeneity of the reaction mixture, both the salts and the metals are insoluble in ether. A local enrichment and subsequent coupling of intermediates partially bonded to the surface of the metal would be dependent on the crystalline structure of either the salt or the metal formed. A possible preference of open-chained polyphenyls can be rationalized by postulating a slow decomposition of organometallic intermediates to free radicals thus making the hydrogen atom abstraction from the solvent the chain terminating step.

A related mechanism was postulated in relating the products obtained from the reaction of 2,2′-dilithiobiphenyl with transition metal halides.[2]

The formation of tetraphenylene and octaphenylene in reaction of particular transition metal halides can be considered analogous to the catalytic action of certain nickel complexes in the tetramerization of acetylene to cyclooctatetraene.[8] In these reactions a coordination complex is considered intermediate to the formation of the ring compound.[9] The tempting analogy of a similarly coordinated complex of four dehydrobenzene molecules (formally containing one bent acetylenic bond each) must be considered with reservation since tetraphenylene should predominate as a product of the reaction with nickel salts, a reaction which leads predominantly to octaphenylene. The possible formation of a complex containing two central metal atoms each coordinated to four dehydrobenzene molecules as a route to octaphenylene is only speculative.

A connection between the oxidation potential of the transition metal and product distribution was sought.



The better a metal can function as a reducing agent, the poorer will be the oxidizing power of the metal cation. Thus, the lower the reduction potential of the metal cation the slower one would expect the reaction to proceed and the higher would be the probability for dissociation of intermediate complexes with the subsequent hydrogen atom abstraction from the solvent and the higher the yields of the open-chained compounds. There exists no apparent relation between the reduction potentials and the ratio of open-chained to closed-chained polyphenyls isolated. A dependence of the yields on the presence of lithium halide was observed in the reaction of 2,2′-dilithiobiphenyl with transition metal halides. The effect was studied in the comparable reactions of *o*-dilithiobenzene but no significant effect could be ascertained.

It has been observed that compounds containing organic radicals linked by σ-bonds to a metal such as chromium can be isolated if tetrahydrofuran is used as the solvent. The compounds accommodate one or several molecules of tetrahydrofuran in their coordination spheres.[7] A series of experiments was hence undertaken to attempt the isolation of a complex of the *o*-phenylene dianion coordinated to a metal and tetrahydrofuran. However, the unusual metalating powers of *o*-dilithiobenzene toward tetrahydrofuran made the preparation of *o*-dilithiobenzene in tetrahydrofuran impracticable. It was, however, possible to prepare *o*-dilithiobenzene in ether, remove the ether by distillation, and dissolve the compound in tetrahydrofuran. Reactions of the thus prepared solutions of *o*-dilithiobenzene with nickel chloride gave product distributions entirely different from that observed for the same reaction in ether; neither octaphenylene nor tetraphenylene could be found. This indicates that tetrahydrofuran contains a more strongly liganding oxygen than does ether, and it appears that the solvent molecules displace the weakly bonded *o*-phenylene dianion from the intermediate complex resulting in the much higher yields of simple lower molecular weight fragments. This effect may be coupled with the higher acidity of the α-hydrogen atoms in tetrahydrofuran.

The reactions of *o*-dilithiobenzene with *cis*-dichlorobis(triphenylphosphine)platinum(II) were performed in the hope of isolating a platinum complex of benzyne similar to the acetylene platinum complexes recently prepared by J. Chatt and co-workers.[10] Instead of the expected product there was obtained a mixture of triphenylphosphine platinum complexes.[11]

$$o\text{-}C_6H_4Li_2 + (Ph_3P)_2PtCl_2 \longrightarrow (Ph_3P)_nPt + 2LiCl$$

The plausible intermediacy of benzyne was demonstrated in the reaction of *o*-dilithiobenzene with *p*-bromoanisole. The prime interest in this reaction was concerned with the estimation of the metalating power of *o*-dilithiobenzene. Unusual metalating powers were not observed, neither from the attempted metalation of *p*-bromoanisole in the position *ortho* to the methoxyl group nor in the attempted metalation of diphenylmethane. It was significant, however, to observe the new route to benzyne *via* halogen–metal interconversion. The expected products were found and are shown in Chart 2 (p. 1736).

Experimental

Preparation of *o*-Phenylenemercury.—Sodium amalgam was prepared in a 500-ml. Schlenk tube, preferably of soft glass, since in the latter type glass it was noticed that, after the reaction, the mercury separated more readily as a liquid instead of as a colloidal suspension. To the nitrogen-filled Schlenk tube was added 50 ml. of pure mercury (680 g., 3.4 g.-atoms). The Schlenk tube was heated to *ca.* 50° and 7 g. (0.305 g.-atom) of sodium, cut into pea-size cubes, was added slowly. The exothermic amalgamation procedure provided sufficient heat to proceed to completion without further external heating. The tube was allowed to cool to room temperature before 28.4 g. (0.12 mole) of *o*-dibromobenzene and 150 ml. of ether were added. The Schlenk tube was then sealed under nitrogen and shaken for 5 days. At the end of this time, the tube was opened under nitrogen and 50 ml. of water was added carefully. If on shaking the tube gently the mercury separated readily from the yellow suspension, the work-up was performed according to method 1. However, if a gray colloidal suspension resulted, then the work-up proceeded according to method 2.

(8) W. Reppe, *et al.*, *Ann.*, **560**, 5636 (1957).
(9) T. L. Cairns, *et al.*, *J. Am. Chem. Soc.*, **74**, 5636 (1953).
(10) J. Chatt, G. A. Bowe, and A. A. Williams, *Proc. Chem. Soc.*, 208 (1957); J. Chatt, R. G. Guy, and H. R. Watson, *J. Chem. Soc.*, 2332 (1961).
(11) L. Malesta and C. Carrello, *ibid.*, 2323 (1958).

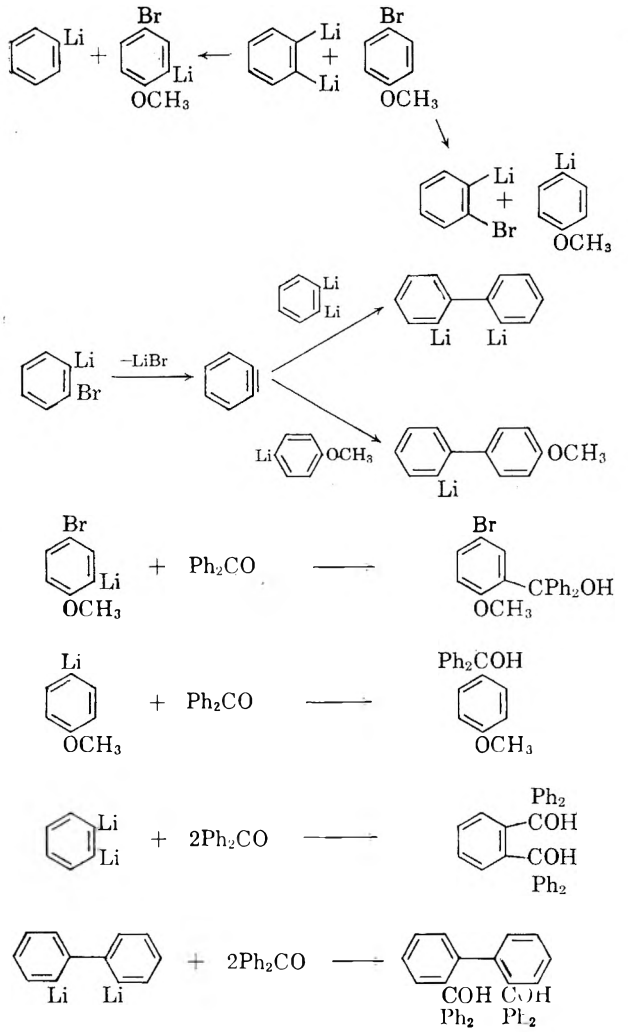


CHART 2

Method 1.—The contents of the Schlenk tube were transferred to a separatory funnel and the mercury removed. The organic and aqueous phases were filtered; solid remaining was washed with water and ether and dried at 80° for 2 hr. This solid was divided in four equal portions and each portion successively placed in 250-ml. round-bottomed flask fitted with a vibro-mixer, N-methylpyrrolidone (100 ml.) was added to the flask and the slurry extracted at 120° for 10 min. under violent agitation. The contents of the flask were decanted into a centrifuge tube and the process repeated with the other portions of crude product. The last traces of mercury were removed by centrifuging these suspensions and the red-brown mother liquors were combined and mixed slowly with 200–300 ml. of methanol, which caused the precipitation of the finely divided *o*-phenylenemercury. This was removed by filtration and the mother liquors concentrated *in vacuo*. The purer fractions thus obtained were combined and recrystallized from dimethylformamide. The product crystallized in small thin needles and was dried at 100° for 24 hr. in a slow current of air. Product melted with decomposition at 332–334°.

Anal. Calcd. for C_6H_4Hg: C, 26.04; H, 1.46. Found: C, 26.24; H, 1.79.

Method 2.—The colloidal suspension was isolated on a filter paper and dried in the air. It was transferred to a cloth which was folded around it and squeezed until no more mercury passed through it. The solid remaining was then treated as described in method 1.

Preparation of *o*-Dilithiobenzene.—Standard solutions of *o*-dilithiobenzene were prepared immediately before the organometallic compound was needed. A 200-ml. Schlenk tube was cleaned with chromic acid cleaning solution and distilled water before drying. The tube was then dried hot by evacuating and filling it three times with purified nitrogen. A few glass splinters were added and 5 g. of *o*-phenylenemercury (sufficient to yield 18 mmoles of *o*-dilithiobenzene). The tube was evacuated still another time to remove the air entrained in the fluffy precipitate. The ether to be used was heated under reflux in the presence of sodium and a trace of benzophenone until the formation of benzophenone ketyl changed the color of the solution to deep blue. The ether then was distilled and kept in the dark over freshly pressed sodium. To the tube being swept by a slow current of nitrogen was then added 50 ml. of ether and 2.6 g. (0.38 g.-atom) of freshly pressed lithium. The lithium was pressed into bands, from a heated sodium press lubricated with a few drops of mineral oil, and cut into short sections falling directly into ether. Another 60 ml. of ether was added after complete transfer of the lithium. The Schlenk tube was sealed under nitrogen and shaken for 4 days. After the elapse of 1 day a brown color was noticed and on complete reaction a deep red solution only containing suspended black mercury and lithium was obtained. It readily may be established whether unchanged *o*-phenylenemercury is present since any such compound can readily be seen as suspended crystals. The agitation should be continued if any such crystals are seen.

Such solutions were analyzed for organolithium content by the method of double titrations (using methyl iodide) according to a published procedure.[12] Agreement was found between the results found by determination of the remaining alkali and subtracting this from the total alkali obtained on simple hydrolysis and the results obtained on determination of the iodide content by the Volhard procedure. The content of *o*-dilithiobenzene was 80–90% of the theoretical not allowing for any volume changes during the formation of the solution of the organometallic compound.

Reaction of *o*-Dilithiobenzene with Transition Metal Halides. General Procedure.—The reactions were performed under comparable conditions by decanting the solution of the organometallic compound through a glass-wool plug in a short section of Teflon tubing connecting the Schlenk tube[13] in which *o*-dilithiobenzene had been prepared with the nitrogen-filled Schlenk tube in which the reaction was to take place. This tube had been dried carefully in advance and the salt (for molar ratios see *a* of Table I) had been introduced and was agitated under 10–20 ml. of dry ether by means of a magnetic stirrer. The reaction vessel was being cooled to −30° in a dry air acetone bath. The reaction usually commenced in the cold, as was evident from darkening of the precipitate and the solution. After 1 hr. at −30° the stirred reaction mixture was allowed to heat to room temperature and color test 1[5] was taken. In most cases it was positive and the tube was sealed under nitrogen and shaken for 1–3 days before the color test was negative, indicating the absence of organolithium compounds.

Work-up was performed in all cases by hydrolysis (in an atmosphere of nitrogen) with water until no more gas was liberated. The solids were removed by filtration and washed on the filter with ether and water before drying. The solids were then placed in the thimble of a Soxhlet extractor and extracted with hot benzene for 5–10 hr. The extracts were concentrated and the oil remaining sublimed *in vacuo* at various temperatures. Only in the case of copper(II) chloride were there any significant yields of hydrocarbon. The organic layer of the filtrates was separated and dried over calcium chloride. This solution was then concentrated to *ca.* 10 ml. and an equal volume of benzene-free ethanol was added. The contents were then transferred to a smaller flask and fractionally distilled to collect any benzene–ethanol azeotrope in the middle fraction. This fraction, and the other ones, for safety, were analyzed for trace amounts of benzene by vapor phase chromatography (v.p.c.). Any irregularities in experimental procedure which could have led to introduction of water would thus have been readily recognizable.

The remaining oil was then evacuated to remove traces of ethanol and triturated with petroleum ether, b.p. 60–70°, before a second removal of the solvent. The oil remaining was then extracted with petroleum ether, b.p. 60–70°, and the extracts passed through a 25-cm. column containing *ca.* 50 g. of neutral alumina. Petroleum ether, b.p. 60–70°, was used as eluent until no more movement of the adsorption bands were noticed. The substance insoluble in petroleum ether was then extracted with cyclohexane (or a mixture of cyclohexane and benzene, 9:1) and these extracts passed through the same column. The chromatogram was developed by the use of cyclohexane, cyclohexane–benzene (9:1), benzene, chloroform, ethyl acetate, and ethanol as eluents. In most cases there was obtained several fractions of triphenylene contaminated with other hydrocarbons. These fractions were extracted with petroleum ether, b.p. 60–70°, and

(12) R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 353 (1951).

(13) See E. Müller, Houben-Weyl, "Methoden d. Org. Chem." I/2, G. Thieme, Stuttgart, 1959, p. 340.

the extracts rechromatographed, eluting with petroleum ether, cyclohexane, cyclohexane–benzene (9:1), and benzene. The pure hydrocarbons were often obtained from this procedure. The fractions of triphenylene remaining after extraction with petroleum ether were recrystallized from ethanol. In some cases the fractions did not dissolve completely in the solvent, and the insoluble residues were often identified as trace amounts of octaphenylene, m.p. 423–425°, presumably swept along with triphenylene.

Reaction of o-Dilithiobenzene with Titanium(IV) Chloride (2:1).—The general procedure was followed, no vigorous reaction occurred and the color test[5] was positive even after the reaction mixture had been allowed to heat to room temperature. The Schlenk tube was sealed and shaken. After 16 hr. of agitation the tube was opened and the color test of the black suspension found to be negative. From the ether phase of the work-up there was obtained by azeotropic distillation with ethanol a fraction which, by v.p.c. analysis, was found to contain benzene amounting to 7% of that expected for the total conversion of o-dilithiobenzene to benzene. The residue from the azeotropic distillation was evacuated and intermittently slurred with petroleum ether (b.p. 60–70°). Chromatography from neutral alumina yielded the compounds shown in Table I.

Part of the triphenylene was recovered as the 2,4,7-trinitrofluorenone complex.

Reaction with Vanadium(II) Chloride.—A sample of this green compound was dried by heating it under refluxing thionyl chloride for 5 hr., followed by removal of the volatile components, and by finally drying for 4 hr. at 95° and for 6 hr. at 130° *in vacuo*.[14] The reaction of 2.44 g. (20 mmoles) of this salt with o-dilithiobenzene (18 mmoles) was carried out under normal conditions. The color test of the reaction mixture was negative after 40 hr. However, a difference in the green color usually obtained in positive color test was observed to develop slowly on addition of the iodine in acetic acid solution. For this reason a titration of the reaction mixture was performed (using methyl iodide instead of benzyl chloride in the double titration method) and it was found that no C–Li was present. The usual work-up gave the indicated yields of aromatic hydrocarbons.

Reaction with Manganese(II) Chloride.—Manganese(II) chloride was dried under refluxing thionyl chloride and then heated *in vacuo*.[14] The dried salt was cream colored, and finely divided; 2.5 g. (20 mmoles) was allowed to react in a Schlenk tube with 18 mmoles of o-dilithiobenzene with 10 ml. of ether. The reaction mixture turned brown and the color test was negative after 16 hr. agitation in the closed Schlenk tube. A strong evolution of heat and/or gas was caused by the hydrolysis. The layers were filtered and the organic phase fractionated as usual with ethanol. V.p.c. analysis indicated the presence of benzene. Careful elution chromatography yielded compounds shown in Table I.

Reaction with Cobalt(II) Chloride.—The cobalt chloride to be used was prepared from cobalt(II) chloride hexahydrate which was placed in a 100-ml. round-bottomed flask into which was distilled thionyl chloride. The apparatus was protected from the atmosphere by a calcium chloride tube. When sufficient thionyl chloride had collected and the flask reached room temperature, then it was equipped with a reflux condenser and the thionyl chloride heated until it refluxed briskly. The cobalt(II) chloride was heated for 4 hr. at which time the evolution of the hydrogen chloride and sulfur dioxide has subsided. The thionyl chloride was removed by distillation and the solid remaining in the flask was dried *in vacuo* (0.1 mm.) for 4 hr. at 120°. The flask was then evacuated and filled with dry nitrogen three times to remove the last traces of thionyl chloride. The lithium chloride used was dried by heating it to 100° for 16 hr. *in vacuo*.

Molar Ratio 1:1.—The reaction was performed as described under the general procedure. An immediate blackening of the light blue suspension resulted. At room temperature there was obtained a brown solution above a black precipitate. The reaction mixture was sealed off and agitated for 3 days at which time the color test was negative. The reaction mixture was hydrolyzed and worked up as described previously. The yields obtained differed insignificantly from those obtained by Bickelhaupt.[1]

Excess Cobalt(II) Chloride.—The reaction was performed as discussed under **Molar Ratio 1:1** but 9.35 g. (72 mmoles, threefold excess) of cobalt(II) chloride was used. The color test was negative after 2 hr. at room temperature and two chromatograms gave the indicated yields (Table II).

TABLE II

Product	Yield, %	M.p., °C.
Benzene	6	
Biphenyl	8	66–67
o-Terphenyl	14	53–54
Triphenylene	15[a]	191–192

[a] This yield was increased by 3% by obtaining from the many colored and oily fractions a complex with 2,4,7-trinitrofluorenone from benzene, m.p. 230–231°. That this complex consisted of a 1:1 mixture of complexing agent and triphenylene was shown by the obtainment of the latter by chromatography.

Molar Ratio 1:1 Containing 1 Mole Lithium Chloride.—To 2.6 g. (20 mmoles) of cobalt(II) chloride was added 0.77 g. (18 mmoles) of lithium chloride and 15 ml. of ether. The suspended salts were allowed to react with o-dilithiobenzene under the same conditions as described previously. The results shown in Table III do not differ significantly from those reported previously.

TABLE III

Product[a]	Yield, %	M.p., °C.
Benzene	5	...
Biphenyl	8	68–69
Triphenylene	17	188–189
Octaphenylene	4	423–424

[a] In some cases o-terphenyl did not crystallize. The yields of noncrystalline o-terphenyl are not reported.

Reaction with Copper(I) Chloride. Ratio 2:1.—Copper(I) chloride was washed with several portions of sulfurous acid and then with glacial acetic acid until the washings were colorless. The solid was then dried in the air until the odor of acetic acid had disappeared and then *in vacuo* at 120° for 6 hr. The reaction proceeded in a manner very similar to that observed for copper(II) chloride and a negative color test was obtained after 24-hr. reaction at room temperature (Table IV).

TABLE IV

Product	Yield, %	M.p., °C.
Benzene	2	
Biphenyl	22	59–60
o-Terphenyl	7	Impure oil
o-Quarterphenyl	1	115–117
Diphenylene	2	111–112
Triphenylene	12	190–191
Tetraphenylene	9	230–231
Hexaphenylene	Trace	325–330

Reaction of Copper(II) Chloride with o-Dilithiobenzene (1:1).—The salt was dried as described under **Cobalt Chloride** using thionyl chloride. The reaction was performed under the usual conditions to give a light green precipitate under a brown solution. The color test was negative after 3 days of shaking. Hydrolysis yielded a precipitate of finely divided copper. The diphenylene was characterized by mixture melting point, infrared spectroscopy (superimposability of a reference spectrum), and melting point and mixture melting point of its red picrate, m.p. 116–118°.

Reaction with Silver Chloride.—Silver(I) chloride was dried at 110° for 4 hr. *in vacuo* and 5.8 g. (40 mmoles) hereof was allowed to react under standard conditions herewith (Table V).

TABLE V

Products	Yield, %	M.p., °C.
Benzene	3	...
Biphenyl	3	59–60
o-Terphenyl	10	53–55
Tetraphenylene	3	228–229
o-Quarterphenyl	1	110–116

Reaction with Chromium(III) Chloride.—The reaction was performed as described under general procedure using 2.5 g. (15.8 mmoles) of chromium(III) chloride and 18 mmoles of o-

(14) The drying procedures were generally those recommended by G. Brauer, "Handbuch d. Präparativen Anoganischen Chemie," I and II, F. Enke, Stuttgart, 1960.

dilithiobenzene. The chromium(III) chloride was purified by heating it in concentrated hydrochloric acid until the reaction discontinued and then it was dried after washing with distilled water *in vacuo* at 200° for 6 hr. The reaction with *o*-dilithiobenzene proceeded in the cold (−30°) to give a dark brown suspension but since the color test was not negative after 1 hr., the tube was sealed and shaken for 3 days after which time the color test was negative. A gas was evolved during the hydrolysis. The following reactions were performed in addition to those shown in Table I using the same general procedure.

Reaction with Palladium(II) Chloride.—The standard reaction of 18 mmoles of *o*-dilithiobenzene with 3.5 g. (18 mmoles) of dry palladium chloride was performed. The color test was found to be negative after 3 days. A very large fraction of an unidentifiable brown oil (15% yield by weight) was obtained in addition to the compounds shown in Table VI.

TABLE VI

Product	Yield, %	M.p., °C.
Benzene	2	...
Biphenyl	14	59–60
Tetraphenylene	9	230–231

Reaction with Thallium(I) Chloride.—The salt was dried at 130° *in vacuo* and 9.6. g. (40 mmoles) thereof was allowed to react under the usual conditions with *o*-dilithiobenzene (18 mmoles). Color test I was negative after 16 hr. A voluminous precipitate was obtained. Since extraction with benzene caused some apparent decomposition noted by the separation of metallic thallium, the extraction was performed under milder conditions over a water bath. The extracts were concentrated to give a precipitate which did not dissolve in benzene after standing overnight in the air. The experiment was repeated and the precipitate, in part obtained by extraction with hot dioxane, was allowed to stand under petroleum ether, b.p. 60–70°. After repeated recrystallizations from a mixture of chloroform and ethanol (20:1), there was obtained a solid which decomposed with gas evolution at 145° and which at its point of decomposition yielded a needle-like product which itself decomposed to a brown liquid at 180–185°.

Anal. Found: C, 85.31; H, 7.61.

Reaction with Copper(II) Chloride in the Presence of 2,5-Dimethylfuran.—The reaction was performed as described previously by the addition of *o*-dilithiobenzene (18 mmoles) to a slurry of 2.8. g. (20 mmoles) copper(II) chloride in 7.5 ml. (69 mmoles) of 2,5-dimethylfuran maintained at −30° (the furan had been distilled under nitrogen from sodium directly into the reaction vessel). The reaction mixture underwent color changes similar to those observed for the same reaction in the absence of the furan. The color test was negative after 2 hr. reaction at room temperature. The usual work-up yielded the compounds shown in Table VII. None of the adduct was isolated or could be detected by its characteristic odor.

TABLE VII

Compound	Yield, %	M.p., °C.
Benzene	8	...
Biphenyl	10	70–72
Triphenylene	8	193–194
Tetraphenylene	17	229–230
o-Terphenyl	1	57–58
o-Quarterphenyl	1	115–117

Reaction with Copper(II) Chloride in the Presence of 1,3-Diphenylisobenzofuran.—A sample of 1,3-diphenylisobenzofuran was purified by recrystallization from cyclohexane, m.p. 131–133°. A slurry of this compound (4.86 g., 18 mmoles) and copper(II) chloride (2.8 g., 20 mmoles) in 20 ml. of ether was placed in the reaction Schlenk tube and the *o*-dilithiobenzene in ether was added to the reaction vessel cooled to −60°. The color test was negative after a reaction time of 1 hr. and heating to room temperature during a second hour. The reaction mixture was worked up essentially as before with the difference that basic alumina was used to prevent decomposition of a possible dehydrobenzene adduct. The precipitate consisting of inorganic and organic substances was filtered and washed with excess ether. The ether layer was worked up as usual by azeotropic distillation and chromatography. The precipitate from the reaction mixture was extracted with benzene, this solution was concentrated, and cyclohexane was added. The material which separated on standing for 16 hr. (1.2 g., m.p. 110–115°) was chromatographed to give 0.5 g. of diphenylisobenzofuran (m.p. 126–128°) and 0.62 g. of *o*-dibenzoylbenzene (m.p. 141–144°). The ether solution on concentration after fractionation gave a yellow substance of considerable melting range. The solid was dissolved in benzene and air was passed through it to oxidize the unchanged 1,3-diphenylisobenzofuran to *o*-dibenzoylbenzene (m.p. 141–142°). The compounds isolated are indicated in Table VIII.

TABLE VIII

Compound	Yield, %	M.p., °C.
Benzene	6	...
Biphenyl	6	60–62
o-Terphenyl[a]	10	...
o-Quarterphenyl	3	115–117
Triphenylene	9	189–190
Tetraphenylene	13	221–232
Hexaphenylene	1	336–338
o-Dibenzoylbenzene	58	141–142

[a] In some cases *o*-terphenyl did not crystallize. The yields of noncrystalline *o*-terphenyl are not reported.

Reaction of Dehydrobenzene with 1,3-Diphenylisobenzofuran.—To substantiate that the proper isolation procedure was used the reaction of dehydrobenzene, prepared by an independent route, with diphenylisobenzofuran was carried out as a control experiment. To a solution of *o*-bromofluorobenzene (1.05 g., 6 mmoles, freshly distilled, 92–94° at 70 mm., $n^{20}D$ −1.5335) and diphenylisobenzofuran (1.6 g., 6 mmoles) in 40 ml. of ether and 20 ml. of tetrahydrofuran was added predried magnesium turnings. The reaction was allowed to proceed at room temperature for 2 hr. and at the boiling point of the solution for 1 hr. After standing for 16 hr. at room temperature, 100 ml. of benzene was added. Concentration after washing with a solution of ammonium chloride (saturated) and drying gave 2.06 g. of a crude product, m.p. 187–188°. One half of this compound (1.0 g.) was dissolved in benzene and oxidized for 12 hr. in a current of air. Chromatography yielded 9,10-diphenyl-9,10-dihydroanthracene-endoxide-9,10 (0.65 g., 62%) and *o*-dibenzoylbenzene (0.24 g., 16%).

Preparation of Dichlorobis(triphenylphosphine)platinum(II).—The complex was prepared according to a published procedure[11] by agitation of a mixture of 5.2 g. of triphenylphosphine and 4.16 g. of potassium tetrachloroplatinate(II) in 100 ml. of 50% aqueous alcohol for 24 hr. The compound was purified by washing it on the filter with excess ether, to remove triphenylphosphine, and with ethanol–water to remove excess inorganic materials, and finally with ether to aid the drying process. The sample was dried *in vacuo* at 80–100° for 16 hr. A sample of this complex (m.p. 308–312° dec.) was analyzed without further purification.

Anal. Calcd. for $C_{36}H_{30}P_2PtCl_2$, $(Ph_3P)_2PtCl_2$: C, 54.68; H, 3.82. Found: C, 54.97; H, 3.85.

Reaction of Dichlorobis(triphenylphosphine)platinum(II). In Benzene–Ether I.—A solution of *o*-dilithiobenzene (prepared from 4.05 g., of *o*-phenylenemercury) in 65 ml. of benzene containing 7 ml. of ether was prepared. The reaction was followed by titrating 3-ml. aliquots by the double titration method.[12] The total solution containing 7.5 mmoles of *o*-dilithiobenzene was added to a suspension of dichlorobis(triphenylphospine)platinum(II) in benzene. The reaction mixture liberated heat and the color of the solution changed from red to brown. The color test was negative after 1 hr. but the reaction mixture was agitated for an additional 4 hr. No care was taken in this experiment to isolate the reaction products in the absence of the atmosphere. There was isolated 2.34 g. of a solid which was partly lithium chloride. The inorganic salt was removed by washing with ethanol and water. The washings were combined, diluted to volume, and aliquots were titrated for chloride content. A total of 12 out of a possible 15 mmoles of lithium chloride was found (80%). Innumerable unsuccessful attempts were made to bring this compound to crystallization. There was obtained a recovery of 1.16 g. of the dichlorobis(triphenylphosphine)platinum(II) (an excess of 1.20 g. of the platinum complex had been present). The brown residues did not yield any crystalline compounds on treatment with the common organic solvents. The amorphous powder

obtained from treatment with ethanol was soluble in chlorinated solvents to give dark red solutions. The brown amorphous fractions (m.p. 120–130°) underwent no observable change on boiling with pyridine, piperidine, 5% aqueous sodium hydroxide, dilute acids, or a solution of diphenylisobenzofuran. Heating of the crude product with thiourea (which combines preferentially with any platinum chlorides present) in benzene–ethanol (1:5) gave a product of similar appearance.

Another sample (0.5 g.) of the product was heated for 2 hr. in boiling concentrated hydrochloric acid. The solid was filtered and washed with ethanol. The filtrates were combined and fractionally distilled. There was found no benzene by v.p.c. in any of the fractions collected. The gray precipitate was recrystallized to yield 0.39 g. (80% recovery) of dichlorobis(triphenylphosphine)platinum(II). The various mother liquors and the filtrate from the crude reaction mixture were evaporated to dryness *in vacuo*, slurred with benzene–cyclohexane (1:7), and chromatographed from 200 g. of alumina. There was obtained the following compounds: triphenylene (partly isolated as the trinitrofluorenone, complex), 17 mg., m.p. 195–196°; various oils, 71 mg.; and triphenylphosphine oxide, 0.90 g., m.p. 154–155°. A red lacquer, m.p. 115–120° dec., was also obtained. The infrared spectrum of the crude but dry product tentatively indicated the presence of *o*-substituted aryl groups in the 600–900-cm.$^{-1}$ region as shoulders on the two monosubstituted phenyl out-of plane deformation absorptions.

In Benzene–Ether II.—The reaction between 6 mmoles of platinum complex (recrystallized from chloroform) and a benzene solution of *o*-dilithiobenzene (analyzed to contain 5.9 mmoles) was carried out as described in I. The reaction vessel, however, was in case a double Schlenk tube containing a fine fritted glass plug between the two compartments.[13] The appearance of the reacting mixture was the same as described under I. The benzene slurry was cooled to −60° and the Schlenk tube sealed *in vacuo*. On thawing the frozen reaction mixture and cooling the second compartment it was possible to filter the solution into the other compartment. Distillation of the benzene solvent of the filtrate was accomplished and the noncrystalline residue from removal of the solvent was agitated with freshly distilled ether. The ether was removed from the dark amorphous residue and carbon monoxide was passed through a furan suspension of this residue. The reaction mixture was freed from solvents and chromatographed by preferential solution, elution chromatography. Several unidentifiable red lacquers were obtained but none of the expected 1,4-dihydronaphthalene-endoxide-1,4 could be detected.

The precipitate which had been obtained by filtration of the original reaction mixture was suspended in the benzene solvent, distilled by cooling the receiver back into the reaction vessel, filtered, and the precipitate was washed with benzene and chloroform to give a benzene- and a chloroform-soluble fraction. From the benzene washings was obtained on evaporation of the solvent and trituration with ethanol, a brown, amorphous solid (0.515 g., m.p. 168–180° dec.). Chloroform washings gave, on fractional crystallization, 3.47 g. of dichlorobis(triphenylphosphine)platinum(II), m.p. 305–307°, identified by comparison of infrared spectra between the sample thus obtained and the starting material. The precipitate from these washings consisted mainly of lithium chloride which was dissolved in ethanol–water, diluted to volume, and aliquots were analyzed to give a total liberation of 11.7 mmoles of lithium chloride (theory, 11.8 mmoles not considering the recovery of 3 mmoles platinum complex, see discussion).

In Ether III.—An ether solution of *o*-dilithiobenzene (prepared from 2.76 g., of *o*-phenylenemercury) was analyzed and part of the solution (containing 4 mmoles of *o*-dilithiobenzene) was added to 3.2 g. (4 mmoles) of dichlorobis(triphenylphosphine)platinum(II) which had been recrystallized from chloroform and heated under refluxing petroleum ether (b.p. 60–70°) for 6 hr. before drying *in vacuo* for an additional 12 hr. at 50°. The reaction did not proceed rapidly at room temperature. The Schlenk tube was sealed off and, after 14 hr. of agitation, the tube was opened and the color test found to be negative. The precipitate was collected on the filter paper under nitrogen and dried in the dark *in vacuo* after successively evacuating the desiccator and filling it with nitrogen. A sample of this solid (m.p. 162–168° dec.) was exposed to the atmosphere and the melting point observed with 24-hr. intervals; there was no significant change in decomposition point. There was found practically no lithium chloride in the ether solution from the filtration of the crude solid. From the filtrates there was obtained two fractions of solids, m.p. 152–154° and 121–123°, respectively. The precipitate (2.66 g.) was extracted with 200 ml. of hot chloroform. These extracts produced 1.03 g. (30% recovery) of unchanged platinum complex. The precipitate from the chloroform extracts yielded 5.2 mmoles of lithium chloride (65%) on extraction with ethanol–water and analysis as before. The chloroform extracts were concentrated and ether was added to give several fractions of brown amorphous solids (m.p. 150–160° dec. with gas evolution). Two of these fractions were analyzed after careful drying.

Anal. Calcd. for $C_{42}H_{34}P_2Pt$, $(Ph_3P)_2PtC_6H_4$: C, 63.38; H, 4.30. Found for sample I: C, 58.13; H, 4.35. Calcd. for $C_{54}H_{45}P_3Pt$, $(Ph_3P)_3$-Pt (m.p. 125–130° dec.): C, 66.04; H, 4.61. Found for sample II: C, 65.34; H, 4.57.

Further evaporation of the solvents and addition of ethanol (since addition of ether only produced oils) gave 0.235 g. of a product, m.p. 149–153°, triphenylphosphine oxide.

Attempted Preparation in Tetrahydrofuran.—To a dry nitrogen-filled Schlenk tube was added 2.6 g. of *o*-phenylenemercury, 1.5 g. of freshly cut lithium, some glass splinters, and 50 ml. of freshly purified tetrahydrofuran. The reaction tube was closed and shaken for 15 days. A gray suspension of lithium metal resulted. The tube was opened intermittently and aliquots analyzed for total base and C–Li content as usual (theory, C–Li 0.4 *N*). It proved impossible to duplicate the total base content of the aliquots removed because of the difference in content of lithium metal of the samples. It was concluded, however, that no or very little C–Li was present since the color test was negative. The mixture was poured on Dry Ice–ether. When the carbonation mixture had reached room temperature, methanol was added to destroy the finely divided lithium metal. Acidification produced a suspension with oily droplets floating on top. Extraction of the gray precipitate (containing drops of mercury) with dimethylformamide (50 ml.) and addition of methanol yielded no recovery of *o*-phenylenemercury. The oils were dissolved in ether and the ether solution dried over anhydrous sodium sulfate. Distillation of the oils remaining after removal of the solvent gave a slightly yellow oil (565 mg.), b.p. 158–160° (0.1 mm.), $n^{20}D$ 1.4893. Infrared analysis showed that the compound was aliphatic and contained a carbonyl group and an ether group.

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.42; H,10.27; O, 16.37; for $C_{12}H_{18}O_2$: C, 74.18; H, 9.34; O, 16.47. Found: C, 73.35; H, 9.58 (O, 17.07).

Reaction with Tetrahydrofuran.—A solution of *o*-dilithiobenzene (analysis 0.25 *N* or 70%) was prepared from 5 g. of *o*-phenylenemercury, 2 g. of lithium, and 100 ml. of ether. The dark red solution was decanted into another nitrogen-filled Schlenk tube and 20 ml. of tetrahydrofuran, freshly distilled from lithium aluminum hydride, was added. The Schlenk tube was then sealed and shaken for 6 days. A red precipitate formed which redissolved after 2 days. Analysis for organolithium compounds (by determining total base and remaining alkali after reaction with methyl iodide) indicated that the solution was 0.04 *N* or more than 80% of the organometallic reagent had decomposed. The analysis was repeated using ethylene bromide for determining the amount of remaining alkali liberated after organolithium compounds including phenyllithium had been removed as a source of alkali on hydrolysis. The solution was now found to be 0.06 *N* in C–Li by this method. The reaction mixture was then poured on Dry Ice in ether. The organic layer was extracted once more with 1 *N* sodium hydroxide and the aqueous layers combined and acidified before repetition of ether extraction. Benzoic acid, m.p. 120–121°, was found in both extracts (673 mg., 32%). The mother liquors were combined and chromatographed twice but no crystalline fractions could be obtained.

Reaction with Nickel(II) Chloride in Tetrahydrofuran.—The normal preparation of *o*-dilithiobenzene in ether was decanted into a double Schlenk tube and the tube was sealed *in vacuo*. This allowed the distillation of the solvent into the other branch. The ether was poured off and 100 ml. of freshly distilled tetrahydrofuran was added to the residue. The red solution which resulted was in one branch and 2.1 g. of nickel(II) chloride, dried as described in a previous report, was added to the other branch. The red *o*-dilithiobenzene solution was concentrated by slow removal of the solvent at room temperature into the other branch over a period of 16 hr. No crystalline products were obtained. The solution had changed appearance to a brown color. The solution was then filtered into the other branch containing the nickel(II) chloride while cooling was provided from the outside. A green solution resulted, but the color changed to a dark brown

during the subsequent increase in temperature to room temperature. At this time the color test was negative. The double Schlenk tube was resealed *in vacuo* and part of the tetrahydrofuran was distilled into the other branch in the hope of isolating a crystalline product. Since none was found hydrolysis was performed and the reaction products isolated as described in a previous section. Chromatography yielded 266 mg. of biphenyl in addition to several fractions of intractable oils which on addition of trinitrofluorenone gave 21 mg. of the triphenylene complex, m.p. 230–232°. Since the solution of *o*-dilithiobenzene had been allowed to stand for 16 hr. at room temperature the reaction was repeated without storing the solution before reaction. The same color changes were noticed and there was found no octaphenylene. Chromatography yielded biphenyl, 256 mg., m.p. 64–65° (18%), and a triphenylene complex with trinitrofluorenone, m.p. 230–231°. Particular care was taken to dissolve the metal to search for octaphenylene but none was found.

Attempted Preparation of *o*-Dilithiobenzene in Ethylene Glycol Dimethyl Ether.—Ethylene glycol dimethyl ether was purified by a standard procedure, b.p. 85°, $n^{20}D$ −1.37965. A slurry of 2.5 g of *o*-phenylenemercury and 1 g. of lithium in 50 ml. of ethylene glycol dimethyl ether was shaken for 7 days. A gray-black suspension resulted. Neither the precipitate nor the solution gave a positive color test. Filtration of the slurry yielded no crystalline product on concentration of the filtrates. A small amount of lithium carbonate was found, 71 mg.

Reaction of *p*-Bromoanisole with *o*-Dilithiobenzene.—Distillation of *p*-bromoanisole under reduced pressures yielded a pure sample, $n^{20}D$ −1.599 (lit. 1.5605), b.p. 132–134° (20 mm.).

A solution containing 18 mmoles of *o*-dilithiobenzene in 100 ml. of ether was added to 3.35 g. (18 mmoles) of *p*-bromoanisole and the reaction mixture was left at room temperature for 15 min. before 6.6 g. (36 mmoles) of benzophenone was added. The color test was negative after 10 min. and hydrolysis with water was performed. The aqueous extracts of the organic phase contained 9.6 mmoles of lithium bromide (on Volhard analysis). The *p*-bromoanisole remaining was recovered by distillation, 2.3 g. (35%), and partly also by later chromatograms. Biphenyl was contained in the higher boiling fractions (estimated 150 mg.). The oils remaining from the distillation were combined and chromatographed. A fraction containing 34% biphenyl and 66% *p*-bromoanisole was obtained in addition to several oily and solid fractions. These fractions were recombined and chromatographed anew. From the second chromatogram was obtained *o*-xylyleneglycol-tetraphenyl, 776 mg. (1.75 mmoles); this sample showed no depression with an authentic sample, m.p. 196–197°; 2-methoxy-5-bromotritanol, 1.13 g. (3 mmoles); *p*-methoxytritanol, 1.40 g. (3.8 mmoles). Several other fractions were obtained but none corresponding to *p*-methoxybiphenyl, bis(*p*-methoxyphenyl). A fraction, m.p. 121–122°, was assigned the structure 2-*p*-methoxyphenyltritanol on basis of spectral data and analysis. In addition there was obtained a compound, 0.5 g., m.p. 246–247°, after several recrystallizations. This compound gave no melting point depression with bis(-2-diphenyloxymethyl)diphenyl, m.p. 246–247°.

Attempted Metalation of Diphenylmethane with *o*-Dilithiobenzene.—Diphenylmethane was purified by distillation. A solution containing 18 mmoles of *o*-dilithiobenzene was added to 36 mmoles of diphenylmethane in ether (5.7 g.). The reaction mixture was left standing for 16 hr. before 6.6 g. of benzophenone was added. The color test was negative almost immediately after addition and the reaction mixture was worked up by removing 5.185 g. (91%) of diphenylmethane by distillation. From the residue left after the removal of the diphenylmethane there was obtained 2.876 g. (22%) of tetraphenyl-*o*-xylylene glycol, m.p. 196–197° (lit. reports a 15% yield). The mother liquors yielded 1.807 g. of benzophenone (27% recovery), m.p. 48–49°, on distillation and the oils now remaining were chromatographed to yield triphenylmethane, 33 mg. (probably present in the diphenylmethane as an impurity). There was found no tetraphenyl-*o*-xylylene glycol from this chromatogram, 18 mg. of tritanol, and a total of 130 mg. of tetraphenylphthalan after the various oily fractions were dehydrated with glacial acetic acid.

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Base-Catalyzed Reaction of Acetylene and Vinylacetylenes with Carbonyl Compounds in Liquid Ammonia under Pressure

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A high productivity, catalytic method for the ethynylation of aldehydes and ketones to the corresponding secondary and tertiary acetylenic carbinols is described. The method uses catalytic amounts of potassium or sodium hydroxide in liquid ammonia with acetylene, vinylacetylene, or isopropenylacetylene under pressure.

The condensation of aldehydes and ketones with acetylene at atmospheric pressure in the presence of excess, finely divided potassium hydroxide is known as the Favorskiĭ[1,2] reaction. At temperatures below 5° ethynylcarbinol (I) is formed almost exclusively, while acetylenic glycol formation predominates at higher temperatures (25–35°).

$$3R_1R_2C{=}O + 2CH{\equiv}CH \xrightleftharpoons{KOH} R_1R_2C(OH){-}C{\equiv}CH \;(\mathbf{I}) + R_1R_2C(OH){-}C{\equiv}C{-}CR_1R_2(OH) \;(\mathbf{II})$$

This reaction, since its discovery, has been extensively studied[3–6] and modified.[7–10] Results of these investigations have shown that ether, acetal, or amine solvents used with stoichiometric to excess amounts of finely ground potassium hydroxide give optimum results at atmospheric pressure (Favorskiĭ conditions).

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To avoid the use of excess base, a number of catalytic processes have been reported through the years utilizing the mass action effect of excess acetylene under pressure, polar solvents, or various catalysts. Prominent among these methods are those of Reppe[11] (heavy metal acetylides), Whitfield[12] (basic ion exchange resins), Schachat and Bagnell,[13] Blumenthal[14] (polar solvents either at atmospheric or higher pressures), and Nedwick and Watanabe[15] (continuous high pressure liquid phase technique). Recent work[8,13,14] has emphasized the fact that the ethynylation reaction gives maximum catalytic results in highly polar organic solvents (dimethylsulfoxide, N-methylpyrrolidone, and hexamethylphosphoramide, etc.). These results are in agreement with data[16] on the high solubility of acetylene in donor solvents.

However, preceding catalytic methods for general use with aldehydes and ketones are limited, due to either low conversions,[11,12,15] failure to react successfully with aldehydes and sensitive ketones,[12,13,15] or isolation problems.[13,14] Polar solvents boiling in the broad range of 80–200° have a characteristic tendency to form stable hydrogen-bonded complexes with the resulting polar ethynylcarbinols. Consequently, either inseparable azeotropes result with the more volatile solvents (acetonitrile, ethylenediamine, and dioxane) or else the higher boiling carbinols cannot be readily distilled pure from the tenacious solvent. To eliminate this problem, isolation is generally effected by dilution with water, followed by ether extraction, and subsequent fractional distillation. This method, besides being tedious, is still somewhat unsatisfactory since some of the polar solvent is also extracted into the ether layer.

In contrast, liquid ammonia, well known as a solvent for noncatalytic acetylene reactions,[17] should be free of isolation problems with the majority of ethynylcarbinols, due to its low boiling point (−33°). Furthermore, the use of catalytic amounts of alkali hydroxides in liquid ammonia with excess acetylene under pressure might lead to a more efficient ethynylation system. Solubility studies of acetylene in liquid ammonia under pressure at temperatures from −40° to +30° showed a large and fairly constant solubility of approximately 1 mole of acetylene per mole of ammonia. This small change in acetylene concentration in the liquid phase over a wide temperature range strongly indicated the formation of a hydrogen-bonded complex (H—C≡C—H···NH_3), and strengthened the belief that liquid ammonia should be a superior reaction medium. Subsequent work verified the above assumptions.

The ammonia–alkali hydroxide–acetylene system is so specific for ethynylation that even a base-sensitive aldehyde such as acetaldehyde gives conversions of 30–50% depending on the initial aldehyde concentration. Higher aliphatic aldehydes (propionaldehyde, isobutyraldehyde, and 2-ethylhexaldehyde) give minor to insignificant amounts of expected side products such as aldols, aldehyde–ammonia adducts, and Schiff bases. Formaldehyde, however, either as 30% formalin, or paraformaldehyde was the only aldehyde observed not to yield any acetylenic carbinol (1-propyn-3-ol).

The liquid ammonia system is characterized by a much higher productivity of ethynylcarbinol per unit solvent volume than that realized by earlier methods. When 18 moles of acetone reacted in a system composed of 24 moles of acetylene, 1.5 moles of potassium hydroxide, and 500 cc. of liquid ammonia, a minimum yield or conversion of 75% (1138 g.) to pure, distilled 3-methyl-1-butyn-3-ol is realized with a catalytic conversion based on potassium hydroxide of 900% (*cf.* Table I). In contrast, the highly polar dimethyl sulfoxide when used under identical conditions gives a conversion to methylbutynol of only 42% based on ethynyl group analysis.[21] In practice pure methylbutynol can be isolated only in 15% conversion by direct distillation; therefore, actual results are considerably inferior to those in ammonia.

TABLE I

3-METHYL-1-BUTYN-3-OL. VARIATION OF CONVERSION[a] (YIELD) AND PRODUCTIVITY[b] WITH ACETONE LOADING[c] AND SOLVENT

Acetone loading, moles	Solvent, 500 cc.	Per cent distilled conversion based on (—C=O)	Per cent distilled conversion based on KOH	Productivity MB (2), g.
1	NH_3	95	95	80
6	NH_3	95	381	478
12	NH_3	82	660	830
12	NH_3[d]	81	647	815
18	NH_3	75	902	1138
24	NH_3	52	835	1050
1	Methylal	90	60	76
18	Methylal	32	388	487
18	Acetone	23	276	347
1	Diisopropyl ether	80	53	67
10	Diisopropyl ether	16	107	135
18	Dimethyl sulfoxide[e]	42	497	635

[a] Conversion is defined as the moles of ethynylcarbinol formed divided by the moles of ketone or base used times 100. Where the conversion is in the 75–90% range excess acetone is usually not recoverable and yield and conversion are identical. For example, at low conversions (16–32%) excess acetone is recoverable but yields are seldom higher than 70–80% due to the formation of ketone self condensation products such as mesityl oxide, phorone, and losses due to entrainment. [b] Productivity is the total weight (g.) of ethynylcarbinol obtained from 500 cc. of solvent. MB is 3-methyl-1-butyn-3-ol. [c] Loading is the concentration in moles, of carbonyl compound used in 500 cc. of solvent. In all catalytic runs described in Table I, 1.5 moles of NaOH or KOH are used with 24 moles of acetylene to ethynylate 6–24 moles of carbonyl compound at 30–35° under ambient (190–200-p.s.i.g.) pressure. One-mole acetone runs were carried out at atmospheric pressure and 0–5° using 1.5 moles of acetylene and 1.5 moles of KOH, except in the case of liquid ammonia where a stoichiometric amount of KOH and acetylene can be successfully employed at −40 to −45°. [d] Powdered NaOH (96%) was used as catalyst in place of KOH. [e] Methylbutynol could not be isolated pure by simple distillation. Data are based on solution analysis (ref. 21).

When vinylacetylene and isopropenylacetylene (3-methyl-3-butene-1-yne) are substituted for acetylene under previous conditions (*cf.* Table III) using methyl ethyl ketone and acetone concentrations (loadings) of 18 moles and 6 moles, respectively, conversions of 46% and 69% based on ketone of the corresponding eneyn-ols are obtained. The corresponding catalytic con-

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Table II

CATALYTIC ETHYNYLATION OF KETONES AND ALDEHYDES IN LIQUID AMMONIA[a]

Carbonyl compound	2° or 3° ethynyl carbinol	Loading, moles	Reaction conditions: Time, hr.	Temp., °C.	Pressure, C_2H_2	Per cent distilled conversion based on: (>C=O)	KOH	B.p., °C.	Press., mm.	Purity[b]
$(CH_3)_2CO$	3-Methyl-1-butyn-3-ol	18	4	20–27	154–184	75	900	104–105	760	99–100
$C_2H_5COCH_3$	3-Methyl-1-pentyn-3-ol	18	2	28–35	176–239	67	800	121–122	760	99–100
$C_2H_5COC_2H_5$	3-Ethyl-1-pentyn-3-ol	6	4	0–6	110–180	66	264	138–140	760	97–99
$(CH_3)_2CHCH_2COCH_3$	3,5-Dimethyl-1-hexyn-3-ol	17	5	30–35	151–174	47	524	150–151	760	97–99
$C_6H_{10}O$	1-Ethynylcyclohexanol	18	2	30–42	290–309	71	846	102–103	50	99–100
$C_6H_5COCH_3$	3-Phenyl-1-butyn-3-ol	12	4.5	35–40	324–376	58	463	110–112	10	95–98
CH_3CHO	1-Butyn-3-ol	6	3	0–5	75–135	31	178	106–107	760	92–97
C_2H_5CHO	1-Pentyn-3-ol	5	3	19–27	195–220	46	587	72–74	100	93–99
C_3H_7CHO	1-Hexyn-3-ol	6	4	18–20	190–230	53	206	88–89	100	98–100
$(CH_3)_2CHCHO$	4-Methyl-1-pentyn-3-ol	12	4	25–30	190–205	72	615	79–81	100	97–99
$C_4H_5CH(C_2H_5)CHO$	4-Ethyl-1-octyn-3-ol	7.3	4	18–20	340–350	75	650	106–126	50	96–99

[a] A standard charge of 500 cc. of liquid ammonia, 1.5 moles of powdered (90%) KOH, and 24 moles of acetylene (dry) was used in all runs. [b] Purity is based on solution analysis (ref. 21).

TABLE III

CATALYTIC[a] FORMATION OF SECONDARY AND TERTIARY ENE-YN-OLS[b] AT 30–40°

Moles	Ene-yne	Moles	Carbonyl compound	Distilled[c] conversion based on: >C=O	KOH	B.p., °C.	Press., mm.	Purity by (C, H, O)
6	$CH_2=CH-C\equiv CH$	6	$(CH_3)_2CO$	62	249	68	24	96.5
12	$CH_2=CH-C\equiv CH$	6	$(CH_3)_2CO$	54	217	68	24	...
18	$CH_2=CH-C\equiv CH$	18	$CH_3-COC_2H_5$	46	554	75	20	98.0
6	$CH_2=CH-C\equiv CH$	6	$(CH_3)_2CHCHO$	52	209	173–175	760	97.5
6	$CH_2=CH-C\equiv CH$	6	$C_4H_9CH(C_2H_5)CHO$	61	242	228–230	760	99.0
6	$CH_2\equiv C(CH_3)C\equiv CH$	6	$(CH_3)_2CO$	69	274	70	14	99.4
12	(3) $CH_2=C(CH_3)C\equiv CH$	18	$(CH_3)_2CO$	21	982	[d]		[d]
12	$CH\equiv CH$			60				
				Total 81%				

[a] Ethynylation charge was 500 cc. of ammonia and 1.5 moles of KOH used with carbonyl and ene-yne loadings specified in table. [b] The following ene-yn-ols are obtained from the above reactants: VA = vinylacetylene, IPA = 3-methyl-3-butene-1-yne: VA + acetone, 2-methyl-5-hexene-3-yn-2-ol; VA + methyl ethyl ketone, 3-methyl-6-hexene-4-yn-3-ol; VA + isobutyraldehyde, 2-methyl-6-heptene-4-yn-3-ol; VA + 2-ethylhexaldehyde, 6-ethyl-1-decene-3-yn-5-ol; IPA + acetone, 2,5-dimethyl-5-hexene-3-yn-2-ol. [c] Conversions are defined in footnote *a*, Table I. No attempt was made to recover the low boiling VA, hence yields cannot be given, although they are probably higher. For example, the mixed acetylene–IPA run (12 moles each) gave a total conversion of 81% and a total yield of 95% based on careful recovery of starting materials. (Total catalytic yield based on KOH is 1134%.) [d] The products were readily separable by distillation to give typical (*cf.* table) purity values, which are the average of C, H, O combustion analyses.

versions based on potassium hydroxide are 554% and 274%. The competitive reaction of 12 moles each of isopropenylacetylene and acetylene with 18 moles of acetone results in a 60% conversion to methylbutynol and a 21% conversion to the ene-yn-ol, 2,5-dimethyl-5-hexene-3-yn-2-ol, with a total catalytic conversion of 982%. The results of Tables II and III show that vinyl- and isopropenylacetylenes are comparable in ethynylation reactivity, but noticeably inferior to acetylene.

The results in Table I show the variation in ketone and potassium hydroxide conversions together with grams of methylbutynol produced at different acetone concentrations (loadings) in 500 cc. of solvent. The superiority of the catalytic ammonia system over stoichiometric ethynylation in typical Favorskiĭ solvents is clearly evident. Further, a marked drop in conversion is noted at atmospheric pressure in methylal, if the acetone loading is increased substantially beyond one mole.[8] Total yields and conversions are generally 5–10% higher than the distilled values. As shown in the formation of methylbutynol, the liquid ammonia system can produce eight to ten times more ethynylcarbinol per unit of solvent than typical ether or acetal solvents using the noncatalytic method at atmospheric pressure. The point of diminishing returns is reached beyond 18 moles of ketone. A 23% drop in conversion (75%–52%) results at a 24 moles loading of acetone.

A further, interesting property of this solvent system is the high specificity for ethynylcarbinol formation. No significant amount of 1,4-acetylenic glycol is obtained at temperatures of 20–40° even when a stoichiometric amount of acetylene is used. When acetal or ether type solvents are used at atmospheric pressure with excess base only by operating at temperatures below 5° are good conversions to the ethynylcarbinol realized. At higher temperatures (20–40°) the acetylenic glycol is the principal product.

While sodium hydroxide (powdered) cannot be employed successfully using Favorskiĭ conditions, it gives results comparable to potassium hydroxide in liquid ammonia particularly at high ketone loadings as shown in Table I. The results in Table II show that the average productivity (grams) of ethynylcarbinol in 500 cc. of ammonia even for less reactive ketones is quite high (900–1200 g).

Potassium acetylide prepared *in situ* in liquid ammonia was found to be a good ethynylation catalyst, but

surprisingly inferior to sodium or potassium hydroxides in the critical loading (concentration) range of 18–24 moles of ketone. Using standard reaction charge of 18 moles of acetone, 24 moles of acetylene, and 1.5 moles of potassium acetylide in 500 cc. of ammonia, conversions based on acetone and potassium acetylide were 45% and 545%. These results show that potassium acetylide is approximately half as effective a catalyst as either potassium or sodium hydroxide, and indicates that base-catalyzed ethynylation may not proceed through the intermediate formation of alkali metal acetylide[18] from the corresponding hydroxide. An attempt to ethynylate acetone (18 moles) in the absence of base gave a 4% total conversion to methylbutynol, showing that solvated acetylene is not present in any degree as the hypothetical ammonium acetylide. This species would presumably react with acetone in a manner analogous to sodium acetylide.

Experimental

General Ethynylation Procedure.—All catalytic runs were carried out in a 1-gallon stainless steel autoclave,[19] equipped with an inner coil, jacket cooling, and a turbotype stirrer. The total free volume of the autocalve was 3800 cc. when the head (includes coil, stirrer, and thermocouple well) piece was in place. The autoclave had a 1000-p.s.i.g. blowout disk which was substantially below its maximum rated operating pressure (7500 p.s.i.g.). Efficient cooling to as low as −40° could be realized by the use of a 3-gallon, Dry-Ice cooled, refrigeration system using an equal volume mixture of methanol and ethylene glycol as the circulatory coolant.

Ammonia was introduced as liquid under its own vapor pressure to a graduated glass pressure buret,[20] or weighed directly into the autoclave. Acetylene could be conveniently measured and introduced by the use of a 1-l. to 1-gallon high pressure cylindrical buret. The buret was calibrated in terms of pressure drop (p.s.i.g.) *vs.* liters of acetylene. Moles of acetylene introduced at a given temperature were calculated from the Ideal Gas Law. Vinyl- or isopropenyl acetylenes were conveniently introduced *via* the pressure buret.

The ethynylation was started by quickly adding 92 g., 91.4%, of powdered potassium hydroxide (84 g., 100%, 1.5 moles) to the dry autoclave under a nitrogen atmosphere, and immediately sealing the autoclave. The reactor was purged several times with 50–100-p.s.i.g. portions of nitrogen followed by venting to zero-gage pressure. The reaction temperature was lowered to 0 to 5° and liquid ammonia (500 cc.) and acetylene (24 moles) were consecutively added. The liquid ammonia–potassium hydroxide mixture was stirred during acetylene addition. Ammonia and acetylene can be introduced at 25–30° if desired, but the addition is much faster if prior cooling is used. The initial pressure of the potassium hydroxide–ammonia mixture at 0–5° is 60–75 p.s.i.g. After the introduction of 24 moles of acetylene the total pressure is 190–200 p.s.i.g.

The reaction temperature was raised to the 25–40° range and optimum reaction temperature determined (*cf.* Tables I, II, and III). The carbonyl compound (6–18 moles) was added uniformly during a period of 15 min. to 1 hr. For more reactive aldehydes such as acetaldehyde and propionaldehyde an addition time of 1–2 hr. is preferable. A slight reaction exotherm was noted during a 1–2-hr. reaction time, and intermittent cooling was applied to maintain the desired reaction temperature. For the more reactive carbonyl compounds reaction is complete in about 30 min. or less.

Isolation was effected by venting the ammonia and acetylene either into a cooled (−30 to −50°) pressure vessel or directly to the atmosphere. During the venting about 500 cc. of a replacement solvent (diethyl or diisopropyl ether, hexane, etc.) was gradually added over a period of 15–30 min. It was preferable to allow the venting of ammonia to proceed overnight to avoid loss of product by entrainment. When the autoclave temperature again reached 25–35° (cooling effect due to ammonia evaporation), the vapor space was purged with two 100-p.s.i.g. nitrogen chasers, and the reactor then cooled to 0–5°.

Dry carbon dioxide gas was then added to the autoclave to a pressure of 200 p.s.i.g. and this pressure maintained for 10 min. with good stirring. The excess carbon dioxide was then vented and the autoclave contents removed. The resulting mixture of ethynylcarbinol, solvent, a minor amount of unchanged carbonyl compound, and ammonium (small) and potassium bicarbonates was filtered to remove inorganic salts which were washed with solvent. An alternate method of isolation involved the usual addition of water instead of carbon dioxide, followed by layer separation, neutralization of the organic layer with carbon dioxide, azeotropic removal of water, and finally distillation. The combined organic phase was fractionally distilled through a column of about 15–20 theoretical plates. The choice of replacement solvent was dictated primarily by the boiling point distribution of the carbonyl compound and the resulting ethynylcarbinol. If the boiling point difference between an ether solvent and an ethynylcarbinol was less than 20°, difficulty was often experienced due to azeotrope formation. A one-pass careful fractionation was sufficient in most cases to yield purities of 96–99.5%.

The simplest and most direct method[21] of analyzing the ethynylcarbinols is to treat the compound with 50% silver nitrate followed by titration of the liberated nitric acid with standard alkali using methyl purple indicator. Vapor phase chromatographic analysis using pure starting carbonyl compound and ethynylcarbinol as references has also been used successfully, but offers no advantages over the volumetric method.

Acknowledgment.—The authors wish to thank Mr. Joseph Improta for his valuable assistance in setting up and operating the reaction system.

(18) R. J. Tedeschi, work to be published in connection with the mechanism of base-catalyzed ethynylations.

(19) High pressure stainless steel autoclave, designed and fabricated by Autoclave Engineers, Inc., serial no. 10943, working pressure, 5000 p.s.i.g.; test pressure, 7500, p.s.i.g.

(20) Strahman glass pressure buret (100 cc.), type 100 c, size 7, working pressure, 2000 p.s.i.g.

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Preparation and Solvolysis of 6β,19-Oxido-17-ethylenedioxy-3α,5α-cycloandrostane

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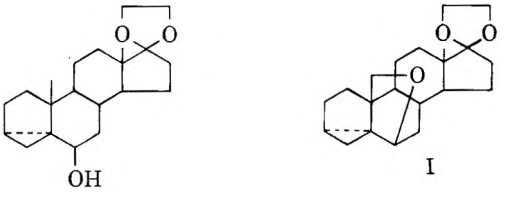
Lead tetraacetate oxidation of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane led to the isolation, in 22% yield, of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I). A study was made of the solvolytic behavior of I under conditions of acid catalysis. The nature of the solvolysis products indicated that the 6β,19-oxide ring is cleaved with C-6 oxygen heterolysis to yield the 19-hydroxyhomoallylic cation, and that the stereochemistry of the reactions of this intermediate at both C-3 and C-6 is analogous to that of related 10-methyl-homoallylic cations. Reactions of I were, thus, those anticipated from the solvolysis reactions of 6-substituted 10-methyl-3α,5α-cyclosteroids.

Recently a number of methods[1] have been developed to introduce functional groups at the C-10 and C-13 angular methyl groups of steroids. In each method advantage has been taken of favorable geometric relationships between the angular methyl groups and other functional groups present in the molecules, which have enabled selective, intramolecular reactions. C-19 Oxygenated steroids are of potential value both from the standpoint of their application as intermediates in the synthesis of useful 19-norsteroid hormones[2] as well as the interest in their intrinsic physiological activities. Successful conversions of C-10 methyl steroids to 19-nor derivatives recently have been reported by several groups[3] and have involved lead tetraacetate oxidation of 6β-hydroxy steroids and photolysis of 6β-nitrite esters. The former method has been found to give rise to 6β,19-oxides, the conversions of which have depended on cleavage of the 6β,19-oxide ring.

The present work was undertaken to determine whether lead tetraacetate oxidation of 6β-hydroxy-3α,5α-cyclosteroids would lead to 6β,19-oxide ring formation.[4] From the behavior of 10-methyl-3α,5α-cyclo-6-substituted steroids[5] it was anticipated that 6β,19-oxido-3α,5α-cyclosteroids would react under conditions of mild acid catalysis to yield various 3β-substituted 19-hydroxy-Δ⁵-steroids. It was hoped that the solvolytic behavior of 6β,19-oxido-3α,5α-cyclosteroids would, thus, prove to be of both practical and theoretical interest.

Although the yield of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I) isolated from the lead tetraacetate oxidation of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane was disappointingly low (22%), as yet only preliminary attempts have been made to determine optimum conditions for the reaction. In addition to the 6β,19-oxide (I) about 17% of crude starting material, which was present as the acetate, was isolated. The balance of the product mixture, the composition of which has not yet been examined in detail, showed infrared absorptions which suggested the presence of acetate. It has been reported[1c] that lead tetraacetate oxidation of 3β,17β-diacetoxy-6β-hydroxy-5α-androstane yielded, in addition to the 6β,19-oxide (68%), 7.5% of 3β,17β-diacetoxy-5α-androstan-6-one. Similarly, in the present work, in a preliminary run, a small amount of 17-ethylenedioxy-3α,5α-cycloandrostan-6-one was isolated.



I

Solvolyses of 6β,19-Oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I).—Under conditions of acid catalysis, the 6β,19-oxide ring of I was readily cleaved to yield C-19 substituted products. In each case the conditions were such that conversion of the 17-ethylenedioxy to the 17-keto group occurred.

A. Hydrolysis.—The major product, isolated in 55% yield by acid-catalyzed hydrolysis of I in 1:5 water–tetrahydrofuran (0.3 *M* in *p*-toluenesulfonic acid monohydrate), was 3β,19-dihydroxyandrost-5-en-17-one (II). This material was converted in good yield to 3β,19-diacetoxyandrost-5-en-17-one (IV) by acetylation with acetic anhydride in pyridine.

Chromatography of the product mixture obtained by acid-catalyzed hydrolysis of I in 1:10 water–tetrahydrofuran (0.09 *M* in *p*-toluenesulfonic acid monohydrate) led to the isolation of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III, 15.4% yield) in addition to the 3β,19-dihydroxy isomer (II, 42.5% yield).

B. Acetolysis.—Chromatography of the product mixture obtained by acetolysis of I in glacial acetic acid (0.1 *M* in *p*-toluenesulfonic acid monohydrate) yielded 60% of 3β,19-diacetoxyandrost-5-en-17-one (IV), which proved to be identical with the material obtained by acetylation of 3β,19-dihydroxyandrost-5-en-17-one (II). In addition, 3β-acetoxy-19-hydroxyandrost-5-en-17-one (V) was isolated in 4.6% yield.

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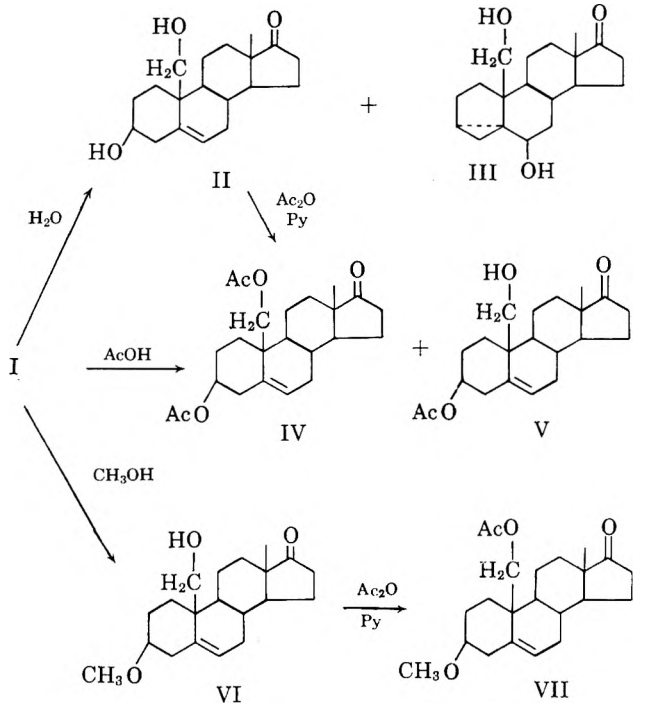
(4) Since completion of this work a communication has appeared describing the preparation and solvolysis of 6β,19-oxido-3α,5α-cycloandrostan-17-one. K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, and Y. Morisawa, *Chem. Pharm. Bull.* (Japan), **10**, 1126 (1962).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 314–318.

The crude product mixture obtained by attempted acetolysis of I in 1:10 acetic acid–tetrahydrofuran (0.095 *M* in *p*-toluenesulfonic acid monohydrate) showed infrared absorptions indicative of the presence of *p*-toluenesulfonate ester. This material was chromatographed to yield an oil showing infrared absorptions characteristic of both *p*-toluenesulfonate and acetate. In addition there was isolated 13.1% of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III) and about 20% of 3β,19-dihydroxyandrost-5-en-17-one (II).



The nature of the *p*-toluenesulfonate was not determined but it is presumably 3β-*p*-toluenesulfonoxy-19-hydroxyandrost-5-en-17-one. Further experiments are planned for the isolation and characterization of this product.

C. Methanolysis.—Acid-catalyzed methanolysis (0.106 *M* in *p*-toluenesulfonic acid monohydrate) of the 6β,19-oxide (I) yielded 98.6% of 3β-methoxy-19-hydroxyandrost-5-en-17-one (VI). Acetylation of this material yielded 3β-methoxy-19-acetoxyandrost-5-en-17-one (VII).

Structural Assignments.—The structures of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane and its solvolysis products are based primarily on n.m.r. spectra which are summarized in Table I.

A. 6β,19-Oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I).—The n.m.r. spectrum of the 6β,19-oxide (I) in deuteriochloroform showed complex absorption between 0–50 c.p.s. characteristic of the cyclopropyl protons at C-3 and C-4, and the absence of vinyl proton absorption. The spectrum showed only a single, sharp angular methyl absorption at 55.5 c.p.s. The nonequivalent C-19 methylene protons gave rise to the characteristic four-peak absorption of the AB spin system.[6,7] In deuteriochloroform one of the peaks was obscured by the sharp absorption peak[8] of the 17-ethylenedioxy protons, but in pyridine[9] all four peaks were separated from the 17-ethylenedioxy absorption, which in this solvent showed some indication of splitting. Unfortunately the C-6 proton absoption was not observable in either solvent and presumably overlaps that of the 17-ethylenedioxy protons.

B. Solvolysis Products.—The nonequivalent C-19 methylene protons of each of the solvolysis products gave rise to characteristic four-peak absorptions of AB spin systems and only a single angular methyl absorption was present. The presence of C-19 acetoxy and hydroxy substituents apparently effects a paramagnetic shift of the C-6 vinyl proton absorptions. Each of the Δ^5 derivatives showed vinyl proton absorption which occurred at 15–25 c.p.s. lower field than related C-10 methyl steroids such as 3β-acetoxyandrost-5-en-17-one (Table I).

In all known cases rearrangements of 6-substituted 10-methyl-3α,5α-cyclosteroids to Δ^5-3-substituted steroids have given products in which the substituents at C-3 have β-orientations.[5,10] The stereospecificity of reaction at C-3 has been attributed to reactions of nonclassical homoallylic cations. Evidence to be discussed later indicates that the acid-catalyzed solvolyses of the 6β,19-oxide (I) proceed *via* a 19-hydroxyhomoallylic cation. In the absence of an unexpected effect of the 19-hydroxyl group, the stereochemistry of reaction at C-3 of this latter intermediate would be expected to be the same as that of C-10 methylhomoallylic cations. The apparent identity of the diacetate (IV) with the 3β,19-diacetoxyandrost-5-en-17-one recently reported by Heusler and coworkers[3d] provides evidence that IV and the diol (II), from which it could be prepared by acetylation, both have β-oriented substituents at C-3. The stereochemistry of reaction at C-3 of 19-hydroxyhomoallylic cations thus appears to be identical to that of the 10-methylhomoallylic cations, and the substituents at C-3 of the 3,19-disubstituted steroids prepared in the present work are, accordingly, all assigned β-orientations.

The melting point of the diol (II) is in reasonable agreement with that of the product obtained by Mihina[11] by degradation of 17,19,21-trihydroxypregn-4-ene-3,20-dione. In the latter work, the orientation of the hydroxyl group at C-3 of the resulting 3,19-dihydroxyandrost-5-en-17-one was not specified, but was determined by the stereochemistry of an aqueous sodium bromohydride reduction of a 3,19-diacetoxy-3,5-diene. In the C-10 methyl series it nas been established[12] that the Δ^5-3-ols formed in this manner have 3β-hydroxyl groups. The present results, thus, suggest that 19-acetoxyl substituents have no unexpected neighboring group effect on the stereochemistry of

(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 89.

(7) H. Conroy, "Nuclear Magnetic Resonance in Organic Structural Elucidation," in "Advances in Organic Chemistry: Methods and Results," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1960 p. 301.

(8) Sharp absorption peaks of the ethylenedioxy protons of steroids in n.m.r. spectra determined in deuteriochloroform have also been observed by W. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

(9) The use of pyridine as an n.m.r. solvent to change the relative chemical shifts of protons, the absorptions of which overlap in deuteriochloroform, was suggested by G. Slomp and F. MacKellar, *J. Am. Chem. Soc.*, **82**, 999 (1960).

(10) E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4347 (1956).

(11) J. S. Mihina, U. S. Patent 2,856,415 (October 4, 1958).

(12) (a) B. Belleau and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 4458 (1951); (b) W. G. Dauben and J. F. Eastham, *ibid.*, **73**, 4463 (1951); (c) E. Schwenk, M. Gut, and J. Belisle, *Arch. Biochem.*, **31**, 456 (1951).

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA[a]

A. C-19 Oxygenated 3α,5α-cyclosteroids[b]

	C-6	$J_{ae} \simeq J_{ee}$[c]	C-18	O—CH₂—O	H_A—C_{19}—H_B[d] H_A	H_B	$\Delta\nu_{AB}$	$\lvert J_{AB}\rvert$
I	...	...	55.5	234.4[e]	241.4, (234.2)[f]	210.6, 203.4	30.0	7.2
II[g]	...	...	58.4	230.6[h]	243.8, 236.9	213.4, 206.2	29.7	7.0
III	202.0, 198.8, 195.8	3.1	59.6	...	228.3, 217.5[i]	204.8, 194.0	20.9	10.8
III[j]	200.7, 197.5, 194.2	3.2	58.8	...	227.5, 216.7	203.5, 192.5	21.5	10.9

B. C-19 Hydroxy-Δ⁵-3β derivatives

	C-6	C-18	—OCOCH₃	—OCH₃	H_A—C_{19}—H_B[d] H_A	H_B	$\Delta\nu_{AB}$	$\lvert J_{AB}\rvert$
II[k]	350.8	56.9	...	...	241.4, 230.0	223.0, 212.0	14.4	11.2
V	350.0	55.9	121.8	...	241.4, 229.6	222.7, 210.8	14.6	11.8
VI	342.5	57.0	...	202.0	240.2, 229.5	221.6, 210.0	16.1	11.2

C. C-19 Acetoxy-Δ⁵-3β derivatives

	C-6	C-18	—OCOCH₃	—OCH₃	H_A—C_{19}—H_B[d] H_A	H_B	$\Delta\nu_{AB}$	$\lvert J_{AB}\rvert$
IV	344.0	54.0	121.4, 122.5	...	282.2, 269.9	245.2, 233.2	34.8	12.1
VII	340.0	54.8	124.0	202.0	278.2, 267.0	244.0, 232.2	32.5	11.5

D. C-10 Methyl steroids

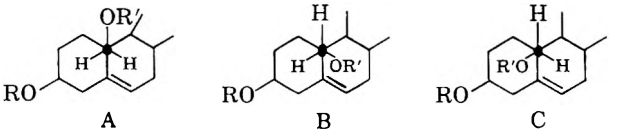
	C-6	$J_{ae} \simeq J_{ee}$[c]	—OCOCH₃	C-18	C-19
6β-Hydroxy-3α,5α-cycloandrostan-17-one	203.5, 200.5, 198.0	2.8	...	56.2	66.5
3β-Acetoxy-androst-5-en-17-one	326.0	...	121.6	53.2	63.3[l]
Cholesterol[m]	321.6				
3α-Acetamidoandrost-5-en-17-one[n]	322.0				
3β-Acetamidoandrost-5-en-17-one[n]	322.0				

[a] The spectra were recorded with a Varian A-60, n.m.r. spectrometer at 60 Mc. Unless otherwise specified, 5–10% solutions in deuteriochloroform were employed using tetramethylsilane as an internal reference. Chemical shifts are reported in c.p.s. from tetramethylsilane (0 c.p.s.) in the direction of decreasing field. J_{AB} is expressed in c.p.s. [b] Complex absorption of the C-3 and C-4 cyclopropyl protons occurred between 0–50 c.p.s. [c] Approximate coupling constants for the interaction of the C-6 proton with C-7 axial and C-7 equatorial protons. [d] H_A and H_B refer to the C-19 methylene protons which absorb at lower and higher field, respectively. [e] Apparent singlet. [f] Overlapped by the ethylenedioxy proton absorption. [g] Determined in 5% pyridine solution using an internal tetramethylsilane reference. [h] Some indication of splitting. [i] Overlapping absorption was present. [j] Added deuterium oxide. The low-field doublet (H_A) was fully resolved. A sharp water peak was present at 276.8 c.p.s. [k] Determined in 2 % deuteriochloroform solution because of limited solubility. [l] R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961), has reported 62.8 c.p.s. [m] High Resolution N.m.r. Spectra Catalogue," Varian Associates, Palo Alto, Calif. [n] J. Tadanier and Wayne Cole, *J. Org. Chem.*, **27**, 4624 (1962).

aqueous sodium borohydride reductions of 3-acetoxy-3,5-dienes.

The structures of the unsymmetrical derivatives V, VI, and VII follow from the AB absorption patterns of their C-19 methylene protons. The AB patterns of both the 3β-methoxy-19-ol (VI) and the 3β-acetoxy-19-ol (V) are almost superimposable on that of the 3β,19-diol (II), while the AB pattern of the C-19 methylene protons of the 3β-methoxy-19-acetate (VII), prepared by acetylation of VI, is almost superimposable on that of the 3β,19-diacetate (IV).

It has been established that acetylation of aliphatic alcohols causes a paramagnetic shift in the absorptions of their α-protons. The magnitudes of the shifts are characteristic for primary alcohols (~0.5 p.p.m.) and secondary alcohols (1.0–1.15 p.p.m.), and in steroid molecules the shifts are independent of axial or equatorial orientations.[13] In the present series the paramagnetic shifts resulting from acetylation of the 19-hydroxyl groups differ for the nonequivalent C-19 methylene protons, as is evident from comparison of the chemical shifts for the 19-acetates ($\Delta\nu_{AB}$ = 32.5–34.8 c.p.s.) with the corresponding values for the 19-alcohols ($\Delta\nu_{AB}$ = 14.4–16.1 c.p.s.), Table IB and IC. The large difference between these values may reflect different rotamer populations (A, B, and C) of the acetoxy derivatives and the hydroxy compounds.[14]



The equatorial C-3 substituents of the compounds in question should have little effect on the rotamer population. The small differences in the AB patterns of the hydroxy compounds II, V, and VI, on the one hand, and the acetoxy derivatives IV and VII, on the other, are of the magnitude to be expected of long-range shielding effects of the C-3 substituents on C-19 proton absorptions.[9,15]

To obtain a measure of the paramagnetic shielding effect on the C-19 methylene protons due to acetylation of the C-19 hydroxyl, the mean chemical shifts of the C-19 methylene protons of the 19-hydroxy and 19-acetoxy derivatives in both the 3β-methoxy and 3β-acetoxy series were determined from the difference between the midpoints of their AB patterns. In the case of the 3β-methoxy derivatives the paramagnetic shift thus calculated was 0.50 p.p.m. while for the 3β-acetoxy derivatives the shift was 0.53 p.p.m. These values are, thus, in good agreement with the value, 0.50 p.p.m., cited by Jackman[13] for the paramagnetic

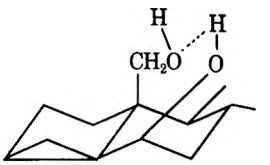
(13) Ref. 6, p. 55.
(14) Ref. 6, pp. 99–103.
(15) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Japan), **10**, 338 (1962).

shift of the α-protons of primary alcohols which is effected by acetylation.

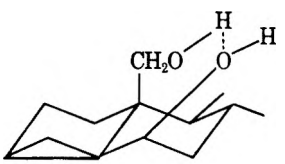
N.m.r. spectra of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III) showed complex absorption between 0–50 c.p.s. characteristic of the cyclopropyl protons at C-3 and C-4 and the absence of vinyl proton absorption. Only a single, sharp angular methyl absorption was present. In dry deuteriochloroform there was complex absorption between 190–230 c.p.s. The high-field portion appeared to consist of a triplet with peaks at 195.8, 198.8, and 202.0 c.p.s. and a doublet with peaks at 194.0 and 204.8 c.p.s. (total integrated area, 1.9 protons). The low-field portion showed peaks at 217.5 and 228.3 c.p.s., but these were overlapped by a broad absorption (total integrated area, 2.3 protons). Since the infrared spectrum of III showed strong hydrogen bonding, it was suspected that the absorption overlapping the low-field doublet was due to absorption of a hydrogen-bonding proton.[16] Accordingly, a small amount of deuterium oxide was added to the solution and the sample was agitated to effect a rapid exchange of the steroid hydroxy protons for deuterons.[17] The n.m.r. spectrum run on the resulting sample showed a sharp water peak at 276.8 c.p.s. The low-field doublet peaks at 216.7 and 227.5 c.p.s. were clearly resolved (integrated area, 0.9 proton) as the low-field doublet of the C-19 methylene AB spin system. The high-field doublet could then be identified directly from the coupling constant determined from the low-field doublet as consisting of the peaks at 192.5 and 203.5 c.p.s. (J_{AB} = |10.9|c.p.s.). The triplet absorption with peaks at 194.2, 197.5, and 200.7 c.p.s. is assigned to the absorption of the C-6 equatorial proton which is coupled to the C-7 equatorial and C-7 axial protons with $J_{ee} \simeq J_{ae} \simeq 3.2$ c.p.s. The total integrated area of the triplet and the high-field doublet was 1.8 protons.

The position of the triplet absorption of the C-6 proton of the diol (III) is close to that of the C-6 proton of 6β-hydroxy-3α,5α-cycloandrostan-17-one which has peaks at 198.0, 200.5, and 203.5 c.p.s. ($J_{ee} \simeq J_{ae} \simeq 2.8$ c.p.s.). Similar triplet absorptions were observed[18] for the C-6 protons of the acetate ($J_{ee} \simeq J_{ae} \simeq 2.7$ c.p.s.) and the *p*-nitrobenzoate ($J_{ee} \simeq J_{ae} \simeq 2.6$ c.p.s.) of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane. Since these coupling constants are of the magnitude expected if the dihedral angles between the C-6 protons and the C-7 axial and C-7 equatorial protons are both about 60°,[19] the C-6 protons must be equatorial and the substituents at C-6 were assigned the 6β-axial orientations. A similar argument applies to the C-6 proton absorption of III and thus establishes the 6β-axial orientation of the C-6 hydroxyl.

Independent evidence for the *cis* relationship of the C-6 hydroxyl and the C-10 hydroxymethyl groups of III as well as the 6β-axial orientation of the 6-hydroxyl is furnished by the OH absorptions in the infrared. It has been shown that the difference ($\Delta\nu$) in wave numbers (cm.$^{-1}$) between free and bonded OH absorptions provides a measure of both the strength of the hydrogen bond[20] and the hydrogen bond distance (H - - - O).[21] Infarred spectra of III were determined in carbon tetrachloride solutions at concentrations (0.005 and 0.0025 *M*) at which it has been shown that absorptions due to hydrogen bonded OH are due to intra- rather than intermolecular bonding.[21a] At both concentrations sharp bands due to both free and bonded OH absorptions were observed at 3610 and 3460 cm.$^{-1}$, respectively. At the higher concentration a broad shoulder was present, centered at 3250 cm.$^{-1}$ which indicated that a small amount of intermolecular hydrogen bonding persisted. The large value of $\Delta\nu$ (150 cm.$^{-1}$) indicates strong intramolecular hydrogen bonding and is of the magnitude observed[21a] for *cis*- and *trans*-1,2-bishydroxymethylcyclohexane. In these latter compounds the O - - - H bond distance could not be calculated[21a] since the closest approach of the hydrogen-bonded H and O was found to be less than the length of the covalent OH bond (0.96 Å.). Similarly, in both of the possible hydrogen-bonded species (D and E) with the 6β-axial hydroxyl, the closest approach of the bonding H and O is only 0.4 Å.[22]



D



E

The frequencies measured in the present work with sodium chloride optics were not sufficiently accurate (±15 cm.$^{-1}$) to allow a choice between the two possibilities based on the frequency of the free OH absorption.[21c]

The coupling constants (J_{AB}) for the methylene protons of the 19-hydroxy and 19-acetoxy compounds were almost equal within the experimental error, while that of the 6β,19-oxide (I) was significantly smaller. Although the calculations of Gutowski, Karplus, and Grant[23] predicted that the magnitudes of the coupling constants between geminal protons should be a sensitive function of the H–C–H bond angle, recent work[24] has indicated that the signs of geminal coupling constants are opposite to those predicted by the theory, and that their magnitudes are too sensitive to the effect of substituents to allow an empirical correlation with dihedral angles. Thus, while the small coupling constant of I is presumably related to the strain in the puckered tetrahydrofuran ring, the nature of the effect is not clear.

(16) N.m.r. absorptions of hydrogen-bonded hydroxyl protons occur at lower field than free hydroxyl proton absorptions (ref. 6, p. 66). In the other C-19 hydroxy compounds prepared in this work, no hydroxyl proton peak was observed and these are presumed to absorb at higher field than about 150 c.p.s., which overlaps the complex absorption of the steroid ring protons. Since only the low-field doublet of III was obscured by the overlapping absorption, while both peaks of the low-field doublet appeared to be present, the complexity is believed to be due to overlapping absorption of one bonded hydroxy proton with the low-field doublet rather than to spin–spin coupling of the C-19 methylene protons with the 19-hydroxy proton. This interpretation is consistent with integrated intensities measured before and after addition of deuterium oxide.

(17) This technique was suggested by Jackman, ref. 6, p. 71.

(18) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4610 (1962).

(19) See ref. 7, pp. 308–311.

(20) R. F. Badger, *J. Chem. Phys.*, **8**, 288 (1940).

(21) (a) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952); (b) L. P. Kuhn, *ibid.*, **76**, 4323 (1954); (c) L. P. Kuhn, *ibid.*, **80**, 5950 (1958).

(22) Calculated from Dreiding Models of 6β,19-dihydroxy-5α-androstane.

(23) H. S. Gutowski, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959).

(24) (a) M. Karplus, *J. Am. Chem. Soc.*, **84**, 2458 (1962); (b) P. C. Lauterbur and R. J. Kurland, *ibid.*, **84**, 3405 (1962); (c) F. A. L. Anet, *ibid.*, 3767 (1962); (d) H. J. Bernstein and N. Sheppard, *J. Chem. Phys.*, **37**, 3012 (1962). (The author is indebted to a referee for graciously calling his attention to the latter reference.)

The optical rotations (Table II) of the products are all consistent with the structures assigned. Both the 6β,19-oxide (I) and the 6β,19-diol (III) have high positive rotations characteristic of 3α,5α-cyclo-6-substituted steroids relative to their Δ⁵-3 isomers. The molecular rotation difference, ΔMD, between these

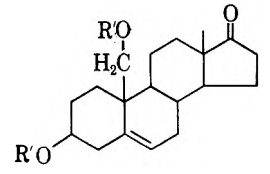
TABLE II

MOLECULAR ROTATIONS

A. 3α,5α-Cyclosteroids

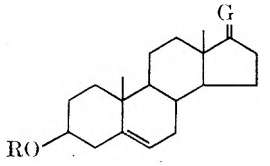
	MD		MD	ΔMD
I	+149°	III	+426°	+277°
6β-Hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane	+39°[a]	6β-Hydroxy-3α,5α-cycloandrostan-17-one	+348°[b]	+309°

B. C-19-Substituted-Δ⁵-3β steroids



R	MD(R′ = $COCH_3$)	MD(R′ = H)	ΔMD
H	...	+45°	...
$COCH_3$	−138°	+24°	+162°
CH_3	−134°	+32°	+166°

C. C-10-methyl-Δ⁵-3 β Steroids[c]



X	G = 17α-H, 17β-C_8H_{17} MD	G = O MD
H	−150°	+6°
$COCH_3$	−184°	−25°
CH_3	−168°	0°[d]

[a] Calculated from the value reported by S. Julia, C. Neuville, and M. Davis (ref. 31). [b] Calculated from the value for a solution in 95% ethanol, quoted in "Pouvoir Rotatoire Naturel, I. Steroides," by J.-P. Mathieu and A. Petit, Masson and Co., Paris, France, 1956, p. 18. [c] Calculated from values quoted in footnote *b* for chloroform solutions. [d] It has been reported that this material shows no observable rotation in 2.5% chloroform solution. A. Butenandt and W. Grosse, *Ber.*, 69, 2776 (1936).

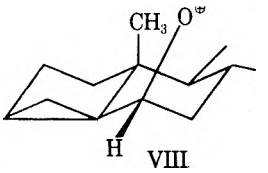
products is almost the same as that between 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane and 6β-hydroxy-3α,5α-cycloandrostan-17-one (Table IIA) and thus must be due almost entirely to the difference between the 17-ketal and 17-keto functions.

For the Δ⁵-C-19 substituted derivatives, the optical rotations are only slightly sensitive to the nature of the substituent at C-3 as is evident from comparison of the 19-hydroxy compounds (II, V, and VI), on the one hand, and the 19-acetoxy derivatives (IV and VII), on the other. The insensitivity of optical rotation to the nature of the substituent at C-3 is also observed for C-10 methyl steroids (Table IIC). In contrast, a relatively large difference is observed between the rotations of the 19-hydroxy and 19-acetoxy compounds (Table IIB). In both 3β-methoxy and 3β-acetoxy series, the optical rotations of the 19-acetoxy derivatives are much more negative than are those of the 19-hydroxy derivatives.

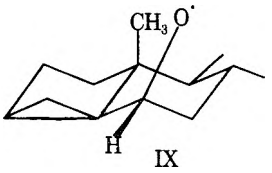
The optical rotations of the 19-hydroxy compounds (II, V, and VI), on the one hand, and the 19-acetoxy compounds (IV and VII), on the other, are almost identical. This is only to be expected if the rotamer populations (A, B, and C) within the C-19 hydroxy series and within the C-19 acetoxy series are the same, and essentially unaffected by the nature of the substituent at C-3. This is in accord with the n.m.r. chemical shift differences ($\Delta\nu_{AB}$) of the two series, described previously.

Discussion

It has been suggested[1e] that the first step in the lead tetraacetate oxidation of the angular methyl groups of hydroxysteroids is the formation of an alkoxylead(IV) derivative. Although, by analogy with the reaction of the *p*-toluenesulfonate of 1,3,3-trimethylcyclohexyl peroxide prepared by Corey and White,[25] this intermediate may undergo subsequent heterolysis to form a cationic species (VIII) followed by proton abstraction from the angular methyl to form the 6β,19-oxide; homolytic cleavage to an alkoxy radical (IX), similar



VIII



IX

to that formed by nitrite ester photolysis,[1g] followed by hydrogen atom abstraction from the angular methyl, has not been excluded. At present, however, in view of the uncertainty with regard to the mechanism of the reaction, and the epimerization which has recently been reported to occur on photolysis of the nitrite ester of "α"-caryophyllene alcohol,[26] formation of the 6β,19-oxide (I) by lead tetraacetate oxidation of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane cannot be considered a chemical proof[27] of the configuration of the alcohol. Since the yield of the 6β,19-oxide (I) was relatively low under the conditions employed, an investigation of the behavior of the epimeric 6α-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane did not seem to offer an unequivocal conclusion.

The evidence for the configurations of C-6 epimeric 6-hydroxy-3α,5α-cyclosteroids, based on the multiplet absorption patterns of the C-6 protons of the acetates and *p*-nitrobenzoates of the C-6 epimeric 6-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostanes, has been previously described.[18] In the present work, the complementary infrared and n.m.r. evidence regarding the configuration of the 6β,19-diol (III), together with the almost identical chemical shifts and multiplet absorption patterns of III and of 6β-hydroxy-3α,5α-cycloandrostan-17-one, provides essentially conclusive evi-

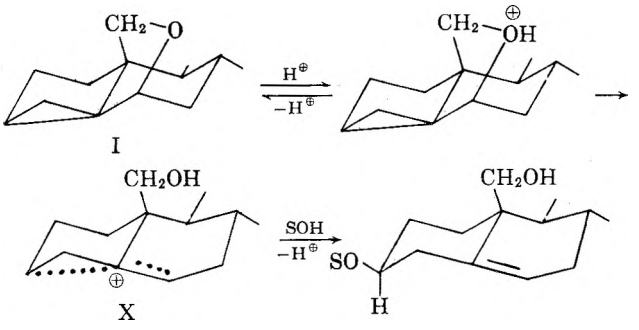
(25) E. J. Corey and R. W. White, *J. Am. Chem. Soc.*, **80**, 6686 (1958).

(26) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961).

(27) As yet there has been no direct chemical proof for the configurations of C-6 epimeric 3α,5α-cyclo-6-ols. See ref. 10, footnote 16.

dence regarding the configurations of 3α,5α-cyclo-6-ols in the C-10 methyl series.[28]

Examination of the solvolytic behavior of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I) indicates that its reactions are those predictable from the behavior of related 10-methyl-3α,5α-cyclosteroids.[5,10] Under conditions of acid catalysis in each of the solvent systems studied, the major products isolated were Δ^5-3β substituted steroids. Although formation of the symmetrically substituted 3β,19-dihydroxy and 3β,19-diacetoxy compounds (II and IV) by hydrolysis and acetolysis, respectively, furnishes no evidence for the direction of heterolysis of the 6β,19-oxide ring, the isolation of 3β-methoxy-19-hydroxyandrost-5-en-17-one as the sole product from the acid-catalyzed methanolysis provides strong evidence that these reactions all occur *via* C_6-O heterolysis to form the intermediate 19-hydroxyhomoallylic cation (X).



Formation of 3β,19-diacetoxyandrost-5-en-17-one (IV) as the major product of the acid-catalyzed acetolysis in acetic acid seems most probably the result of subsequent esterification of the expected 3β-acetoxy-19-hydroxyandrost-5-en-17-one (V). Although formation of the minor product, V, is conceivably the result of preferential esterification or hydrolysis reactions, this product is significantly that isomer which would be predicted on the basis of reaction of the 19-hydroxyhomoallylic cation (X) with acetic acid.

The isolation of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one from both the attempted acetolysis in 1:10 acetic acid–tetrahydrofuran (0.095 *M* in *p*-toluenesulfonic acid monohydrate) and the hydrolysis in 1:10 water–tetrahydrofuran, demonstrates that the stereochemistry of reaction of the 19-hydroxyhomoallylic cation at C-6 is identical to that observed for reactions of related 10-methylhomoallylic cations.

Since 6β,19-oxido-3α,5α-cyclosteroids should prove a convenient source of a variety of 3β,19-disubstituted steroids, it is hoped that further studies of the lead tetraacetate oxidation of 6β-hydroxy-3α,5α-cyclosteroids will lead to conditions more favorable for 6β,19-oxide ring formation.

Experimental

The lead tetraacetate used was that of Matheson Coleman and Bell, and was dried over potassium hydroxide prior to use.

Infrared spectra were determined for all compounds and were consistent with functional groups present. The infrared studies on the hydrogen bonding of the 6β,19-diol (III) were carried out with solutions in Mallinckrodt analytical reagent carbon tetrachloride with a Perkin-Elmer, Model 21, spectrophotometer equipped with sodium chloride optics, using a 3.0-cm. cell.

Optical rotations were determined with 1% solutions in Mallinckrodt analytical reagent chloroform using a Hilger and Watts polarimeter.

The tetrahydrofuran used as solvent was purified by the method of Fieser.[29] The neutral activity III alumina used for the chromatographic separations was prepared by the addition of the appropriate amount of water[30] to Woelm, neutral activity I alumina. The petroleum ether used for recrystallizations was a fraction boiling 66–70°.

Unless otherwise specified, melting points were taken in open capillaries and are uncorrected.

A. 6β,19-Oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I).—Two runs were carried out in the following manner. A solution prepared from 5.03 g. (0.0151 mole) of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane,[31] 18.7 g. (0.042 mole) of lead tetraacetate, and 300 ml. of benzene was heated under reflux, with stirring, for 24 hr., during which time a white solid separated. At the end of the reaction time the resulting supernatant gave a positive starch iodide test. The excess lead tetraacetate was destroyed by addition of 30 ml. of ethylene glycol, and the resulting two-phase mixture was filtered through a Celite mat. The Celite mat was then washed with 300 ml. of benzene, and the washings were added to the original filtrate. The resulting mixture was washed with 500 ml. of water, and the aqueous phase was separated and extracted with 300 ml. of benzene. The benzene solutions were washed in series with 400 ml. of 5% sodium bicarbonate solution, and six 300-ml. portions of water; then they were combined and dried over anhydrous magnesium sulfate. The benzene was evaporated under reduced pressure, leaving 5.58 g. of a pale yellow glass.

The product mixture was treated with 100 ml. of boiling pentane with vigorous stirring, and the pentane supernatant was separated by decantation. This procedure was repeated five times leaving only a small fraction of the material undissolved. The pentane solutions were combined, swirled to effect homogeneity, and placed on a column of 200 g. of neutral, activity III alumina. The pentane eluate was essentially dry. Elution with 1:15 ether–pentane solution (ten 100-ml. fractions) yielded 1.95 g. of an oil showing medium intensity absorptions indicative of the presence of acetate at 1724 cm.$^{-1}$ (C=O)[32] and 1250 cm.$^{-1}$ (C—O).[32] The corresponding fractions from run II exhibited a similar infrared spectrum and amounted to 2.45 g. of an oil (fractions 1).

Further elution of the column with 1:15 ether–pentane solution (three 100-ml. fractions) yielded 128 mg. of an oil. The remainder of the product was eluted with 1.5 l. of ether. These latter fractions were combined to yield 3.1 g. of a clear, pale yellow oil, the infrared spectrum of which showed strong bands at 1745 cm.$^{-1}$ and 1235 cm.$^{-1}$ and a medium intensity band at 1706 cm.$^{-1}$. This material was not further investigated.

The initial fractions eluted with 1:15 ether–pentane solution, obtained from runs 1 and 2 (fractions 1) were combined (4.4 g. total) and heated under reflux for 2 hr. with 200 ml. of 5% methanolic potassium hydroxide solution. The resulting solution was concentrated to about one-quarter volume under aspirator pressure and poured into 400 ml. of water. The resulting mixture was extracted twice with 300-ml. portions of ether, and the ether solutions were washed in series with six 100-ml. portions of water. The ether solutions were then combined and dried over anhydrous magnesium sulfate. The ether was evaporated, leaving 4.09 g. of a cloudy pale yellow oil. This product showed no absorption in the carbonyl region, but weak absorption, free and bonded, was present in the OH stretching region. This product was placed on a column of 200 g. of neutral, activity III alumina in 50 ml. of pentane solution. Elution with 1:15 ether–pentane solution (fourteen 100-ml. fractions) yielded an oil with a trace of orange coloration. This material was dissolved in pentane, and the pentane solution was treated with carbon and filtered through Celite. The pentane filtrate was colorless. The pentane was evaporated, leaving an oil which crystallized on standing, yielding 2.18 g. (22%) of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I), m.p. 95–101.5°. For analysis

(28) As described by Kosower and Winstein (ref. 10), 3α,5α-cyclo-6β-ols are formed stereospecifically by hydrolysis of the *p*-toluenesulfonates of their Δ^5-3β-isomers, while the epimeric 3α,5α-cyclo-6α-ols are formed stereospecifically by lithium aluminum hydride reduction of 3α,5α-cyclo-6-ones.

(29) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed. D. C. Heath and Co., Boston, Mass., p. 292, 1959.

(30) H. Brockmann and H. Schodder, *Ber.*, **74** (1), 73 (1941).

(31) S. Julia, C. Neuville, and M. Davis, *Bull. soc. chim. France*, 297 (1960).

(32) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

1.16 g. was recrystallized from methanol–water solution to yield 992 mg., m.p. 102–103°, $[\alpha]^{24}D$ +45°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.62; H, 9.22.

Elution of the column with ether (1 l.) yielded 1.72 g. (17%) of a pale orange oil which crystallized on standing. The infrared spectrum of this material (7% chloroform solution) was essentially identical to that of the starting material, 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane. Recrystallization of this material from ether–petroleum ether yielded 1.18 g., m.p. 142–145° (lit.[31] m.p. 142–144°). The melting point of a mixture of this material with authentic 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane was not depressed.

B. Hydrolysis.—1. A solution prepared from 604 mg. (0.00182 mole) of I, 3 g. (0.02 mole) of *p*-toluenesulfonic acid monohydrate, 10 ml. of water, and 50 ml. of tetrahydrofuran was heated under reflux for 3 hr. The tetrahydrofuran was removed by distillation under reduced pressure, and the residue was shaken with 180 ml. of water and 300 ml. of ether. The aqueous phase was separated and extracted with 250 ml. of ether. The ether solutions were washed in series with 100 ml. of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water; then they were combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 444 mg. of a crystalline solid, m.p. 190–200°. Three recrystallizations from ethyl acetate–petroleum ether yielded 305 mg. (55%) of 3β,19-dihydroxyandrost-5-en-17-one (II), m.p. 212–219° dec., $[\alpha]^{23}D$ +15° (lit.[11] m.p. 204–206°).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27. Found: C, 74.69; H, 9.28.

2. A solution prepared from 659 mg. (0.00200 mole) of I, 1 g. (0.005 mole) of *p*-toluenesulfonic acid monohydrate, 5 ml. of water, and 50 ml. of tetrahydrofuran was heated under reflux for 1 hr. and then poured into 400 ml. of water. The resulting aqueous suspension was extracted three times with 250-ml. portions of ether. The ether solutions were washed in series with 100-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water, then combined and dried over anhydrous magnesium sulfate, after the addition of a few drops of pyridine. The ether was evaporated, leaving a crystalline solid impregnated with an orange impurity (712 mg.).

The product was heated under reflux for 5 min. with 80 ml. of benzene. A small amount of material remained undissolved. The supernatant was separated by decantation, leaving 25 mg. of a white crystalline solid, m.p. 186–192°.

The benzene solution was cooled to room temperature and placed on a column of 50 g. of neutral activity III alumina. The benzene eluate contained 30 mg. of an orange oil. Elution with 1:5 ether–benzene (eight 50-ml. fractions) yielded 115.1 mg. of a crystalline solid, m.p. 146–153°.[33] Two recrystallizations from benzene–petroleum ether yielded 93.4 mg. (15.4%) of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III), m.p. 171–173°. The infrared spectrum of this material (7% chloroform solution) was identical to that obtained from the attempted acetolysis, described below. The melting point of a mixture of these products was not depressed.

Further elution of the column with 1:1 ether–benzene solution (two 50-ml. fractions) gave no more material. Elution with 1:10 methanol–chloroform solution (100 ml.) yielded 302.3 mg. of a white crystalline solid, m.p. 197.5–202°. Recrystallization of this material from ethyl acetate–petroleum ether yielded 258.3 mg. (42.5%) of 3β,19-dihydroxyandrost-5-en-17-one (II), m.p. 213–219° dec. The infrared spectrum of this material (potassium bromide pellet) was identical to that of the material obtained from the acid-catalyzed hydrolysis of I in 1:5 water–tetrahydrofuran solution as described previously. The melting point of a mixture of these products was not depressed.

C. Acetolysis.—1. A solution prepared from 330 mg. (0.00100 mole) of I, 190 mg. (0.0010 mole) of *p*-toluenesulfonic acid monohydrate, and 10 ml. of glacial acetic acid was heated at 60° for 2 hr. Water (2 ml.) was added and heating was continued for 10 min. The reaction product mixture was isolated by ether extraction. The ether solutions were washed with 5% sodium bicarbonate solution and then to neutrality with water, combined, and dried over anhydrous magnesium sulfate. Evaporation of the ether left 372.4 mg. of a deep orange oil.

The product was placed on a column of 25 g. of neutral activity III alumina in 60 ml. of 1:10 ether–pentane solution. Elution with 1:10 ether–pentane (four 50-ml. fractions) yielded 25 mg. of oils. Elution with 1:5 ether–pentane (nine 50-ml. fractions) yielded 233 mg. (60%) of 3β,19-diacetoxyandrost-5-en-17-one (IV), m.p. 106–108.5°. Recrystallization of this material from ether-pentane solution yielded the analytical sample (162 mg.), m.p. 108–109°, $[\alpha]^{21}D$ −35.4° [lit. m.p. 103–105°, $[\alpha]D$ −40° (chloroform)].[3d] The infrared spectrum of this material was identical to that of the product prepared by acetylation of 3β,19-dihydroxyandrost-5-en-17-one (II) as described later. The melting point of a mixture of these samples was not depressed.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.09; H, 8.30. Found: C, 71.05; H, 8.12.

Elution of the column with 1:1 ether–pentane (three 50-ml. fractions) yielded 50 mg. of an oil which crystallized on trituration with 1:1 ether–pentane solution. One recrystallization from methanol–water solution followed by two recrystallizations from ether–petroleum ether solution yielded 16.0 mg. (4.6%) of 3β-acetoxy-19-hydroxyandrost-5-en-17-one (V), m.p. 157–158°,[33] $[\alpha]^{23}D$ +7°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73. Found: C, 72.86; H, 8.59.

2. A solution prepared from 508 mg. (0.00154 mole) of I, 1.0 g. (0.0052 mole) of *p*-toluenesulfonic acid monohydrate, 5 ml. of acetic acid, and 50 ml. of tetrahydrofuran was heated under reflux for 2 hr. Water (10 ml.) was added and reflux was continued for 15 min. The reaction solution was poured into 400 ml. of water and the resulting white suspension was extracted with two 250-ml. portions of ether. The ether solutions were washed in series with two 100-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water, then combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 603 mg. of a white glass. The infrared spectrum of this material (7% chloroform solution) showed bands at 3584 and 3413 $cm.^{-1}$ [(w), OH free and bonded],[34] 1736 $cm.^{-1}$ (OAc and 17-keto carbonyls),[32] 1603 $cm.^{-1}$ [(w), aromatic ring],[35] 1237 $cm.^{-1}$ (C–O of acetate),[32] doublet 1173 (s), 1183 (w) $cm.^{-1}$, and 1357 $cm.^{-1}$, (–O–SO_2– of *p*-toluenesulfonate).[36]

The product mixture was placed on 50 g. of neutral, activity III alumina in benzene solution and chromatographed as described. Fifty-milliliter fractions were collected.

Fractions	Eluent	Content
1–5	Benzene	Trace amounts of oils
6–10	1:20 Ether–benzene	40 mg. of oils
11–15	1:10 Ether–benzene	Trace amounts of oils
16–21	1:4 Ether–benzene	175 mg., clear, pale green oil
22–23	1:1 Ether–benzene	88 mg., crystalline solid
24–27	1:1 Ether–benzene	Dry
28–32	Chloroform	Dry
33–35	1:10 Methanol–chloroform	91.3 mg., crystalline solid
36–37	1:10 Methanol–chloroform	Dry

The infrared spectrum of combined fractions 16–21 (7% chloroform solution) showed the bands present in the original crude sample described.

The combined fractions 22–23 (m.p. 152–155°) were recrystallized three times from benzene–petroleum ether to yield 61.2 mg. (13.1%) of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III), m.p. 172–174°,[33] $[\alpha]^{25}D$ +140°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27. Found: C, 74.80; H, 9.23.

The material obtained from fractions 33–35, m.p. 175–190° (19.5%), was not further characterized, but its chromatographic behavior indicated that it was impure II.

D. Methanolysis.—A solution prepared from 715 mg. (0.00216 mole) of I, 710 mg. (0.00373 mole) of *p*-toluenesulfonic acid monohydrate, and 35 ml. of absolute methanol was heated under reflux for 2 hr. Water (3.5 ml.) was added and reflux was continued for 15 min. The major portion of the methanol was

(33) Melting point was determined on a Fisher-Johns block and is uncorrected.

(34) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 95.

(35) Ref. 34, p. 64.

(36) Ref. 34, p. 364.

then evaporated under reduced pressure on the steam bath with a rotatory evaporator. The residue was shaken with a mixture of 250 ml. of ether and 100 ml. of water. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with 100 ml. of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water; they were then combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 679 mg. (98.6%) of 3β-methoxy-19-hydroxyandrost-5-en-17-one (VI), m.p. 143–146°. Recrystallization of this material from methanol–water solution yielded 574 mg., m.p. 147–149°. For analysis 272.9 mg. of this latter sample was recrystallized from methanol–water solution to yield 241 mg., m.p. 147.5–149°, $[\alpha]^{23}D$ +10.2°.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.44; H, 9.50. Found: C, 75.64; H, 9.50.

E. Acetylation of 3β,19-Dihydroxyandrost-5-en-17-one (II).—A solution prepared from 151 mg. (0.00050 mole) of II, 2 ml. (0.02 mole) of acetic anhydride, and 6 ml. of pyridine was allowed to stand at room temperature for 23 hr. The resulting solution was shaken with a mixture of 150 ml. of ether and 100 ml. of water. The aqueous phase was separated and extracted with 100 ml. of ether. The ether solutions were washed in series with 100 ml. of water, 100 ml. of 1 *N* hydrochloric acid, two 50-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, and three 50-ml. portions of water; they were then combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 191 mg. (99%) of 3β,19-diacetoxyandrost-5-en-17-one (IV) as an oil which crystallized on cooling in a Dry Ice–acetone bath, m.p. 104–107°. For analysis this material was recrystallized from ether–petroleum ether solution to yield 164 mg., m.p. 109–110°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 71.09; H, 8.30. Found: C, 71.22; H, 8.50.

F. Acetylation of 3β-Methoxy-19-hydroxyandrost-5-en-17-one (VI).—A solution prepared from 302 mg. (0.00095 mole) of VI, 4 ml. (0.04 mole) of acetic anhydride, and 12 ml. of pyridine was allowed to stand at room temperature for 23 hr. The product was isolated as described previously for the acetylation of 3β,19-dihydroxyandrost-5-en-17-one (II), to yield 332 mg. (97%) of 3β-methoxy-19-acetoxyandrost-5-en-17-one (VII), m.p. 66–67.8°. For analysis this material was recrystallized from ether–petroleum ether solution to yield 272 mg., m.p. 67–68°, $[\alpha]^{21}D$ −37.3°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.27; H, 9.09.

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Synthesis of Amitriptyline and Related Substances. Hydroboration of 5-Allylidene-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene

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A new route to 5-(γ-dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene and related systems by way of hydroboration of a butadiene intermediate has been realized.

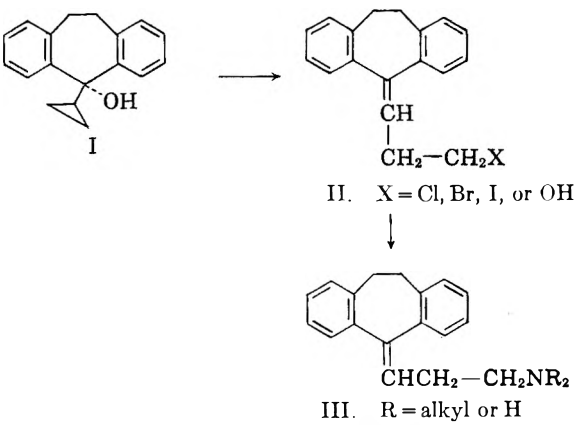
Synthesis of the psychotherapeutic drug, amitriptyline (XI), has been accomplished heretofore in the main by way of simple Grignard coupling of γ-dimethylaminopropylchloride with 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one followed by dehydration.[1]

Recently we showed[2] that the carbinol (I), derived from 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one (IV) and cyclopropylmagnesium bromide, rearranges quantitatively to 5-(γ-halopropylidene) (II. X = Cl or Br) and 5-(γ-hydroxypropylidene)-5*H*-dibenzo-10,11-dihydrocycloheptene (II. X = OH) in the presence of anhydrous halogen acids or aqueous mineral acids, respectively. The γ-halo[3] as well as the γ-hydroxy systems, moreover, possess the distinct advantage of providing not only a direct route to amitriptyline, but also to nearly any γ-substituted derivative through choice of the appropriate nucleophile.

A new route to the key γ-halopropylidene and γ-hydroxypropylidene derivatives, II, has now been realized and constitutes the subject of the present report.

The allylcarbinol V formed from 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one (IV) and allylmagnesium bromide is a somewhat unstable compound and readily loses water; for example, by refluxing a cyclohexane solution of this carbinol with a trace of *p*-toluenesulfonic acid, there is afforded the unstable diene 5-allylidene-5*H*-dibenzo-10,11-dihydrocycloheptene (VI) absorbing at 268 mμ (17,200). The same diene is obtained from amitriptyline by Hofmann degradation by way of the quarternary methiodide (VII).

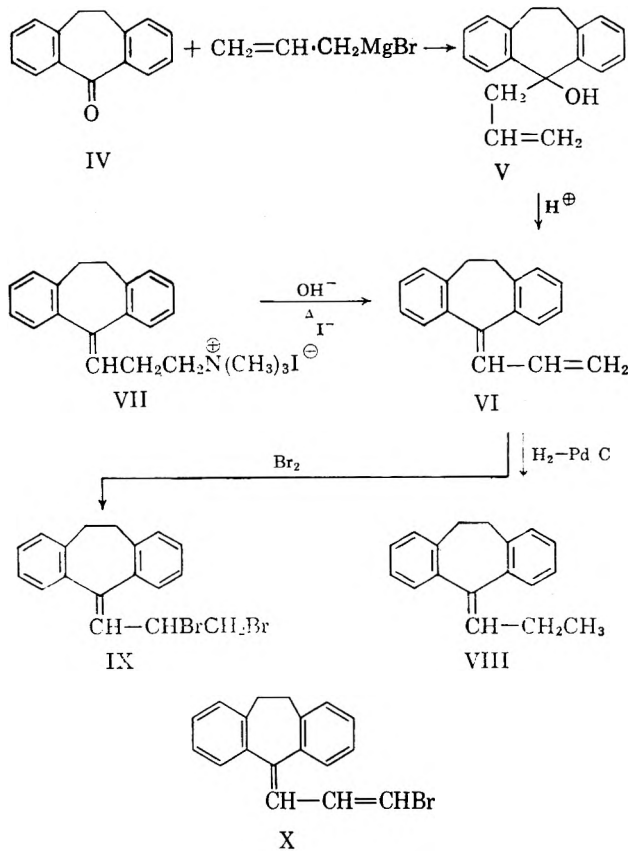
The diene VI exhibits a pronounced tendency toward polymerization. Samples stored in closed containers slowly deteriorate with the production, to a limited extent, of formaldehyde as ascertained by



(1) (a) Belgian Patent 584,061, Merck & Co., Inc; *Cf.* E. Jucker, "Chemie der Psychotropen Pharmaka," *Chimia*, **15**, 267 (1961); (b) British Patents, 858,187; 858,188, Hoffmann-LaRoche A.G.; (c) Belgian Patent 609,095, Kefelas A/S; (d) M. Protiva, V. Hnevsova-Seidlova, Z. J. Vejdelek, F. Jerkovsky, Z. Votava, and J. Metysova, *J. Med. Pharm. Chem.*, **4**, 411 (1961); (e) see also F. J. Villani, C. A. Ellis, C. Teichman and C. Bigos, *ibid.*, **5**, 373 (1962); and South African Patent R611/1889, Kefalas A/S.

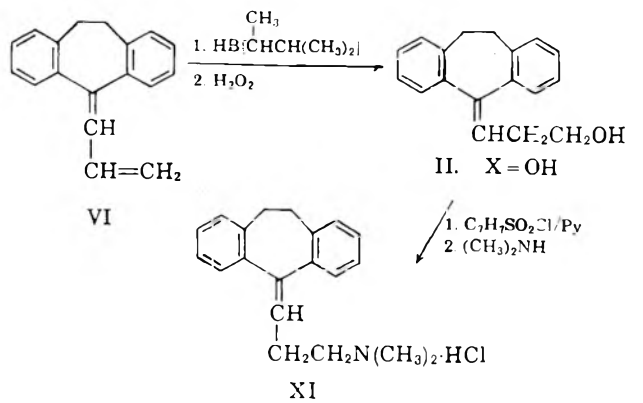
(2) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **27**, 4134 (1962).

(3) Compare also S. O. Winthrop, M. A. Davis, G. S. Meyers, J. G. Gavin, R. Thomas, and R. Barber, *ibid.*, **27**, 230 (1962).



chromotropic acid titration. The diene can be readily separated from polymeric impurities by virtue of its exclusive solubility in petroleum ether, thereby providing material of adequate quality for further chemical transformations. The diene VI readily absorbed one mole of hydrogen to give the crystalline propylidene derivative VIII, m.p. 49–51.6° with λ_{max} 238 mμ (12,700). Similarly, the diene VI added one mole of bromine to provide the crystalline dibromide IX, m.p. 92–94° with λ_{max} 243 mμ (15,400). The same dibromide was obtained from the allylcarbinol V when the latter was allowed to stand with bromine in chloroform solution for several days. Attempts to prepare a γ-dieneamine derivative by reaction of the dibromide IX with dimethylamine were unsuccessful. The major product from this reaction appeared to be the bromodiene X, λ_{max} 280 mμ (21,500).

Conversion of the diene VI to 5-(γ-hydroxypropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (II. X = OH) was accomplished in good yield by hydroboration with di-*sec*-isoamylborane and concluding oxidation according to the method of Zweifel, Nagase, and Brown.[4] The primary carbinol II (X = OH) in the form of its *p*-toluenesulfonic ester was smoothly converted to amitriptyline XI with dimethylamine in benzene solution at 85°. This same carbinol was likewise converted essentially quantitatively with thionyl chloride to the corresponding chloro derivative II (X = Cl).



Experimental

5-Allyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (V).—To a solution of allylmagnesium bromide prepared from 2.88 g. of magnesium and 14.5 g. of allyl bromide in 120 cc. of ether was added dropwise 8.3 g. of 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one dissolved in 50 cc. of ether. The reaction mixture was stored overnight and subsequently decomposed with ammonium chloride solution. The ether layer was separated, dried, and concentrated to a viscous oil. Although this product was chromatographed on neutral alumina and obtained as single spot material by t.l.c. on alumina (1:1 hexane–benzene) [wt., 9.5 g. (75%); $\lambda_{max}^{CH_3OH}$ 263.5, ε 600; $\lambda_{max}^{CHCl_3}$ 2.8 μ (OH), 6.08, 6.26, and 6.71 μ (φ)], it could not be obtained analytically pure.

A 200-mg. sample of the allylcarbinol in 5 cc. of chloroform was treated with one equivalent of bromine. The bromine was consumed immediately, the solution was concentrated to an oil which crystallized after several days to give 240 mg. of the dibromide IX, m.p. 94–96°, identical with a sample prepared by bromination of the diene VI.

Formation of the Diene VI. (A) — A solution of 1.3 g. of allylcarbinol V in 100 cc. of hexane was treated with 130 mg. of *p*-toluenesulfonic acid and refluxed 0.5 hr. on the steam bath. At the end of this period, the reaction mixture was cooled, washed with potassium bicarbonate solution, dried over magnesium sulfate, and concentrated to a thick oil. The latter was submitted to short-path distillation and afforded 0.5 g. of diene, b.p. 160° at 0.3 mm., $\lambda_{max}^{CH_3OH}$ 267.5 mμ, ε 17,200. N.m.r. spectrum: 2.88 (m) (aromatic), 3.50 (m) and 4.75 (m) (vinylic H), 6.97 τ (broad) (10,11-CH). This compound proved to be too unstable to permit ready analysis, low carbon values being obtained.

(B) **From 5-(γ-Dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene Methiodide (VII).**—A solution (10.0 g.) of 5-(γ-dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene hydrochloride in 250 ml. of water was treated with 7 ml. of concentrated ammonium hydroxide and the resulting mixture extracted with one 100-ml. portion and three 50-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and taken to dryness *in vacuo*. The residual yellow oil, as the free base, was dissolved in 75 ml. of methyl ethyl ketone, treated with 5.68 g. of methyl iodide in 25 ml. of methyl ethyl ketone, and allowed to stand overnight at room temperature. The reaction mixture was then chilled and filtered to yield 12.73 g. (85% yield) of the methiodide, VII. Recrystallization of a 1-g. sample from 25 ml. of hot acetone containing 4 ml. of ethanol yielded crystals with m.p. 187–188.5°, and $\lambda_{max}^{CHCl_3}$ 4.15, 6.2, and 6.7 μ.

Anal. Calcd. for $C_{21}H_{26}NI$: C, 60.14; H, 6.25; I, 30.26. Found: C, 60.10; H, 6.14; I, 30.58.

A suspension of 1.0 g. of the methiodide of 5-(γ-dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (VII) in 30 ml. of 10% aqueous potassium hydroxide solution was heated on a steam bath for 0.5 hr. At the end of this time, the reaction mixture was cooled to room temperature and extracted with two 25-ml. portions of ether. The combined ether extracts were washed successively with three 10-ml. portions of water, 10 ml. of saturated salt solution, and dried over magnesium sulfate. The solvent was removed *in vacuo* to yield 580 mg. of a yellow oil with $\lambda_{max}^{dioxane}$ 267 mμ, ε 15,000; $\lambda_{max}^{CHCl_3}$ 6.19, 6.75, 6.95, 10.0, and 10.98 μ. The infrared spectrum of this material was the same as that of diene obtained in part A.

5-Propylidene-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (VIII).—A solution of 200 mg. of the diene VI in 25 ml. of benzene was hydrogenated at atmospheric pressure over 100 mg. of 5% palladium on charcoal. Removal of the solvent and catalyst yielded 170 mg. of crystalline propylidene compound VIII with m.p. 49–51.6°; $\lambda_{max}^{dioxane}$ 238 mμ, ε 13,300; $\lambda_{max}^{CHCl_3}$ 3.4, 6.05, 6.75, 6.9, 6.96 (sh), 7.38 and 8.85 μ.

(4) G. Zweifel, K. Nagase, and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 190 (1962).

Anal. Calcd. for $C_{18}H_{18}$: C, 92.25; H, 7.74. Found: C, 91.81; H, 7.47.

5-(β,γ-Dibromopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (IX).—A solution of 1.39 g. of bromine in 25 ml. of chloroform was added dropwise to a solution of 2.0 g. of the diene VI in 75 ml. of chloroform at room temperature and at such a rate that the reaction mixture remained colorless. After a total of 1.28 g. of bromine had been added (the reaction mixture failed to absorb bromine further), the addition was stopped and stirring continued for 40 min. The reaction mixture was taken to dryness *in vacuo*, the residual oil dissolved in hexane, filtered through Celite, concentrated to a small volume, seeded, and chilled to yield 3.0 g. of crystalline dibromide with m.p. 92–94°; λ_{max}^{MeOH} 242.5 mμ, ε 15,300; $\lambda_{max}^{CHCl_3}$ 6.2, 6.78, 6.92, 7.36, and 8.83 μ.

Anal. Calcd. for $C_{18}H_{16}Br_2$: C, 55.12; H, 4.11; Br, 40.76. Found: C, 55.33; H, 4.29; Br, 40.80.

Reaction of the Dibromide IX with Dimethylamine.—A solution of 1.0 g. of the dibromide IX in 10 ml. of benzene saturated with dimethylamine was heated in a sealed tube at 85° overnight. The reaction mixture was taken to dryness, the residue triturated with ether, and 480 mg. (74.5%) of dimethylamine hydrobromide, m.p. 132–133.6°, was filtered off. The filtrate yielded 770 mg. of oily residue which was chromatographed over 25 g. of neutral alumina. The hexane fractions eluted 400 mg. of noncrystalline material, essentially single spot by t.l.c., which had λ_{max}^{MeOH} 280 mμ, and an n.m.r. spectrum compatible with the vinyl bromide X. This substance could not be obtained analytically pure.

5-(γ-Hydroxypropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (II. X = OH).—A solution of 2.0 g. of the diene VI in 25 ml. of dry tetrahydrofuran was treated, at 0° and under dry nitrogen, with 3.8 ml. of a 2.28 *M* solution of di-*sec*-isoamylborane[4] in 4 ml. of tetrahydrofuran and allowed to stand at 0–5° for 1 hr. Water, 2 ml., was added (at 0°) to decompose any excess di-*sec*-isoamylborane, the mixture was allowed to come to room temperature and was oxidized by the addition of 4 ml. of 2.5 *N* sodium hydroxide and 2.7 ml. of 30% hydrogen peroxide. The aqueous layer was saturated with solid, anhydrous potassium carbonate, the layers separated, and the aqueous layer extracted with 10 ml. of tetrahydrofuran. The combined organic extracts were dried over magnesium sulfate, and the solvent removed *in vacuo*. The residue, on trituration with petroleum ether (b.p. 30–60°), yielded 1.45 g. (67%) of first crop crystalline alcohol identical (mixture melting point, ultraviolet, and infrared) with a sample produced by the procedure reported previously.[2]

5-(γ-Chloropropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (II. X = Cl).—A solution of 50 mg. of the primary carbinol II (X = OH) in 3 ml. of benzene containing 1 drop of pyridine was treated dropwise with 65.6 mg. of thionyl chloride in 2 ml. of benzene at room temperature and refluxed on a steam bath for 3 hr. The reaction mixture was then evaporated to dryness *in vacuo*. The residue was triturated with benzene, the benzene solution filtered, and taken to dryness *in vacuo* to give a quantitative yield of the crystalline chloride II (X = Cl identical with a sample obtained by a previously reported method.[2]

Conversion of the Primary Carbinol II (X = OH) to 5-(γ-Dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene Hydrochloride (XI).—A solution of 400 mg. of the pirmary carbinol II (X = OH) in 5 ml. of dry pyridine, chilled to 0°, was treated with 400 mg. of *p*-toluenesulfonyl chloride. The reaction mixture was allowed to stand overnight at 0–4°. At the end of this period, the reaction mixture was poured over 15–20 ml. of crushed ice and extracted with three 10-ml. portions of chloroform. The combined extracts were washed with 5-ml. portions of cold 2.5 *N* hydrochloric acid until the last wash was acidic, then washed with 10 ml. of excess potassium bicarbonate solution, followed by 10 ml. of saturated salt solution. The solution was finally dried over magnesium sulfate and taken to dryness *in vacuo* to yield 620 mg. (96.5%) of crude, noncrystalline tosylate. This material had $\lambda_{max}^{CHCl_3}$ 6.3, 7.40, 8.45, 8.55, 9.15, and 12.29 μ.

Anal. Calcd. for $C_{25}H_{24}O_3S$: S, 7.92. Found: S, 7.21.

This tosylate was treated with dimethylamine in benzene in a sealed tube at 85° as described previously[2] to yield 360 mg. (77.5%) of first crop crystalline product, m.p. 191–193°, which was identical with an authentic sample of amitriptyline XI.

1,5-Naphthyridine and Some of Its Alkyl Derivatives

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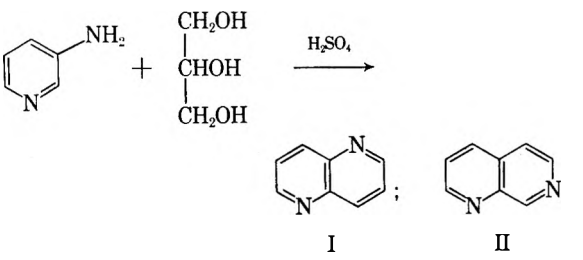
The preparation of 1,5-naphthyridine from 3-aminopyridine and glycerol in the Skraup reaction led to the isolation of 1,2,3,4-tetrahydro-1,5-naphthyridine and 3-methyl- and 3-ethyl-1,5-naphthyridine as by-products. The structures of these products were established by independent syntheses and explanations for their mode of formation are suggested. The isomeric 1,7-naphthyridine, prepared independently, was totally absent as a product of the 3-aminopyridine reaction. Oxidation of 3-ethyl-1,5-naphthyridine gave the expected 1,5-naphthyridine-3-carboxylic acid; however, 3-methyl-1,5-naphthyridine under the same conditions surprisingly gave 3-acetamidopicolinic acid. A possible mechanism for this oxidation is proposed. The infrared spectra of the various 1,5- and 1,7-naphthyridines have been correlated.

1,5-Naphthyridine (I) has appeared in the literature several times,[1-4] resulting from the Skraup reaction with 3-aminopyridine. In no instance was the isomeric 1,7-naphthyridine (II) detected, although its formation cannot be excluded rigorously, since purification was by crystallization exclusively. It seemed reasonable to expect that some of the 1,7-isomer would be formed, particularly since the analogous reaction with *m*-substituted anilines invariably gave both possible isomers.[5] For this reason, and also because we required a large quantity of pure 1,5-naphthyridine, we have examined the Skraup reaction with 3-aminopyridine in detail.



Preliminary experiments established that (1) the maximum crude yield was obtained in the presence of boric acid, and (2) this crude product, on chromatography, gave a fraction with the characteristic 1,5-naphthyridine ultraviolet spectrum and a fraction with the characteristic 3-aminopyridine spectrum. A convenient large-scale purification method then was

(1) B. Bobranski and E. Sucharda, *Ber.*, **60**, 1081 (1927).
(2) C. R. Hauser and G. A. Reynolds, *J. Org. Chem.*, **15**, 1224 (1950).
(3) E. P. Hart, *J. Chem. Soc.*, 1879 (1954).
(4) A. Albert, *ibid.*, 1790 (1960).
(5) M. H. Palmer, *ibid.*, 3645 (1962), and references therein.

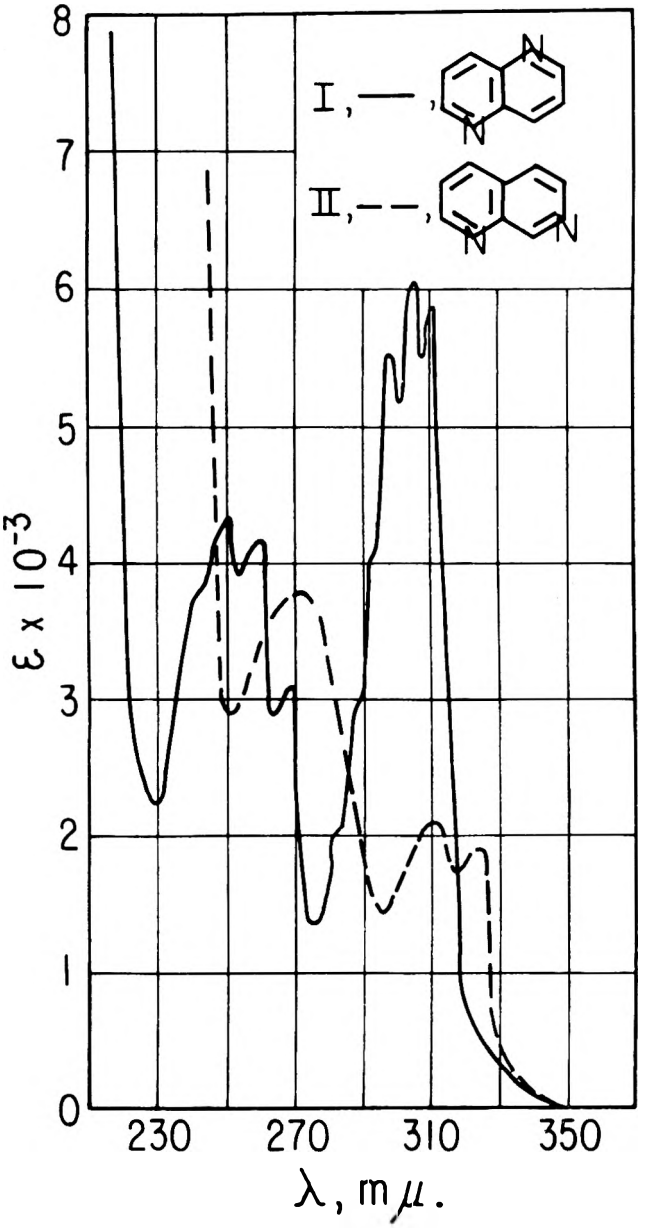


Fig. 1.—Ultraviolet absorption spectra of 1,5-naphthyridine (I) and 1,7-naphthyridine (II) in methanol.

developed by considering the differences in basicity and polarity between the naphthyridine and 3-aminopyridine fractions. Taking 1,5-naphthyridine and 3-aminopyridine as typical of the two fractions, the pK_a values were determined by partition methods and found to be 3.2 for 1,5-naphthyridine[6] and 6.0 for 3-aminopyridine.[7] Also, 1,5-naphthyridine has a partition coefficient of 0.3 between pentane and water, while that of 3-aminopyridine is less than 0.01. Thus, continuous extraction at pH 3 with pentane cleanly and completely removed the weak naphthyridine bases, and the 3-aminopyridine fraction then was extracted by ether after making the solution alkaline.

Vapor phase chromatography (v.p.c.) of the ether extract, fraction A, demonstrated the presence of two compounds, A-1 and A-2, obtained in quantity by fractional distillation. Fraction A-1 was recovered 3-aminopyridine. Fraction A-2, $C_8H_{10}N_2$, had an ultraviolet absorption very similar to that of 3-aminopyridine and was shown to be 1,2,3,4-tetrahydro-1,5-naphthyridine (III)[8] by comparison with an authentic sample prepared by catalytic hydrogenation of 1,5-naphthyridine. By extending the reaction time from six to twenty hours, the yields of A-1 and A-2 become negligible with a corresponding increase in the naphthyridine fraction.

The initial pentane fraction, N, was shown by v.p.c. to contain three components which were separable by fractional distillation. Fraction N-1, by elemental analysis and comparison of physical properties with the literature values, was obviously 1,5-naphthyridine (I) and was obtained in 31% yield.

Fraction N-2, $C_9H_8N_2$, m.p. 73–75°, was obtained in 4% yield. Its ultraviolet absorption was very similar to that of 1,5-naphthyridine, and Kuhn–Roth oxidation gave acetic acid. Thus, N-2 was probably a methyl-1,5-naphthyridine, and, since it failed to condense with benzaldehyde, the methyl group was assigned to position 3.

As confirmation, and since we wished to establish some infrared correlations (given later), all three methyl isomers were synthesized. This was conveniently done by the reaction of 3-aminopyridine with crotonaldehyde, methylacrolein, and methyl vinyl ketone, to yield 2-methyl-, 3-methyl-, and 4-methyl-1,5-naphthyridine, respectively. These isomers can be clearly distinguished by melting point, infrared absorption, and v.p.c. The 3-methyl-1,5-naphthyridine (IV) was identical with compound N-2.

Compound N-3, $C_{10}H_{10}N_2$, also was obtained in 4% yield as a colorless liquid. Its ultraviolet absorption was almost identical with that of N-2, and it contained one C-methyl group, indicating that the additional two carbons represented an ethyl substitutent, rather than two methyl groups, on the 1,5-naphthyridine nucleus. Since the infrared absorption (given later) of N-3 in the 700–900-cm.$^{-1}$ region was quite similar to that of N-2, the former was assumed to be 3-ethyl-1,5-naphthyridine. To synthesize this compound, we followed the example provided by the synthesis of 3-ethylquinoline[9] in which 2-hydroxymethyl-2-methyl-1,3-propanediol was used and may be considered as a source of ethylacrolein, generated *in situ*. When this triol and 3-aminopyridine were treated under conditions of the Skraup reaction, 3-ethyl-1,5-naphthyridine (V) resulted. It was identical with compound N-3 in ultraviolet and infrared absorption and by v.p.c.

Thus, the various products isolated from the reaction of 3-aminopyridine and glycerol were: 1,2,3,4-tetrahydro-1,5-naphthyridine (III), 1,5-naphthyridine (I), 3-methyl-1,5-naphthyridine (IV), and 3-ethyl-1,5-naphthyridine (V). Although we had not found any 1,7-naphthyridine (II), it conceivably might have been formed to a very slight extent and have been a contaminant among the products above. To settle this question, we synthesized 1,7-naphthyridine and established its behavior in our isolation scheme and its limit of detection in the several fractions.

An improved synthesis of 1,7-naphthyridine[4,10] was developed, starting with the readily prepared 1,7-

(6) Reported pK_a 2.91 in ref. 4.

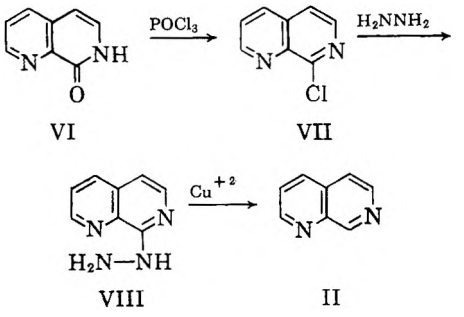
(7) Reported pK_a 6.1 [J. G. Murray and C. R. Hauser, *J. Org. Chem.*, **19**, 2008 (1954)] and 6.6 [H. Tropsch, *Monatsh. Chem.*, **35**, 777 (1914)].

(8) K. Miyaki, *J. Pharm. Soc. Japan*, **62**, 257 (1942).

(9) R. W. Brown and G. Dougherty, *J. Am. Chem. Soc.*, **69**, 2232 (1947).

(10) N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **6**, 401 (1958).

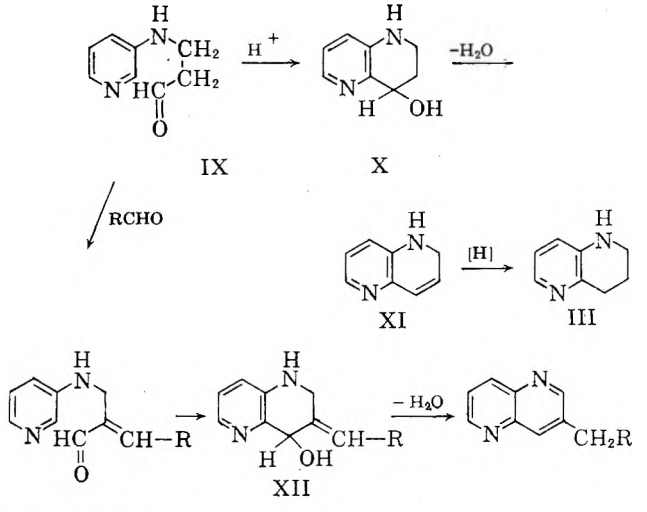
naphthyridin-8(7*H*)-one (VI).[11] Treatment with phosphorus oxychloide gave the 8-chloro compound (VII). Although hydrogenolysis of the chloro compound could not be effected without concurrent hydrogenation of the naphthyridine nucleus, the 8-hydrazino compound (VIII) was easily prepared and with cupric ion this was reduced to 1,7-naphthyridine (II).



The ultraviolet absorption of 1,7-naphthyridine is quite different from that of 1,5-naphthyridine (Fig. 1). The pentane/water partition coefficient of the 1,7-isomer is 0.02 and its pK_a is 3.7.[12] Since continuous extraction with pentane completely removed it from an aqueous solution at pH 3, any 1,7-naphthyridine present would have appeared in the N (naphthyridine) fraction. From the ultraviolet spectra and v.p.c. behavior of the compounds in this fraction as compared to that of 1,7-naphthyridine, it was established that the presence of 0.3% of 1,7-naphthyridine in this fraction would have been detected easily. Thus, we conclude that essentially none of the 1,7-isomer was formed.

Several aspects of the Skraup reaction with 3-aminopyridine deserve further comment: these are (1) the formation of 1,2,3,4-tetrahydro-1,5-naphthyridine; (2) the formation of the methyl and ethyl homologs; and (3) the fact that cyclization takes place exclusively to the 2-position.

The presence of the tetrahydro compound may result from the dihydro intermediate through the action of another molecule of dihydro compound acting as a reducing agent. By analogy with the quinoline case, the dihydro compound XI undoubtedly arises from dehydration of the carbinol (X) formed by cyclization of the arylamino aldehyde (IX), itself the product of



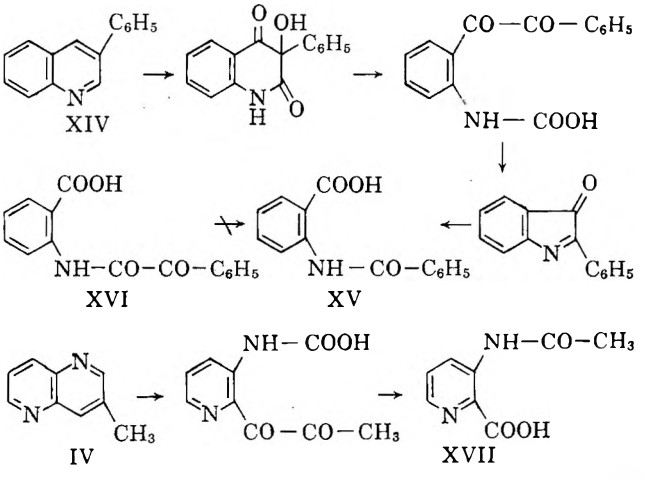
3-aminopyridine addition to acrolein. Since extending the reaction time leads to disappearance of the tetrahydro compound, it must be slowly oxidized to the completely aromatic system.

To explain the formation of the alkyl naphthyridines, we have assumed that alkylation occurs prior to aromatization. If the intermediate arylaminopropionaldehyde (IX) condenses with formaldehyde or acetaldehyde and then cyclizes, dehydration of the resulting carbinol (XII) would give the 3-methyl or 3-ethyl compound. Equimolar amounts of formaldehyde and acetaldehyde could be formed by a retro-aldol condensation of the intermediate dehydration product of glycerol, β-hydroxypropionaldehyde.

Why cyclization takes place only at the 2-position and not at all at the 4-position is puzzling. Similar orientation has been observed in other electrophilic substitutions into pyridines bearing activating substituents at the 3-position. It has been suggested[13] that a possible chelating effect involving the protonated ring-nitrogen may be responsible.

Before establishing the structure of N-3 as 3-ethyl-1,5-naphthyridine (V) by independent synthesis, an effort was made to relate it to N-2, 3-methyl-1,5-naphthyridine (IV), by oxidizing both compounds to 1,5-naphthyridine-3-carboxylic acid (XIII). Since the aromatic portion of both molecules had been oxidized in preference to the side chain under acidic conditions, alkaline permanganate was used.

From 3-ethyl-1,5-naphthyridine, a good conversion to 1,5-naphthyridine-3-carboxylic acid, m.p. 279°, was obtained. However, oxidation of 3-methyl-1,5-naphthyridine under identical conditions gave a new acid which melted with decarboxylation at 212°. This acid, $C_8H_8N_2O_3$, had two carbonyl bands in the infrared, one at 5.95 μ (aromatic acid) and the other at 6.04 μ (amide). The decarboxylated product was identical with 3-acetamidopyridine. Therefore, the oxidation product obtained from 3-methyl-1,5-naphthyridine was 3-acetamidopicolinic acid (XVII). The formation of XVII from 2-methyl-1,5-naphthyridine might be accepted; its formation from the 3-methyl isomer was surprising.



Therefore, we sought an explanation for this reaction, and a previous observation made in the quinoline series was strongly suggestive. This was the oxidation of 3-phenylquinoline (XIV) to benzoylanthranilic acid

(11) A. Albert and A. Hampton, *J. Chem. Soc.*, 4985 (1952).

(12) Reported pK_a 3.63 (ref. 4) and 3.6-3.7 [N. Ikekawa, *Chem. Pharm. Bul.* (Tokyo), **6**, 408 (1958)].

(13) K. Schofield, *Quart. Rev.* (London), **4**, 382 (1950).

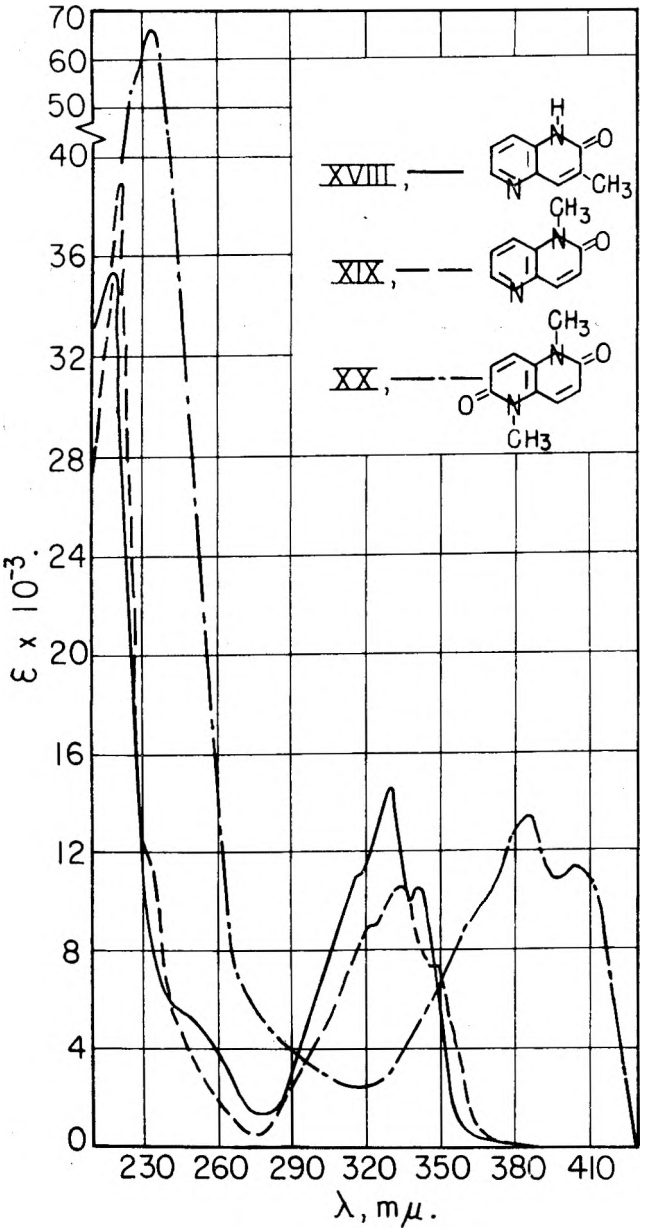
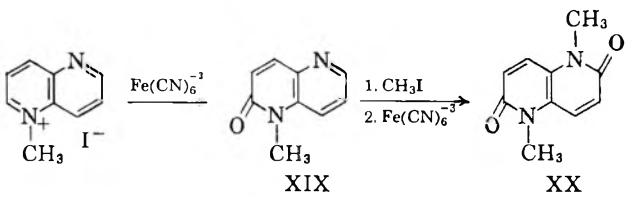


Fig. 2.—Ultraviolet absorption spectra of 3-methyl-1,5-naphthyridin-2(1*H*)-one (XVIII), 1-methyl-1,5-naphthyridin-2(1*H*)-one (XIX), and 1,5-dimethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione (XX) in methanol.

(XV)[14] which had been construed as arising from a 1,2-shift of unknown mechanism.[15] It was shown[14] that the benzoylformamide of anthranilic acid (XVI) was not an intermediate in the formation of XV. This reaction can be rationalized by assuming initial oxidation to the quinolone, followed by attack at the double bond. Oxidation now between C_2–C_3 leads to a diketone which cyclizes after decarboxylation. Oxidation of the imino ketone now gives the observed product. By an analogous mechanism, 3-methyl-1,5-naphthyridine (IV) would give 3-acetamidopicolinic acid (XVII), as it does. This mechanism provides a satisfactory explanation for the behavior of 3-methyl-1,5-naphthyridine on oxidation. And, of ccurse, the side-chain oxidation observed with 3-ethyl-1,5-naphthyridine is quite reasonable. We have no explanation for the difference in behavior between the 3-methyl and 3-ethyl compounds.

In a continuation of oxidation experiments, 3-methyl-1,5-naphthyridine was heated with dichromate in 6 N sulfuric acid. The product was assigned the structure 3 - methyl - 1,5 - naphthyridin - 2(1*H*) - one (XVIII) on the basis of its infrared absorption and the similarity of its ultraviolet spectrum with those of naphthyridinones (Fig. 2) prepared through the methiodides. This mode of acidic oxidation of the alkyl naphthyridine is consistent with the high yield of acetic acid obtained in the Kuhn–Roth oxidation.

The N-methylnaphthyridinones were prepared by alkaline ferricyanide oxidation of the corresponding methiodides. Thus, 1,5-naphthyridine was quaternized and oxidized to the mononaphthyridinone (XIX); the process was repeated to obtain the naphthyridinedione (XX). In the case of the ethylnaphthyridine, the mixture of methiodides was oxidized directly to give the 1-methyl-3-ethyl-1,5-naphthyridin-2(1*H*)-one (XXI) and 1,5-dimethyl-3-ethyl-1,5-naphthyridine-2,6-(1*H*,5*H*)-dione (XXII).



Since several substituted naphthyridines were on hand, an examination of their infrared spectra in carbon disulfide was made in an attempt to correlate the aromatic hydrogen out-of-plane vibrations in the 650–1000-cm.$^{-1}$ region with the position of substitution. Previous correlations for this region have led to the assignments for substituted benzenes[16] of 750–810 cm.$^{-1}$ for three adjacent ring hydrogens, 800–860 cm.$^{-1}$ for two adjacent ring hydrogens, and 860–900 cm.$^{-1}$ for an isolated ring hydrogen. These assignments seem to be valid for pyridines and quinolines as well[17]; however, in the naphthyridines examined here, the values are shifted to higher frequencies (Table I). The spectrum of 1,2,3,4-tetrahydro-1,5-naphthyridine (III) shows the expected peak for three adjacent ring hydrogens at 790 cm.$^{-1}$; however, although 1,5-naphthyridine (I) and 2-methyl-1,5-naphthyridine (IVa) have this peak at 816 cm.$^{-1}$ and 818 cm.$^{-1}$, respectively, 4-methyl-1,5-naphthyridine (IVb) absorbs at 786 cm.$^{-1}$. The latter two compounds show peaks at 837 cm.$^{-1}$ and 845 cm.$^{-1}$, respectively, for two adjacent ring hydrogens. For 1,7-naphthyridine (II) and 8-chloro-1,7-naphthyridine (VII), the peaks for three adjacent hydrogens appear at 818 cm.$^{-1}$ and 801 cm.$^{-1}$, respectively.[18] There may be some doubt as to whether the slightly weaker peak at 764 cm.$^{-1}$ might not be due to three adjacent hydrogens, but since this band disappears along with the band at 943 cm.$^{-1}$

(14) K. Ueda, *J. Pharm. Soc. Japan*, **57**, 827 (1937).

(15) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 256.

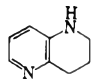
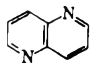
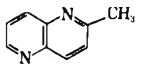
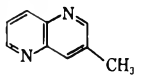
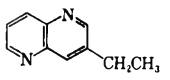
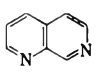
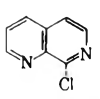
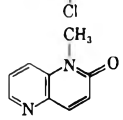
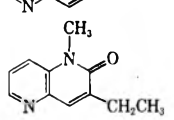
(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen and Co., London, 1958, p. 75.

(17) H. Shindo and S. Tamura, *Pharm. Bull.* (Tokyo), **4**, 292 (1956); H. Shindo, *ibid.*, **5**, 472 (1957); C. Karr, P. A. Estep, and A. J. Papa, *J. Am. Chem. Soc.*, **81**, 152 (1959).

(18) N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **6**, 404 (1958), has reported the infrared spectrum of 1,7-naphthyridine in Nujol and it appears to be quite different from ours except for the strong band at 818 cm.$^{-1}$. Consequently, his assignments differ from ours.

TABLE I

INFARED[a] ASSIGNMENTS FOR AROMATIC HYDROGEN OUT-OF-PLANE VIBRATIONS IN 1,5- AND 1,7-NAPHTHYRIDINES

	Compound	Assignments, ν in cm.$^{-1}$ 3 adjacent H's	2 adjacent H's	Isolated H
III		790	...	...
I		816	...	...
IVa		818	837	...
IVb		786	845	...
IV		823	...	890, 773
V		821	...	904, 772
II		818	838	943, 764
VII		801	841	...
XIX		796	841	...
XXI		797	...	912, 754

[a] In carbon disulfide.

when the isolated hydrogen at position 8 is replaced with chlorine, these latter two peaks have been assigned to the isolated ring hydrogen. The spectrum of 1-methyl-1,5-naphthyridin-2(1*H*)-one (XIX) has bands at 796 cm.$^{-1}$ and 841 cm.$^{-1}$ for three and two adjacent ring hydrogens, respectively. The peak at 841 cm.$^{-1}$ disappears when there is an ethyl group at the 3-position (XXI) and two new bands of medium intensity appear for the isolated hydrogen at 912 cm.$^{-1}$ and 754 cm.$^{-1}$. The spectra of 3-methyl- (IV) and 3-ethyl-1,5-naphthyridine (V), which seemed complex at first, now can be interpreted on the basis of previous correlations. The strong peak near 900 cm.$^{-1}$ accompanied by another strong peak near 770 cm.$^{-1}$ is due to the two isolated hydrogens and the band near 820 cm.$^{-1}$ is due to three adjacent ring hydrogens.

Experimental[19]

Skraup Reaction with 3-Aminopyridine.—To a 12-l. flask were added the following ingredients in sequence: 280 g. (1.2 moles) of arsenic pentoxide, 80 g. (0.53 mole) of ferrous sulfate, 220 g. (2.34 moles) of pure 3-aminopyridine, a solution prepared by heating on the steam bath 140 g. (2.3 moles) of boric acid, 830 g. (10 moles) of anhydrous glycerine, and 2 ml. of concentrated sulfuric acid, 240 ml. of concentrated sulfuric acid, and 30 ml. of fuming (15%) sulfuric acid. The reaction mixture was stirred and heated to 100°, and after the initial reaction had subsided, it was heated during 2 hr. to a final internal temperature of 135°. This temperature was maintained for 3 additional hr. The black reaction mixture was made basic and steam distilled until the optical density of the distillate at 304 mμ was less than 10. The distillate (20 l.) was adjusted to pH 3.1 with phosphoric acid and extracted continuously with pentane. Evaporation of the pentane gave 95 g. of semicrystalline product. This material showed three peaks by vapor phase chromatography (v.p.c.).

The residual pH 3 aqueous phase was made alkaline with sodium hydroxide and continuously extracted with ether to yield 34 g. of oil after evaporation of the ether. Fractionation through a 1-m. Podbielniak column gave the following two fractions.

Fraction A-1, 18.3 g. (8% recovery), b.p. 118–120° (44 mm.), was crystallized from benzene–hexane, m.p. 59–61°. It was identical with 3-aminopyridine by melting point, mixture melting point, and infrared and ultraviolet absorption; λ_{max} 303 mμ (ϵ 3200), 242 (11,000).

Fraction A-2 amounted to 15.5 g. (5% yield), b.p. 117–120° (18 mm.). Crystallization from benzene–hexane followed by sublimation at 80° (50 μ) gave 1,2,3,4-tetrahydro-1,5-naphthyridine (III), m.p. 109–111° (reported[8] m.p. 105°); λ_{max} 321 mμ (ϵ 3960), 258 (8830), 209 (9390).

Anal. Calcd. for $C_8H_{10}N_2$: C, 71.6; H, 7.5; N, 20.9. Found: C, 71.7; H, 7.3; N, 20.9.

When the Skraup reaction was repeated, using an increased reaction time of 20 hr. at 135°, a total of 34 l. of steam distillate was collected. Using the same isolation procedure, the pH 3 pentane extract amounted to 118 g., while the alkaline ether extract amounted to only 2 g. The pH 3 extract showed the same three peaks by v.p.c. as previously, and fractionation through a 1-m. Podbielniak column separated this extract into three fractions, N-1, N-2, and N-3.

The fraction N-1, 87.4 g. (31% yield), b.p. 150–152° (54 mm.), was crystallized from pentane to give 1,5-naphthyridine (I), m.p. 74–75° (reported[1,4] m.p. 75°); λ_{max} 250 mμ (ϵ 4430), 259 (4300), 268 (3210), 297 (5620), 304 (6130), 309 (5970); in acid, 235 (5160), 275 (4900), 307 (11,200), 312 (11,400), 363 (1890).

Anal. Calcd. for $C_8H_6N_2$: C, 73.8; H, 4.6; N, 21.5. Found: C, 73.6; H, 4.5; N, 21.4.

Fraction N-2, 14.7 g. (4.4% yield), b.p. 173–175° (56 mm.), was crystallized from pentane and sublimed at 60° (0.2 mm.) to give 3-methyl-1,5-naphthyridine (IV), m.p. 73–75°; λ_{max} 252 mμ (ϵ 4130), 259 (3720), 268 (2390), 302 (6300), 308 (6800), 314 (6700); in acid, 321 (11,000), 313 (10,400 sh), 276 (3090 sh).

Anal. Calcd. for $C_9H_8N_2$: C, 75.0; H, 5.6; N, 19.4; equiv. wt., 144; C–CH_3, 10.4. Found: C, 75.1; H, 5.7; N, 19.5; equiv. wt., 140; C–CH_3, 8.2.

Fraction N-3 amounted to 15.5 g. (4.4%) of 3-ethyl-1,5-naphthyridine (V), b.p. 181–182° (56 mm.), λ_{max} 251 mμ (ϵ 4700), 259 (3900), 268 (2760), 303 (6800), 315 (6700).

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.9; H, 6.4; N, 17.7; equiv. wt., 158; C–CH_3, 9.5. Found: C, 76.1; H, 6.5; N, 17.7; equiv. wt., 153; C–CH_3, 7.0.

3-Methyl-1,5-naphthyridine (IV).—A stirred suspension of 2 g. of ferrous sulfate, 14 g. (0.06 mole) of arsenic pentoxide, 9.4 g. (0.10 mole) of 3-aminopyridine, and 30 ml. of concentrated sulfuric acid was heated to 120° (bath temp.) and 15 ml. of methylacrolein was added dropwise over 2 hr. After 4 hr., an additional 17 ml. (total, 0.4 mole) of methylacrolein was added over 1 hr. The resultant mixture was heated for 15 hr. at 170°. Isolation in the usual manner gave 4.3 g. (30% yield) of 3-methyl-1,5-naphthyridine which was crystallized from pentane, and sublimed at 50° (0.2 mm.); m.p. 73–75°. This material was identical with fraction N-2.

2-Methyl-1,5-naphthyridine (IVa).—A solution of 70 ml. of "sulfo mix,"[20] 25 ml. of water, and 23.5 g. (0.25 mole) of 3-aminopyridine was heated to 125–130° and freshly distilled crotonaldehyde (25 ml., 0.3 mole) was added dropwise over an hour. The bath was raised to 150° and the reaction mixture was heated overnight. The usual isolation procedure gave 3 g. of material which was chromatographed on alumina and sublimed at 40° (0.1

(19) All melting points are corrected, and those above 200° were taken in evacuated capillaries; microanalyses were performed by V. Tashinian, Microchemical Laboratory, University of California, Berkeley. Ultraviolet spectra were determined in methanol, and those in acid (1 *N* hydrochloric acid) and in alkali (0.1 *N* sodium hydroxide) were taken in 90% aqueous methanol. Infrared spectra were taken in carbon disulfide unless otherwise noted. Vapor phase chromatograms were obtained at 140° using a 1.5-m. column packed with silicone grease on firebrick.

(20) W. P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).

mm.) to give 2-methyl-1,5-naphthyridine, m.p., 60–61° (reported[8] m.p. 62°); λ_{max} 242 mμ (ε 3790 sh), 249 (4000), 257 (3740), 265 (2700), 300 (5450), 307 (5930), 313 (5600); in acid, 317 (10,200), 308 (9700), 264 (4680).

Anal. Calcd. for $C_9H_8N_2$: C, 75.0; H, 5.6; N, 19.4; C-CH_3, 10.4. Found: C, 74.7; H, 5.7; N, 19.1; C-CH_3, 5.1.

2-Styryl-1,5-naphthyridine.—A solution of 0.5 ml. of glacial acetic acid, 1.0 ml. of acetic anhydride, 1.0 ml. of benzaldehyde, and 1.04 g. (7.2 mmoles) of 2-methyl-1,5-naphthyridine was heated at reflux for 2 days under a nitrogen atmosphere. Hydrochloric acid (100 ml. of 3 *N*) was added; the solution was extracted with methylene chloride (five 25-ml. portions), back-washing each time with acid. The aqueous phase and washings were combined, made alkaline, and extracted with chloroform to give a total of 1.2 g. of material. A sample was sublimed at 100° (10 μ), and crystallized from hexane–benzene to give 2-styryl-1,5-naphthyridine, m.p. 120–121°; λ_{max} 218 mμ (ε 46,500), 262 (16,500), 270 (16,000), 300 (16,000), 339 (21,200); in acid, 292 (16,700), 306 (11,000), 385 (33,000).

Anal. Calcd. for $C_{16}H_{12}N_2$: C, 82.7; H, 5.2; N, 12.1. Found: C, 82.9; H, 5.1; N, 12.1.

4-Methyl-1,5-naphthyridine (IVb).—The same procedure was used as for the preparation of the 2-methyl compound, except that 18 g. (0.26 mole) of methyl vinyl ketone was substituted for the crotonaldehyde. The yield was 4.0 g. (11%) of 4-methyl-1,5-naphthyridine, m.p. 30–32°; λ_{max} 257 mμ (ε 5370), 265 (5880), 273 (4660), 296 (5030), 303 (5410), 308 (5430); in acid, 281 (7500), 304 (10,500), 309 (10,000).

Anal. Calcd. for $C_9H_8N_2$: C, 75.0; H, 5.6; N, 19.4. Found: C, 74.6; H, 5.7; N, 19.0.

3-Ethyl-1,5-naphthyridine (V).—To a 3-l. flask were added 3 g. of ferrous sulfate, 35 g. (0.15 mole) of arsenic pentoxide, 23.5 g. (0.25 mole) of 3-aminopyridine, 90 g. (0.75 mole) of 2-hydroxymethyl-2-methyl-1,3-propanediol, 15.5 g. (0.25 mole) of boric acid, and 140 ml. of concentrated sulfuric acid. This mixture was stirred and heated until the internal temperature reached 150° at which point the reaction became violent and the heat source was removed. Heating was resumed when the reaction had subsided, and the temperature was maintained at 130° for 4 hr. The usual naphthyridine isolation procedure gave 5.5 g. of liquid which was fractionated and gave 5.0 g. of 3-ethyl-1,5-naphthyridine, b.p. 162–170° (40 mm). This material was identical with fraction N-3.

1,2,3,4-Tetrahydro-1,5-naphthyridine (III).—A suspension of 13 mg. of platinum oxide in a solution of 1.31 g. (10 mmoles) of 1,5-naphthyridine in 10 ml. of 95% ethanol was hydrogenated at room temperature and atmospheric pressure. After 26 hr., absorption ceased with an uptake of 200 mole % of hydrogen. The mixture was filtered, the filtrate was evaporated, and the residue was sublimed at 80° (50 μ) to give a quantitative yield of 1,2,3,4-tetrahydro-1,5-naphthyridine, m.p. 111–113°. This material was identical with fraction A-2.

1,7-Naphthyridin-8(7*H*)-one (VI).—This material was prepared as described[11] except that "sulfo mix"[20] was used. The crude product was purified by crystallization from methanol and sublimation at 180° (10 μ); yield, 90%; m.p. 236–239° (reported[11] yield, 20%, m.p. 233.5°).

8-Chloro-1,7-naphthyridine (VII).—1,7-Naphthyridin-8(7*H*)-one (VI) (17.5 g., 0.12 mole) and 125 g. of phosphorus oxychloride were heated at reflux overnight. Excess phosphorus oxychloride was distilled *in vacuo*, the residue was treated with 200 g. of ice–water, the pH was adjusted to 5 with sodium hydroxide, and the aqueous phase was extracted continuously with methylene chloride. Evaporation of the methylene chloride and sublimation of the residue at 80° (0.5 mm.) gave 11.5 g. (58% yield) of 8-chloro-1,7-naphthyridine which, on crystallization from benzene–hexane, melted at 87–88°; λ_{max} 228 mμ (ε 25,000), 268 (4100), 308 (3600), 319 (3200).

Anal. Calcd. for $C_8H_5N_2Cl$: C, 58.4; H, 3.1; Cl, 21.5. Found: C, 58.3; H, 3.3; Cl, 21.6.

8-Hydrazino-1,7-naphthyridine (VIII).—A solution of 8.02 g. (0.049 mole) of 8-chloro-1,7-naphthyridine (VII) in 55 ml. of ethanol and 23 ml. (0.40 mole) of 85% hydrazine hydrate was heated to a boil on the steam bath for 10 min. Evaporation of the ethanol *in vacuo* left an oil which solidified and was sublimed at 100° (0.1 mm.), giving 7.73 g. (99% yield) of 8-hydrazino-1,7-naphthyridine, m.p. 98–99°; λ_{max} 229 mμ (ε 12,200), 2–7 (12,700), 316 (4140), 346 (4460).

Anal. Calcd. for $C_8H_8N_4$: C, 60.0; H, 5.0; N, 35.0. Found: C, 59.9; H, 5.2; N, 34.8.

1,7-Naphthyridine (II).—To a solution of 2.68 g. (0.017 mole) of 8-hydrazino-1,7-naphthyridine (VIII) in 25 ml. of water and 6 ml. of acetic acid was added dropwise 60 ml. of a 10% aqueous solution of cupric sulfate. The resulting mixture was heated on the steam bath until gas evolution ceased (45 min.) and cautiously made alkaline with concentrated sodium hydroxide. Continuous extraction with methylene chloride and evaporation of the solvent left a residue which was dissolved in benzene and chromatographed on alumina. The crystalline eluate was sublimed at 60° (0.1 mm.) to give 500 mg. of 1,7-naphthyridine, m.p. 60–62° (reported m.p., 57–60°,[10] 64°[4]); λ_{max} 219 mμ (ε 26,600 sh.), 262 (3820), 302 (2130), 313 (1930).

Anal. Calcd. for $C_8H_6N_2$: C, 73.8; H, 4.7; N, 21.5. Found: C, 73.9; H, 4.7; N, 21.6.

1,5-Naphthyridine-3-carboxylic Acid (XIII).—To a stirred solution of 8.9 g. (0.057 mole) of 3-ethyl-1,5-naphthyridine (V) in 100 ml. of water heated to 70° was added 36 g. (0.23 mole) of potassium permanganate in six equal portions over 1 hr. The suspension was heated for an additional 30 min. and filtered. Manganese dioxide residue was digested with hot water (three 20-ml. portions); these digests were added to the filtrate. Filtrate (pH 9) was extracted continuously with methylene chloride to recover 3.6 g. (40%) of 3-ethyl-1,5-naphthyridine. Adjusting the aqueous phase to pH 3.0 with phosphoric acid and extracting continuously with chloroform gave 2.4 g. of 1,5-naphthyridine-3-carboxylic acid, m.p. 279° after sublimation at 150° (5 μ); λ_{max} 213 mμ (ε 55,000), 254 (8560), 303 (7400), 310 (7200), 316 (7170); in alkali, 246 (8210), 304 (7240), 309 (7470), 317 (7430); in acid, 258 (6800), 312 (10,400), 318 (10,700).

Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.1; H, 3.5; N, 16.1; equiv. wt., 174. Found: C, 62.2; H, 3.4; N, 16.2; equiv. wt., 175.

1,5-Naphthyridine-3-carboxamide was prepared by treating the acid with thionyl chloride, evaporating the excess thionyl chloride, and adding concentrated aqueous ammonia to the residue. Extraction with chloroform, evaporation of the chloroform, crystallization of the residue from methanol–acetone and sublimation at 150° (10 μ) gave the **amide**, m.p. 257°.

Anal. Calcd. for $C_9H_7N_3O$: C, 62.4; H, 4.0. Found: C, 62.6; H, 4.2.

3-Acetamidopicolinic Acid (XVII).—The oxidation procedure was the same as that used for the ethyl compound. From 10.9 g. (76 mmoles) of 3-methyl-1,5-naphthyridine (IV) and 53 g. (33 moles) of potassium permanganate there was obtained a 37% (4.0 g.) recovery of starting material, and a 30% yield (4.5 g.) of 3-acetamidopicolinic acid, m.p. 212° dec. after sublimation at 150° (10 μ); λ_{max} 254 mμ (ε 16,500), 307 (6700); in alkali, 251 (18,700), 293 (6200); in acid, 229 (18,100), 262 (13,400), 318 (5800); λ_{max}^{KBr} 5.95, 6.04 μ.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.3; H, 4.6; N, 15.6; equiv. wt., 180; C-CH_3, 8.3. Found: C, 53.8; H, 4.4; N, 15.8; equiv. wt., 177; C-CH_3, 7.6.

This material was decarboxylated in boiling *p-tert*-butyltoluene to give **3-acetamidopyridine**, m.p. 129–131°, identical with an authentic sample prepared by acetylation of 3-aminopyridine.

3-Methyl-1,5-naphthyridin-2(1*H*)-one (XVIII).—To a solution of 4.0 g. (28 mmoles) of 3-methyl-1,5-naphthyridine (IV) in 100 ml. of 6 *N* sulfuric acid heated at 100° was added dropwise a solution of 8.4 g. (28 mmole) of sodium dichromate dihydrate over 2 hr. Heating was continued overnight, and the solution then was cooled and the pH adjusted to 3.1 with sodium hydroxide. This suspension was filtered and continuously extracted with chloroform. The residue obtained on evaporation of the solvent was dissolved in aqueous sodium carbonate and again extracted with chlofororm. Evaporation of the chloroform gave 2.7 g. of material which was chromatographed on alumina. Methylene chloride eluted 2.3 g. (57%) of starting material. Water removed the remaining material which was extracted at pH 7 with chloroform. The chloroform was evaporated and the residue was sublimed at 100° (10 μ) to give 400 mg. of 3-methyl-1,5-naphthyridin-2(1*H*)-one, m.p. 261–262°; λ_{max} 219 mμ (ε 36,000), 329 (14,700), 342 (10,700); in acid, 224 (24,000), 261 (4600), 340 (17,000), 353 (16,000).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.2; H, 4.9; N, 17.6.

1,5-Naphthyridine Methiodide.—To a solution of 1.00 g. (7.7 mmoles) of 1,5-naphthyridine (I) in 10 ml. of methanol was added 5 ml. (70 mmoles) of methyl iodide and the solution was heated at reflux for 12 hr. on the steam bath. The excess methyl iodide was allowed to boil off and the methanol solution was cooled to

yield 1.6 g. of 1,5-naphthyridine methiodide, m.p. 254–255° dec.; λ_{max} 288 mμ (5500), 319 (10,100), 326 (10,100); in acid, 268 (6250), 311 (11,900), 318 (12,100), 362 (2500).

Anal. Calcd. for $C_9H_9N_2I$: C, 39.7; H, 3.3; N, 10.3; I, 46.6. Found: C, 39.4; H, 3.3; N, 10.0; I, 46.4.

1-Methyl-1,5-naphthyridin-2(1*H*)-one (XIX).—To a stirred solution of 2.0 g. (7.7 mmoles) of 1,5-naphthyridine methiodide in 20 ml. of water, cooled in an ice–methanol bath, was added dropwise a solution of 1.3 g. (32 mmoles) of sodium hydroxide in 2.5 ml. of water during 5 min. and 5.3 g. (16 mmoles) of potassium ferricyanide in 10 ml. of water during 30 min., both additions starting at the same time. After 1.5 hr., the ice bath was removed and stirring was continued for an additional 5 hr. at room temperature. Continuous extraction of the reaction mixture with chloroform and evaporation of the chloroform led to 0.8 g. of residue which was dissolved in 5 ml. of chloroform and applied to 30 g. of alumina packed in benzene. The fractions eluted with chloroform–benzene (2:1) were combined and sublimed at 95° (5 μ) to give 685 mg. (56% yield) of 1-methyl-1,5-naphthyridin-2(1*H*)-one, m.p. 104–105°; λ_{max} 220 mμ (ε 39,900), 335 (11,000), 350 (7500); in acid, 223 (28,000), 261 (6200), 345 (11,700).

Anal. Calcd. for $C_9H_8ON_2$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.4; H, 5.0; N, 17.0.

1-Methyl-1,5-naphthyridin-2(1H)-one methiodide was prepared by heating under reflux for 2 days a solution of the naphthyridinone XIX and methyl iodide in benzene. Cooling and filtering gave a precipitate of methiodide which was crystallized from methanol–ether as orange needles, m.p. 216° dec.

Anal. Calcd. for $C_{10}H_{11}N_2OI$: C, 39.8; H, 3.7; N, 9.3; I, 42.0. Found: C, 39.9; H, 3.8; N, 9.0; I, 42.3.

1,5-Dimethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione (XX).—To a stirred solution of 3.0 g. (10 mmoles) of 1-methyl-1,5-naphthyridin-2(1*H*)-one methiodide in 25 ml. of water, cooled in an ice bath, were added a 5-ml. portion of a solution of 2.8 g. (70 mmoles) of sodium hydroxide in 25 ml. of water and a solution of 10 g. (30 mmoles) of potassium ferricyanide in 50 ml. of water. The remaining 20 ml. of alkali solution was added portionwise over a 5 min. period and the suspension was stirred for 15 min. Continuous extraction with chloroform and evaporation of the chloroform afforded 1.8 g. of crystalline material which was sublimed [190° (10 μ)] and recrystallized from methanol–acetone as yellow needles, m.p. 220–222° dec.; λ_{max} 233 mμ (ε 66,000), 387 (13,000), 405 (11,400).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.1; H, 5.3; N, 14.7. Found: C, 63.2; H, 5.1; N, 14.7.

1-Methyl-3-ethyl-1,5-naphthyridin-2(1*H*)-one (XXI) and 1,5-Dimethyl-3-ethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione (XXII).—A solution of 2.0 g. (13 mmoles) of 3-ethyl-1,5-naphthyridine (V) in 25 ml. of dry benzene and 10 ml. of methyl iodide was heated on the steam bath for 2 days. The benzene and excess methyl iodide were removed *in vacuo*, and to the residue was added 6 g. (50 mmoles) of potassium ferricyanide in 25 ml. of water. This solution was cooled to 5° in an ice bath, and 13 g. (0.33 mole) of sodium hydroxide in 20 ml. of water was added slowly with stirring. After an hour, the solution was extracted with chloroform, the chloroform was evaporated, and the residue taken up in 3 *N* hydrochloric acid. Extraction with chloroform and evaporation of the chloroform led to the isolation of a yellow solid which was sublimed at 150° (10 μ) to give 479 mg. (17% yield) of 1,5-dimethyl-3-ethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione, m.p. 261–262°; λ_{max} 234 mμ (ε 47,000), 383 (15,000), 402 (12,000).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5; N, 12.8. Found: C, 66.1; H, 6.5; N, 12.8.

The acid solution was made alkaline and extracted with methylene chloride which was filtered through alumina. Evaporation of the filtrate gave a white solid which was sublimed at 80° (50 μ) to give 335 mg. (14% yield) of 1-methyl-3-ethyl-1,5-naphthyridin-2(1*H*)-one, m.p. 107–108°; λ_{max} 221 mμ (ε 37,000), 248 (5000), 330 (13,000), 343 (9400); in acid, 219 (25,000), 262 (5900), 343 (16,500), 355 (15,900).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.3; H, 6.4; N, 14.8.

Determination of pK_a values was carried out by partitioning the base between an organic solvent (hexane or ether) and aqueous phosphate buffer at various pH values. Concentrations were determined spectrophotometrically, and the pK_a values were calculated from the equation

$$\frac{P}{P'} = 1 + \frac{(H^+)}{K_a}$$

where P is the true partition coefficient and P' is the apparent partition coefficient at the specific pH.

New Heteroaromatic Compounds. XVII.[1] Fluoro Derivatives of 10-Methyl-10,9-borazarophenanthrene[2]

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Four monofluoro derivatives of 10-methyl-10,9-borazarophenanthrene have been synthesized in the hope that their fluorine n.m.r. chemical shifts may provide information concerning the π-electron distribution. In the course of this work a number of new derivatives of biphenyl have been prepared.

The chemical shifts shown by the fluorine nuclear magnetic resonance in derivatives of fluorobenzene seem to reflect the π-electron density of the ring atom adjacent to fluorine.[3] It occurred to us that the corresponding chemical shifts in monofluoro derivatives of heteroaromatic systems might be used to prepare π-electron density maps of the rings and so used to check the predictions of current MO treatments.

One particularly interesting system from this point of view is 10,9-borazarophenanthrene,[4] and, therefore, we decided to synthesize as many as possible of its eight monofluoro derivatives. For convenience we included a methyl substituent in the 10-position since the parent compounds, being in effect boron hydrides, tend to oxidize rather easily in air. Unfortunately these compounds proved unexpectedly recalcitrant and we were able to obtain only four of the isomers, with fluorine in the 2-, 3-, 6-, and 7-positions.

The fluorine n.m.r. spectra of these compounds, together with those of a number of other fluoro derivatives of various aromatic systems, will be reported elsewhere and discussed. Here we describe the synthesis of the four fluoroborazarophenanthrenes, and of various new derivatives of biphenyl which we obtained as intermediates.

In order to obtain the various fluoroborazarophenanthrenes, we needed[4] the corresponding fluoro derivatives of 2-aminobiphenyl, and the most obvious route

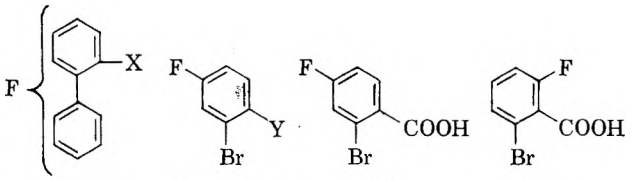
(1) Part XVI, M. J. S. Dewar, C. Kaneko, and M. K. Bhattacharjee, *J. Am. Chem. Soc.*, **84**, 4884 (1962).

(2) This work was supported by a grant (G-346) from the Office of Ordnance Research.

(3) *Cf.* R. W. Taft, S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Am. Chem. Soc.*, **81**, 5352 (1959).

(4) M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3073 (1958).

to them involved reduction of the corresponding nitro compounds. Only three of the isomeric fluoro-2-nitrobiphenyls had been previously reported. Van Hove[5] isolated 4- and 4′-fluoro-2-nitrobiphenyl by fractional crystallization of the nitration product from 4-fluorobiphenyl and 2-fluoro-2′-nitrobiphenyl has also been described.[6] We now have prepared these and the remaining fluoro-2-nitrobiphenyls (I) (except the 3-fluoro isomer) by improved routes. The 2-, 3-, and 4-fluoro-2′-nitrobiphenyls were made by Ullmann condensations from the corresponding fluoroiodobenzene and *o*-bromonitrobenzene, and 4- and 5-fluoro-2-nitrobiphenyl by a similar reaction from iodobenzene and the corresponding fluoro-2-bromonitrobenzene; 2-bromo-4-fluoronitrobenzene (IIa), which had not been described previously, was obtained by nitration of *m*-fluorobromobenzene and characterized by reduction and acetylation to 2-bromo-4-fluoroacetanilide (IIb). The remaining isomer, 2-fluoro-6-nitrobiphenyl, was prepared from 2,6-dinitrobiphenyl by partial reduction to 2-amino-6-nitrobiphenyl followed by a Schiemann reaction.



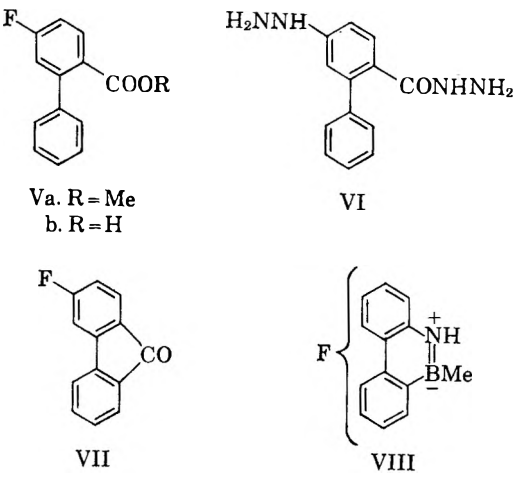
Ia. X = NO_2 IIa. Y = NO_2 III IV
b. X = NH_2 b. Y = NHAc

The nitro compounds were reduced to the corresponding aminofluorobiphenyls by the method of Marler and Turner.[7] Only the 2-amino-2′-fluoro[6] and 2-amino-4′-fluoro[5] isomers had been reported previously. The amines were characterized by their acetyl derivatives.

An alternative route to these amines would have involved replacement of the carboxyl group in a fluorobiphenyl-2-carboxylic acid by amino. We accordingly prepared 2-bromo-4-fluorobenzoic acid (III) by oxidation of 2-bromo-4-fluorotoluene, and 2-fluoro-6-bromobenzoic acid (IV) by oxidation of 2-fluoro-6-bromobenzyl bromide, itself prepared by bromination of 2-fluoro-6-bromotoluene. The methyl ester of III condensed with iodobenzene in presence of copper to give methyl 5-fluorobiphenyl-2-carboxylate (Va), but all attempts to convert this to the corresponding aminofluorobiphenyl by well established methods[8] failed. Thus Va on boiling with hydrazine hydrate gave the hydrazinobiphenylcarbohydrazide (VI). Similar replacement of fluorine by hydrazine in analogous compounds has been noticed by Dewar and Marr.[9]

Attempts to replace the carboxyl group in the corresponding acid (Vb) by amino *via* a Schmidt reaction also failed since the acid underwent cyclization in concentrated sulfuric acid to 3-fluorofluorenone (VII).

The conversion of fluoro-2-aminobiphenyls to the corresponding fluoro - 10 - methyl - 10,9 - borazarophenanthrenes was carried out by the method of Dewar, Kubba, and Pettit.[4] In this way the 2-, 6-, and 7-fluoro derivatives (VIII) were obtained. Similar treatment of 2-amino-3′-fluorobiphenyl gave a single product which must surely have been the 3-isomer; for the Friedel–Crafts ring closure is an electrophilic process and for such processes fluorine is very strongly *para*-directing.



Va. R = Me VI
b. R = H

VII VIII

Numerous attempts to cyclize 2-amino-2′-fluorobiphenyl to a 4-fluoroborazarophenanthrene failed, presumably because of steric hindrance to coplanarity in the biphenyl. The failure cannot be ascribed merely to the deactivating effect of fluorine *meta* to the point of ring closure since we encountered no difficulty in cyclizing 2-amino-4′-fluorobiphenyl to a product where the fluorine is also *meta* to boron.

The fluoro - 10 - methyl - 10,9 - borazarophenanthrenes were as stable as the parent compound, except for the 3-isomer; this darkened slowly on exposure to air.

Experimental

2-Bromo-4-fluoronitrobenzene.—Fuming nitric acid (80 g., *d* 1.5) was added slowly to a mixture of *m*-bromofluorobenzene (200 g.) and concentrated sulfuric acid (400 ml.), shaken vigorously at 30–35°. The mixture was then poured on ice, extracted with dichloromethane, and the organic layer dried and distilled. **2-Bromo-4-fluoronitrobenzene** was collected at 70–75° (0.4 mm.) as a yellow oil (75 g., 30%), $n^{25}D$ 1.5710, which crystallized on standing, m.p. 42°, not raised by recrystallization from petroleum ether.

Anal. Calcd. for $C_6H_3BrFNO_2$: C, 32.7; H, 1.36; N, 6.35. Found: C, 32.6; H, 1.29; N, 6.23.

Reduction and acetylation gave 2-bromo-4-fluoroacetanilide, identical (mixture melting point) with a sample prepared by bromination of *p*-fluoroacetanilide (see following text).

2-Bromo-4-fluoroacetanilide.—A solution of bromine (3.1 g.) in acetic acid (10 ml.) was added dropwise to one of *p*-fluoroacetanilide (10 g.) in acetic acid (50 ml.) at 60°. After 1 hr. the mixture was poured into water. The precipitate of **2-bromo-4-fluoroacetanilide** crystallized from aqueous ethanol in colorless needles (14.1 g., 94%), m.p. 119–120°.

Anal. Calcd. for C_8H_7BrFNO: C, 41.4; H, 3.02; N, 6.09. Found: C, 41.8; H, 3.31; N, 6.07.

2-Bromo-4-fluorotoluene.—A solution of sodium nitrite (55 g.) in water (200 ml.) was added slowly at 0.5° to 4-amino-2-bromotoluene[10] (124 g.) dissolved in concentrated hydrochloric acid (200 ml.) and water (200 ml.). The corresponding diazonium fluoborate, precipitated by adding excess fluoboric acid, was dried and decomposed by heating over a naked flame. The crude distillate was dissolved in ether, washed with dilute hydrochloric acid, water, dilute sodium hydroxide, then again with water, dried, and distilled. **2-Bromo-4-fluorotoluene** was collected at 170–172° as a colorless liquid (82 g., 67%), $n^{25}D$ 1.5265.

Anal. Calcd. for C_7H_6BrF: C, 44.5; H, 3.17. Found: C, 44.4; H, 3.21.

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(6) A. Roe and H. L. Fleishman, *J. Am. Chem. Soc.*, **69**, 509 (1947).
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TABLE I

YIELDS AND PHYSICAL DATA FOR THE AMINOFLUOROBIPHENYLS

Amine	M.p. or b.p., °C.	Lit. m.p. or b.p. °C.	Calcd. C	Calcd. H	Found C	Found H	Yield, %
2-Amino-4-fluorobiphenyl	102–105 (0.2 mm.)	...	77.0	5.35	77.4	5.62	59
2-Amino-5-fluorobiphenyl	92–96 (0.1 mm.)	...	77.0	5.35	77.3	5.22	48
2-Amino-6-fluorobiphenyl	52–55	...	77.0	5.35	See acetyl derivative		30
2-Amino-2′-fluorobiphenyl	91.5–92	91[a]	77.0	5.35	Well characterized		72
2-Amino-3′-fluorobiphenyl	106–110 (0.5 mm.)	...	77.0	5.35	77.0	5.42	53
2-Amino-4′-fluorobiphenyl	42–43	42–42.5[b]	77.0	5.35	Well characterized		68

[a] Ref. 5. [b] Ref. 4.

TABLE II

PHYSICAL DATA FOR THE ACETYLAMINOFLUOROBIPHENYLS

Compound	M.p., °C.	Lit. m.p., °C.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Acetylamino-4-fluorobiphenyl	90–91°	98[a]	73.4	5.24	6.12	72.9	5.23	6.42
2-Acetylamino-5-fluorobiphenyl	136–137	...	73.4	5.24	6.12	73.6	5.16	6.31
2-Acetylamino-6-fluorobiphenyl	102–103	...	73.4	5.24	6.12	73.7	5.40	6.10
2-Acetylamino-2′-fluorobiphenyl	103–104	102[b]	73.4	5.24	6.12	Well characterized		
2-Acetylamino-3′-fluorobiphenyl	102–103	...	73.4	5.24	6.12	73.5	5.16	6.50
2-Acetylamino-4′-fluorobiphenyl	125	120[a]	73.4	5.24	6.12	73.4	5.40	6.10

[a] Ref. 6. [b] Ref. 7.

TABLE III

DATA FOR THE PREPARATION OF THE FLUORO-10-METHYL-10,9-BORAZAROPHENANTHRENES

Yield, %	Position of F	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
33	2	80–81	74.0	5.21	6.64	74.0	5.21	6.35
12	3	52–55	74.0	5.21	6.64	73.7	5.20	...
28	6	54–55	74.0	5.21	6.64	73.9	5.41	6.72
52	7	89–90	74.0	5.21	6.64	73.6	5.38	6.41

2-Bromo-6-fluorotoluene.—Prepared likewise from 2-amino-6-bromotoluene,[11] **2-bromo-6-fluorotoluene** was obtained in 58% yield, b.p. 177–180°, $n^{25}D$ 1.5305.

Anal. Found: C, 44.5; H, 3.36.

2-Bromo-4-fluorobenzoic Acid.—Oxygen was bubbled through a boiling solution of 2-bromo-4-fluorotoluene (148 g.) and cobaltic acetate (0.05 mole) in acetic acid (500 ml.) until a permanent green color appeared. After half the solvent had been distilled, the residue was poured into dilute hydrochloric acid and the **2-bromo-4-fluorobenzoic acid** then collected, washed, and dried. The crude acid (140 g., 82%) had m.p. 168–171°, raised by recrystallization from dilute ethanol to 171–172.5°.

Anal. Calcd. for $C_7H_4BrFO_2$: C, 38.4; H, 1.83. Found: C, 38.6; H, 2.1.

Methyl 2-Bromo-4-fluorobenzoate.—Crude 2-bromo-4-fluorobenzoic acid was esterified by the Fischer Speier method and the **methyl ester** (125 g., 87%) isolated by distillation, b.p. 122° (10 mm.), $n^{25}D$ 1.5372.

Anal. Calcd. for $C_8H_6BrFO_2$: C, 41.2; H, 2.58. Found: C, 40.9; H, 2.46.

2-Bromo-6-fluorobenzyl Bromide.—2-Bromo-6-fluorotoluene (30 g.) in carbon tetrachloride (250 ml.) was heated under reflux for 4 hr. with N-bromosuccinimide (5–8 g.) and a trace of benzoyl peroxide. The solution was cooled, filtered, and the filtrate freed from solvent by distillation. Distillation of the residue gave the pure **benzyl bromide** (29.4 g., 69%), b.p. 128–131 (25 mm.), $n^{25}D$ 1.5912.

Anal. Calcd. for $C_7H_5Br_2F$: C, 31.3; H, 1.87. Found: C, 31.7; H, 2.09.

2-Bromo-6-fluorobenzoic Acid.—2-Bromo-6-fluorobenzyl bromide (10 g.) was heated overnight under reflux with potassium permanganate (20 g.) in water (100 ml.). After cooling, the solution was decolorized with sulfur dioxide and the precipitated *acid* (6.1 g., 74%) filtered, washed, and dried. A sample crystallized from dilute ethanol in white needles, m.p. 155°.

Anal. Calcd. for $C_7H_4BrFO_2$: C, 38.4; H, 1.83. Found: C, 38.8; H, 2.14.

Synthesis of the Biphenyls.—A mixture containing equimolecular quantities of the two halides used in the biphenyl synthesis was heated to 120° and vigorously stirred while copper powder (3 g.-atoms) (Venus National Copper, U. S. Bronze Powder Works) was added over 20 min. The mixture was held at 120° for 20 hr., then cooled, extracted several times with dichloromethane, and the filtered solution evaporated to yield the crude product. The following compounds were prepared by this general method.

2′-Fluoro-2-nitrobiphenyl was prepared from 2-bromonitrobenzene (82 g.), 2-fluoroiodobenzene (90 g.), and copper powder (77 g.). Chromatography of the crude mixture on alumina (Merck) with petroleum ether (b.p. 60–68°) and dichloromethane (gradient elution) gave a major very pale yellow band after a colorless forerun containing some difluorobiphenyl. Evaporation of the eluent containing the major band gave 2′-fluoro-2-nitrobiphenyl which crystallized from petroleum ether (b.p. 30–35°) in pale yellow prisms (53 g., 57%), m.p. 72.5–73°, (lit.[8] m.p. 71–72°).

3′-Fluoro-2-nitrobiphenyl was prepared from 2-bromonitrobenzene (13.3 g.), 3-iodofluorobenzene (14.7 g.), and copper powder (12.5 g.). Distillation of the crude product gave the partially purified biphenyl derivative, b.p. 95–9 8°(0.05 mm.) (7.6 g.). Chromatography as described previously yielded pure **3′fluoro-2-nitrobiphenyl** which crystallized from petroleum ether (b.p. 30–35°) in pale yellow needles (6.5 g., 45%), m.p. 47.5–48°.

Anal. Calcd. for $C_{12}H_8FNO_2$: C, 66.5; H, 3.69; N, 6.45. Found: C, 66.3; H, 3.79; N, 6.84.

4′-Fluoro-2-nitrobiphenyl was prepared from 2-bromonitrobenzene (11 g.), 4-fluoroiodobenzene (12 g.), and copper powder (10.3 g.). Distillation and chromatography as before gave pure 4′-fluoro-2-nitrobiphenyl, b.p. 90–92° (0.05 mm.), which crystallized from petroleum ether (b.p. 30–35°) in very pale yellow needles (3.1 g., 36%), m.p. 60–60.5° (lit.[5] m.p. 59–60°).

4-Fluoro-2-nitrobiphenyl was prepared from 2-bromo-5-fluoronitrobenzene[12] (32 g.), iodobenzene (33 g.), and copper powder (28 g.). Distillation and chromatography gave pure 4-fluoro-2-nitrobiphenyl, b.p. 108–110° (0.05 mm.), which crystallized from petroleum ether (b.p. 30–35°) in pale yellow prisms (13.6 g., 43%), m.p. 72.5–74° (lit. m.p. 53–54°).

Anal. Calcd. for $C_{12}H_8FNO_2$: C, 66.5; H, 3.69; N, 6.45. Found: C, 66.2; H, 4.06; N, 6.75.

5-Fluoro-2-nitrobiphenyl was prepared from 2-bromo-4-fluoronitrobenzene (50 g.), iodobenzene (51 g.), and copper powder (43 g.). Distillation gave **5-fluoro-2-nitrobiphenyl** as a liquid (28.9 g., 58.5%). b.p. 114–118° (0.6 mm.), $n^{24}D$ 1.5954.

Anal. Calcd. for $C_{12}H_8FNO_2$: C, 66.5; H, 3.69; N, 6.45. Found: C, 66.1; H, 3.89; N, 6.70.

(11) E. Noelting, *Ber.*, **37**, 1015 (1904).

(12) E. Berliner and K. C. Monack, *J. Am. Chem. Soc.*, **74**, 1574 (1954).

5-Fluoro-2-methoxycarbonylbiphenyl.—Prepared from methyl 2-bromo-4-fluorobenzoate (103 g.), iodobenzene (91 g.), and copper powder (82 g.), **5-fluoro-2-methoxycarbonylbiphenyl** was collected at 110–118° (0.2 mm.), and redistilled (53 g., 52%), b.p. 108–110° (0.1 mm.), $n^{25}D$ 1.5662. Vapor phase chromatography analysis showed only one peak.

Anal. Calcd. for $C_{14}H_{11}FO_2$: C, 73.0; H, 4.79. Found: C, 73.1; H, 5.10.

2-Amino-6-nitrobiphenyl.—2,6-Dinitrobiphenyl[13] (24 g.) in ethanol (350 ml.) was boiled under reflux for 3 hr. during the addition of a solution of sodium sulfide (28 g.) and sulfur (6.9 g.) in water (85 ml.). The ethanol was mostly removed by distillation and the product poured into water and isolated with dichloromethane. Three recrystallizations from dilute ethanol gave **2-amino-6-nitrobiphenyl** as yellow needles (7.5 g., 35.5%), m.p. 74–75°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.3; H, 4.67. Found: C, 67.5; H, 4.99.

2-Fluoro-6-nitrobiphenyl.—2-Amino-6-fluorobiphenyl (6 g.) in concentrated hydrochloric acid (30 ml.) and water (30 ml.) was diazotized at 0.5°. Fluoboric acid (60 ml.) was added and the diazonium fluoborate filtered, washed with cold methanol and ether, and dried overnight in a vacuum desiccator. The solid was decomposed by heat and the residue extracted with petroleum ether (b.p. 30–35°, six 50-ml. portions). Evaporation of this ether gave an oil which solidified on scratching. Recrystallization from petroleum ether (b.p. 30–35°) gave pure **2-fluoro-6-nitrobiphenyl** as very pale yellow needles (3.5 g., 60%), m.p. 67–68°.

Anal. Calcd. for $C_{12}H_8FNO_2$: C, 66.5; H, 3.69; N, 6.45. Found: C, 66.7; H, 3.99; N, 6.82.

2-Carboxy-5-fluorobiphenyl.—A mixture of the methyl ester of 5-fluorobiphenylcarboxylic acid (2.1 g.), sodium hydroxide (10 ml. of 1 *N*), and ethanol (20 ml.) was kept overnight at 40° and then acidified. The **2-carboxy-5-fluorobiphenyl** was isolated with ether and then crystallized from petroleum ether (b.p. 60–68°) in white needles (1.5 g., 76%), m.p. 110°.

Anal. Calcd. for $C_{13}H_9FO_2$: C, 72.2; H, 4.17. Found: C, 72.0; H, 4.47.

3-Fluorofluorenone.—2-Carboxy-5-fluorobiphenyl (0.5 g.) was allowed to stand in concentrated sulfuric acid (10 ml.) at room temperature for 1 hr. The solution turned deep violet. Pouring into water gave an almost theoretical yield of **3-fluorofluorenone** which crystallized from petroleum ether (b.p. 90–100°)–benzene in yellow needles, m.p. 129–130°.

Anal. Calcd. for $C_{13}H_7FO$: C, 78.8; H, 3.54. Found: C, 79.0; H, 4.00.

5-Hydrazinobiphenyl-2-carboxylic Acid Hydrazide.—2-Carboxy-5-fluorobiphenyl (1 g.) and hydrazine (1 g.) were treated under reflux overnight. Addition of ethanol gave an almost theoretical yield of the **hydrazide** which crystallized from ethanol in cream-colored plates, m.p. 140°.

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.5; H, 5.78; N, 23.2. Found: C, 64.6; H, 6.18; N, 22.9.

Reductions of the Fluoronitrobiphenyls to the Corresponding Amines.—The reductions of the fluoronitrobiphenyls to the corresponding amines were carried out using the method of Marler and Turner.[6] The amines were characterized as their acetyl derivatives. 2-Amino-6-fluorobiphenyl had been characterized previously only by its acetyl derivative. The yields, melting points, and analysis data are shown in Tables I and II.

Synthesis of the Fluoro-10-methyl-10,9-borazarophenanthrenes.—The method of Dewar, Kubba, and Pettit[4] was used to prepare the boron–nitrogen heterocycles. The 10-methyl group was introduced by the action of methylmagnesium iodide on the fluoro-10-chloro-10,9-borazarophenanthrenes. The crude methyl compounds were purified by chromatography on alumina (Merck) with petroleum ether (b.p. 30–35°) as eluent. Sublimation and one or more crystallizations from petroleum ether (b.p. 30–35°) gave the pure compounds. The yields in Table III refer to analytical samples.

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The Reaction of Trimethyl Thioborate with Diazoalkanes[1]

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The interaction of trimethyl thioborate with several diazoalkanes has been studied. Trimethyl thioborate and diazomethane leads only to polymethylene; trimethyl thioborate reacts with phenyldiazomethane to give methyl benzyl sulfide and *trans*-stilbene; trimethyl thioborate reacts with ethyl diazoacetate to give ethyl S-methylmercaptoacetate and diethyl S-methylmercaptosuccinate; trimethyl thioborate reacts with phenylbenzoyldiazomethane to give methyl diphenylthioacetate. These several products are rationalized in terms of the alternate pathways illustrated in Fig. 1.

Numerous examples of the interaction of diazoalkanes, principally diazomethane, with inorganic compounds have been reported in the literature.[3] In some cases the inorganic compound undergoes methylenation with diazomethane as, for example, stannic chloride which reacts to form various chloromethyl derivatives; *e.g.*, $ClCH_2SnCl_3$.[4] In other cases the inorganic material acts as a polymerization catalyst as, for instance, the trialkylborons, the trialkyl borates, and the boron halides,[5] the main action on diazomethane being to form polymethylene.[6] The present work extends the list of boron compounds reactive toward diazo compounds to include trimethyl thioborate. Although, in common with the boron compounds just mentioned, it induces polymerization of diazomethane, it reacts with substituted diazomethanes in several other ways, the nature of which depends upon the particular diazoalkane.

Trimethyl Thioborate and Diazomethane.—This reaction leads to the production of polymethylene, the catalytic action of trimethyl thioborate being rationalized in terms of pathway $A–A_1$ (see Fig. 1) according to a recent suggestion.[7] The tendency for the first-formed complex to react further with diazomethane rather than to undergo internal rearrangement must derive from the very great reactivity of the $-CH_2N_2^{\oplus}$ moiety. If groups hindering the intermolecular reaction with additional molecules of diazo compound are attached to the diazonium center, the reaction may then take

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(2) Postdoctoral research associate 1961–62 on leave of absence from School of Liberal Arts, Kyoto University, Kyoto, Japan.

(3) D. Seyferth, *Chem. Rev.*, **55**, 1155 (1955).

(4) A. Ya. Yakubovich, S. P. Makarov, and G. I. Gavrilov, *J. Gen. Chem. USSR*, **22**, 1788 (1952); *Chem. Abstr.*, **47**, 9257 (1953).

(5) H. Meerwein, *Angew. Chem.*, **60**, 78 (1948).

(6) Under special conditions, however, fluoromethylboron difluoride can be obtained from boron trifluoride and diazomethane [J. Goubeau and K. H. Rohwedder, *Ann.*, **604**, 168 (1957)].

(7) A. G. Davies, D. G. Hare, O. R. Khan, and J. Sikora, *Proc. Chem. Soc.*, 172 (1961).

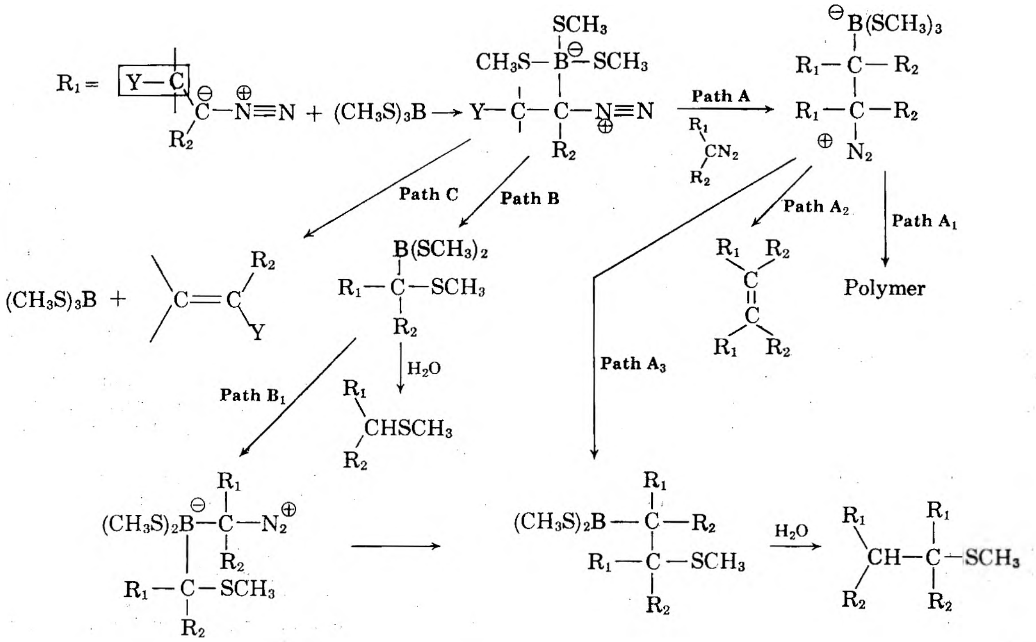


Fig. 1.—Reaction pathways for trimethyl thioborate and diazoalkanes.

alternative courses as illustrated by the following examples.

Trimethyl Thioborate and Phenyldiazomethane.—The major product from this reaction is methyl benzyl sulfide (I), isolated in *ca.* 40% yield, and its formation is rationalized by pathway B (see Fig. 1). A second product, isolated in smaller amount, has been identified

$$C_6H_5CHN_2 + (CH_3S)_3B \longrightarrow \underset{\text{I}}{CH_3SCH_2C_6H_5} + \underset{\text{II}}{C_6H_5CH{=}CHC_6H_5}$$

as *trans*-stilbene. Phenyldiazomethane alone is known to produce stilbene, and it is, therefore, uncertain in the present case whether or not the trimethyl thioborate is involved in its formation. A reasonable mechanism implicating the boron compound is illustrated by pathway $A–A_2$ in which the first-formed complex reacts intermolecularly with a second mole of phenyldiazomethane (path A—similar to the second step in the diazomethane polymerization) to give an intermediate which then achieves stabilization along an intramolecular pathway (path A_2).

Trimethyl Thioborate and Ethyl Diazoacetate.—The major product from the reaction of trimethyl thioborate with ethyl diazoacetate is ethyl S-methylmercaptoacetate (III), and its formation can be rationalized, as in the previous example, by pathway B (see Fig. 1). The second product, however, is not diethyl fumarate

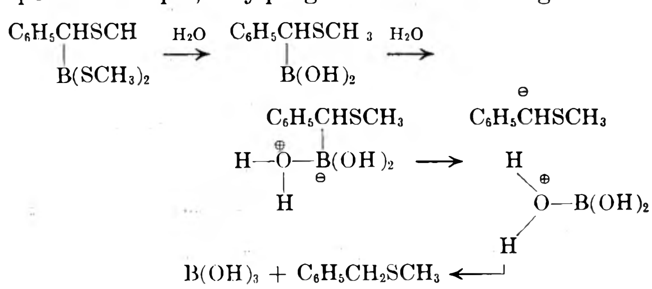
$$N_2CHCO_2C_2H_5 + (CH_3S)_3B \longrightarrow \underset{\text{III}}{CH_3SCH_2CO_2C_2H_5} + \underset{\text{IV}}{CH_3SCH(CO_2C_2H_5)CH_2CO_2C_2H_5}$$

(pathway $A–A_2$) but diethyl S-methylmercaptosuccinate (IV), the formation of which is rationalized by pathway $B–B_1$ (a possible alternative is pathway $A–A_3$).

Trimethyl Thioborate and Phenylbenzoyldiazomethane.—In this case still another possibility arises, *viz.*, rearrangement of the diazo compound itself, and it is this course that appears to be preferred. Thus, from trimethyl thioborate and phenylbenzoyldiazomethane the major product isolated is methyl diphenylthioacetate (V). That it probably forms *via* diphenylketene as an intermediate [*via* path C (see Fig. 1)] was demonstrated by treating diphenylketene with trimethyl thioborate and isolating V as the major product.

$$C_6H_5COC(N_2)C_6H_5 \longrightarrow (C_6H_5)_2C{=}C{=}O \xrightarrow[(2)\ H_2O]{(1)\ (CH_3S)_3B} \underset{\text{V}}{(C_6H_5)_2CHC(=O)SCH_3}$$

The reaction pathway presented in Fig. 1 indicates the last step in the sequences to be a hydrolysis in which a C–B bond undergoes cleavage. This is a conversion which ordinarily requires fairly strenuous conditions as, for example, benzylboronic acid which undergoes C–B cleavage with hot 5% sodium hydroxide solution.[8] The conditions of hydrolysis in the present instances are much milder, and if Fig. 1 is a correct portrayal of the reaction course it must be accepted that the hydrolysis proceeds with unexpected facility in these cases. The hydrolysis of the intermediate from phenyldiazomethane and trimethyl thioborate, to take a specific example, may progress in the following fashion.



According to this mechanism the ease of cleavage of the C–B bond can be related to the ability of the carbon atom of this bond to support a negative charge. That divalent sulfur has the capability of stabilizing an adjacent carbanionic center has been demonstrated in

(8) J. R. Johnson, M. G. Van Campen, and O. Grummitt, *J. Am. Chem. Soc.*, **60**, 111 (1938).

several instances,[9] and it may be this factor that is responsible for the facile cleavage in these cases.

Experimental[10]

Trimethyl thioborate was prepared by the reaction of lead methyl mercaptide and boron tribromide[11] and was obtained as a colorless oil with b.p. 205–208° (750 mm.), 101–103° (20 mm.) (reported m.p. 205–208°[9], 101.1° (17.7 mm.)[12]).

Trimethyl Thioborate and Diazomethane.—A solution of 9.4 g. (0.22 mole) of diazomethane [prepared by base-catalyzed decomposition of N,N′-dinitroso-N,N′-dimethylterephthalamide (Du Pont EXR-101), redistilled, and dried over potassium hydroxide and sodium] in 200 ml. of dry ether was added, over a period of 2 hr., to a stirred and cooled (−45 to −55°) solution containing 11.0 g. (0.072 mole) of trimethyl thioborate in 100 ml. of dry ether. The reaction mixture was allowed to warm to room temperature and to stand overnight. Filtration yielded 2.6 g. (84% based on diazomethane) on a nonvolatile, ether-insoluble white powder assumed to be polymethylene, and evaporation of the ether solution and distillation of the residue yielded unchanged trimethyl thioborate.

Trimethyl Thioborate and Phenyldiazomethane.—A solution containing 9 g. (0.076 mole) of phenyldiazomethane (prepared from phenylbenzoyldiazomethane by the method of Yates and Shapiro[13]) in 100 ml. of anhydrous ether was added, over a period of 100 min., to a solution of 5.2 g. (0.034 mole) of trimehyl thioborate in 50 ml. of anhydrous ether cooled to −30°. The ether was then removed by evaporation, the residue was treated with 200 ml. of 5% sodium hydroxide solution, and the mixture was refluxed for 30 min. Extraction with ether, removal of the ether by evaporation, and distillation of the residue yielded 3.9 g. (36% based on phenyldiazomethane) of material with b.p. 89–92° (15 mm.), identified as methyl benzyl sulfide by comparison with an authentic sample prepared from benzyl chloride and lead methyl mercaptide. The still residue was recrystallized from ethanol to yield 1.0 g. (7%) of pale yellow crystals, m.p. 121.5–124° (124–125° after a second recrystallization), identified as *trans*-stilbene by comparison with an authentic sample, m.p. 124–125°.

Trimethyl Thioborate and Ethyl Diazoacetate.—A solution of 19.2 g. (0.17 mole) of ethyl diazoacetate in 50 ml. of petroleum ether (b.p. 33–36°, dried over sodium) was added, over a period of 20 min., to a stirred solution containing 10.2 g. (0.0067 mole) of trimethyl thioborate in 50 ml. of dry petroleum ether, the reaction being carried out at room temperature. During the addition, the solvent refluxed rather vigorously from the heat of the reaction. The mixture was then cooled to room temperature, treated with 50 ml. of saturated sodium chloride solution, and extracted with ether. After washing with 10% sodium carbonate solution and drying over anhydrous magnesium sulfate, the ether was removed and the residue was distilled to give 6.1 g. (28% based on ethyl diazoacetate) of ethyl S-methylmercaptoacetate with b.p. 62.5–64° (13 mm.), 0.7 g. of a middle fraction with b.p. 65–136° (13 mm.), and 1.5 g. (8%) of diethyl S-methylmercaptosuccinate with b.p. 137° (13 mm.). The lower boiling fraction was identified by an infrared spectral comparison with an authentic sample and by a melting point comparison of its *p*-toluidide, m.p. 102–103°, with an authentic sample, m.p. 102–103° (neat and admixed). The higher boiling fraction was identified by its analysis, by an infrared comparison with a sample synthesized by an alternate route, and by its hydrolysis to the known S-methylmercaptosuccinic acid.

Anal. Calcd. for $C_8H_{16}O_4S$: C, 49.09; H, 7.27. Found: C, 48.96; H, 7.08.

This was effected by treatment of a 0.55-g. sample of the ester with alcoholic potassium hydroxide for 6 hr.[14] The crude product was recrystallized from benzene–acetone to yield 0.20 g. (45%) of S-methylmercaptosuccinic acid, m.p. 131–134°. Further recrystallization of the latter provided material with m.p. 134–136° (reported[15] m.p. 136.8°). An alternate synthesis of diethyl S-methylmercaptosuccinate was achieved by treating 33.0 g. (0.33 mole) of maleic anhydride dissolved in 30 ml. of water containing 3.0 g. of potassium hydroxide and heated to 96–98° with methyl mercaptan bubbled in over a period of 3 hr.[16] The resulting product (*ca.* 27 g.) was refluxed for 1 hr. with 40 g. (0.33 mole) of thionyl chloride. After removal of the excess reagent, the residue was treated with 100 ml. of ice-cold ethyl alcohol. Distillation of the resulting product yielded 13.5 g. (19%) of a colorless liquid, b.p. 82–84° (0.2 mm.). An infrared spectral comparison showed this to be identical with the higher boiling fraction described previously. By hydrolysis of the ester with cold alcoholic potassium hydroxide S-methylmercaptosuccinic acid, m.p. 134–136°, was obtained.

Trimethyl Thioborate and Phenylbenzoyldiazomethane.—A solution of 6.12 g. (0.004 mole) of trimethyl thioborate in 100 ml. of absolute ether was mixed with a solution of 6.25 g. (0.0028 mole) of phenylbenzoyldiazomethane in 300 ml. of absolute ether. Little if any reaction took place at room temperature, and the mixture was refluxed for 20 hr. It was then cooled in an ice bath, treated with 300 ml. of 5% sodium hydroxide solution, and stirred for 10 min. Working up in the usual manner gave 6.37 g. of crude material as a semisolid which, upon crystallization from ethanol, yielded 2.00 g. (29.5% based on phenylbenzoyldiazomethane) of methyl diphenylthioacetate, m.p. 86–90°. Additional recrystallization from ethanol provided colorless plates, m.p. 90–92°.

Anal. Calcd. for $C_{15}H_{14}OS$: C, 74.38; H, 5.78. Found: C, 74.35; H, 5.93.

The methyl diphenylthioacetate was characterized by hydrolysis and by comparison with a sample prepared by an independent route. Base-catalyzed hydrolysis yielded diphenylacetic acid, identical by mixture melting point (146–148°) with an authentic sample, and methyl mercaptan. The latter was characterized as 1-methylmercapto-2,4-dinitrobenzene, m.p. 125–127° (reported[17] m.p. 128°) obtained by treatment with 1-chloro-2,4-dinitrobenzene. An independent synthesis of methyl diphenylthioacetate was achieved by treating diphenylacetyl chloride with methyl mercaptan. The resulting product was shown by mixture melting point (90–92°) to be identical with that isolated from the reaction mixture described previously.

Trimethyl Thioborate and Diphenylketene.—To a solution of 6.00 g. (0.031 mole) of diphenylketene in 200 ml. of dry ether was added a solution of 6.00 g. (0.039 mole) of trimethyl thioborate in 100 ml. of dry ether. The mixture was refluxed for 25 hr. in an atmosphere of nitrogen, cooled in ice, treated with 400 ml. of 5% sodium hydroxide solution, stirred for 10 min., and worked up. From the base-soluble fraction there was obtained 2.91 g. of crude material comprised mainly of diphenylacetic acid, m.p. 144–146° after recrystallization. The neutral fraction consisted of 4.12 g. of solid from which 2.26 g. (28.5%) of methyl diphenylthioacetate was obtained, m.p. 84–87°. Further recrystallization from ethanol raised the melting point to 89–91°.

(9) C. C. Price and S. Oae, "Sulfur Bonding," The Ronald Press Co., New York, N. Y., 1962, p. 55–60.

(10) All melting points are corrected; all boiling points are uncorrected. Microanalyses were performed by Dr. J. Szcek's laboratory in Vienna, Austria.

(11) J. Goubeau and H. W. Whittmeier, *Z. anorg. allgem. Chem.*, **270**, 16 (1952).

(12) L. L. Petterson, R. J. Brotherton, and J. L. Boone, *J. Org. Chem.*, **26**, 3030 (1961).

(13) P. Yates and B. L. Shapiro, *ibid.*, **23**, 759 (1958).

(14) V. C. Barry, L. O'Rourke and D. Twomey, *Proc. Roy. Irish Acad.*, **51**, 223 (1947); *Chem. Abstr.*, **42**, 4134a (1948).

(15) T. Kaneko and S. Mii, *J. Chem. Soc. Japan*, **59**, 1382 (1938).

(16) U. S. Patent 2,581,514 (1952); *Chem. Abstr.*, **47**, 4363 (1952).

(17) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, **54**, 1896 (1932).

Nitrations with Acetyl Nitrate. IV. The Formation and Reactions of β-Nitro Acetates from 1-Phenylcyclohexene and 1-Phenylcyclopentene[1]

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Of the two isomeric β-nitro acetates formed by nitration of 1-phenylcyclohexene, the major isomer was shown by reduction to have the NO_2 and OAc groups *trans* to one another. The more rapid rearrangement of the type, (NH_2, OAc) → (NHAc, OH), observed for the reduction product from the minor isomer supports the *cis* assignment made to it. Hydrogenolysis of the C–O bond in the amino alcohol derivatives with Raney nickel was found to occur with *inversion* of configuration for C–OAc compounds and with *retention* of configuration for C–OH compounds. Base-catalyzed elimination occurred more rapidly with the *trans* β-nitro acetate (*cis* elimination) than with the *cis* β-nitro acetate (*trans* elimination). This result is rationalized in terms of a carbanion mechanism. The nitration of 1-phenylcyclopentene led to a single β-nitro acetate which was shown to have the nitro and acetoxy groups in a *trans* configuration.

The study of the products formed in the reaction of alkenes with acetyl nitrate in acetic anhydride solution[2] now has been extended to 1-phenylcyclohexene and 1-phenylcyclopentene. When 1-phenylcyclohexene was nitrated under the usual conditions[3] and the products separated by chromatography, the successive fractions consisted of about 10% of nitroalkenes (mostly unconjugated), 49% of β-nitro acetate (I), and 16% of β-nitro acetate (II).

Electrolytic reduction of I gave a 75% yield of a β-amino acetate, isolated as its hydrochloride. A 53% yield of the same amine acetate hydrochloride was obtained in a reduction carried out with Raney nickel in absolute ethanol. Neutralization of this hydrochloride with aqueous potassium carbonate, followed by standing overnight in contact with the solvent, brought about a rearrangement of the amine acetate to an acetamido alcohol, m.p. at 164–165°; this is the melting point reported[4] for 2-acetamido-*trans*-1-hydroxy-1-phenylcyclohexane.[5] The same compound was obtained by acetylating the amine acetate hydrochloride to form the N-acetyl O-acetyl derivative followed by selective hydrolysis of the ester link. By benzoylation of the amine acetate hydrochloride the N-benzoyl O-acetyl derivative was obtained; this was then hydrolyzed to the N-benzoyl derivative, m.p. 155–156°. Curtin and Schmulker[4] report m.p. 157–158° for 2-benzamido-*trans*-1-hydroxy-1-phenylcyclohexane.

The infrared spectrum of II resembled that of I closely, but some differences were apparent (see Experimental). Treatment of either isomer with sulfuric acid in acetic anhydride or with alcoholic potassium hydroxide at room temperature resulted in the elimination of a molecular of acetic acid and the formation of 6-nitro-1-phenylcyclohexene (IV). These data indicate that isomers I and II are related as *cis–trans* isomers.

Reduction of II electrolytically, under the conditions used for I, gave a product that was difficult to characterize. Reduction with Raney nickel was successful, but the product proved to be the N-acetyl, rather than the O-acetyl derivative.

The results may be summarized as shown in Chart 1 in which structure assignments are given.

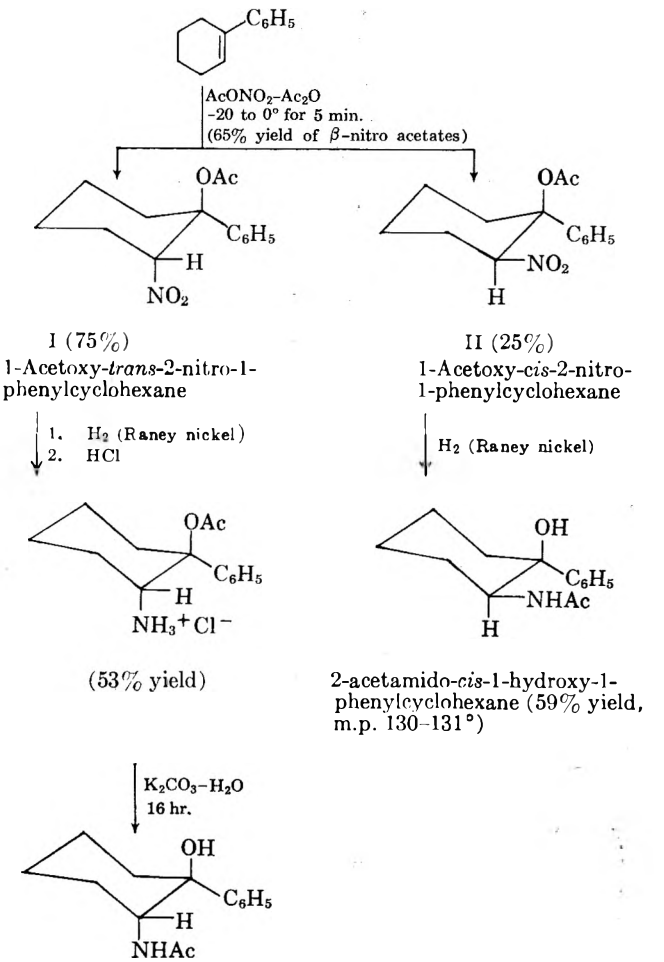


CHART 1

(1) Abstracted from the Ph.D. dissertation of Edgar W. Garbisch, Jr., submitted to Northwestern University, August, 1961.

(2) See F. G. Bordwell and E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 3049 (1962), for paper III in this series.

(3) F. G. Bordwell and E. W. Garbisch, Jr., *ibid.*, **27**, 2322 (1962).

(4) D. Y. Curtin and S. Schmulker, *J. Am. Chem. Soc.*, **77**, 1105 (1955).

(5) The terms *cis* and *trans* cannot be used unambiguously in such names unless some sort of convention is adopted. In this paper the first function mentioned in the name (as decided by the alphabetical order) is always used as the point of reference. The designation *cis* or *trans* refers to the relationship of the second function mentioned relative to this reference. The stereorelationship of the third function is also made obvious in this way. For example, the name 2-acetamido-*trans*-1-hydroxy-1-phenylcyclohexane shows that the acetamido and hydroxyl groups are *trans* to one another; it follows that the acetamido group is *cis* to the phenyl group. (The compound could also have been named 2-acetamido-*cis*-1-phenylcyclohexanol.) This convention is essentially that introduced by Epstein and Rossini for naming geometric isomers of polyalkyl monocycloalkanes [see the American Chemical Society Nomenclature Committee report in *Chem. Eng. News*, **28**, 1842 (1950)].

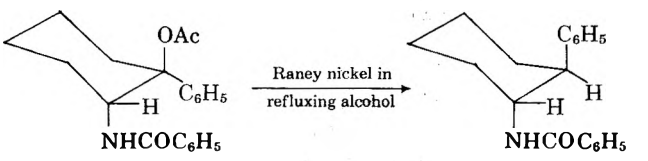
Since the amino and hydroxyl groups in the compound prepared by the action of ammonia on 1-phenylcyclohexene oxide[4] almost certainly bear a *trans* relationship to one another, the structure of the reduction product from I is established as having a *trans* configuration. Since reduction of the nitro group to amino under these conditions has been shown to occur with retention of configuration,[6] a *trans* relationship for the acetoxy and nitro group in I is established, and a *cis* relationship for these groups in II is indicated.

The rearrangements, (NH_2, OAc) → (NHAc, OH), observed with the reduction products from both isomers I and II, presumably both occur by intramolecular mechanisms. The rearrangement required several hours for the reduction product from I, whereas with the reduction product from II it was much more rapid, being complete by the end of the reduction. This difference in the ease of rearrangement is consistent with the structures assigned, since it is known that oxygen to nitrogen acyl migration is more rapid in *cis* (axial–equatorial) than in *trans* (equatorial–equatorial) systems of this type.[7]

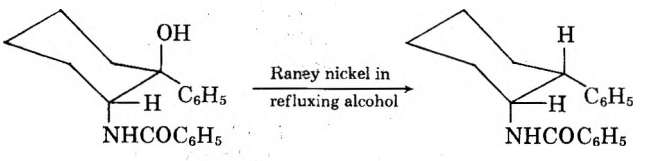
The nitration of 1-phenylcyclopentene gave 34% of nitro alkenes and 40% of a single β-nitro acetate. The latter was reduced electrolytically to an acetate amine hydrochloride in 68% yield. This was identified as 1-acetoxy-*trans*-2-amino-1-phenylcyclopentane hydrochloride by establishing the identity of its N-benzoyl amino alcohol derivative with a comparable derivative derived from the amino alcohol produced by the reaction of aqueous ammonia with 1-phenylcyclopentene oxide.

It is apparent from the previous discussion that the major isomer formed from the nitration of either 1-phenylcyclohexene or 1-phenylcyclopentene has the nitro and acetoxy groups in a *trans* relationship to one another. This corrects our earlier preliminary assignment,[8] which was based on what turned out to be an unjustified assumption with respect to the hydrogenolysis of the acetoxy group (following). It now appears that *trans* additions to C=C bonds, such as those reported here, are about as common in acetyl nitrate additions as are cis additions. The factors determining the stereochemistry in these reactions will be discussed further in a later paper.

Hydrogenolyses.—In an early attempt at structure assignment, I was hydrogenated in methanol containing sulfuric acid using a palladium-on-charcoal catalyst; these conditions led to hydrogenolysis of the acetoxy group. The product from the hydrogenolysis was identified as *trans*-2-phenylcyclohexylamine. Since previously recorded hydrogenolyses of C–O bonds were known to occur with retention of configuration,[9] including *a hydrogenolysis of the alcohol corresponding to one of the isomeric* acetates expected as a product,[4] retention of configuration was at first assumed to be the result in our experiments. This assumption proved to be an unfortunate one, since it led to incorrect structure assignments for the β-nitro acetates formed from 1-phenylcyclohexene and from 1-phenylcyclopentene.[8] The configurational assignments made show that hydrogenolysis of the C–O bonds in both 1-acetoxy-*trans*-1-phenyl-2-nitrocyclohexane and 1-acetoxy-*trans*-1-phenyl-2-nitrocyclopentane (or their reduction products) occurs with *inversion* of configuration. In checking into the matter further it was found that hydrogenolysis of 1-acetoxy-*trans*-2-benzamido-1-phenylcyclohexane with Raney nickel in refluxing ethanol gave *trans*-2-benzamido-1-phenylcyclohexane (inversion of configuration). It is remarkable that the corresponding alcohol undergoes hydrogenolysis with retention of configuration.[4] Similarly, it was observed that 1-acetoxy-*trans*-2-benzamido-1-phenylcyclopentane gave *trans*-2-benzamido-1-phenylcyclopentane with Raney nickel in refluxing alcohol (inversion).[10]

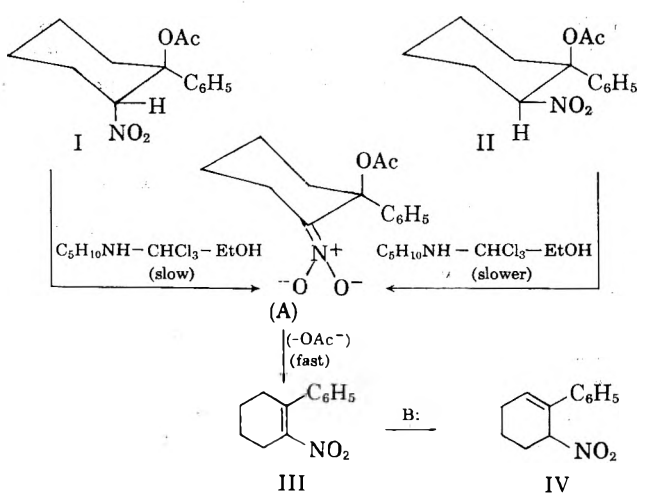


Hydrogenolysis with inversion (72%)



Hydrogenolysis with retention (78%)

Approximate pseudo first-order rates of elimination of acetic acid from I and II, as initiated by reaction with piperidine in chloroform–ethanol solution, were determined by following the disappearance of the 5.70-μ carbonyl stretching frequency. The rate of elimination from 1-acetoxy-*trans*-2-nitro-1-phenylcyclohexane (an apparent *cis* elimination) was found to be about four times as rapid as from 1-acetoxy-*cis*-2-nitro-1-phenylcyclohexane (a *trans* elimination). Since, when the hydrogen atoms involved in the elimination are of comparably acidity, *trans* elimination is usually much faster than *cis* elimination, this result suggests that elimination is proceeding by way of a carbanion intermediate wherein proton abstraction is the rate determining step. Assuming that the molecules react in the conformations shown, the lower reactivity of the *cis*



(6) F. G. Bordwell and R. L. Arnold, *J. Org. Chem.*, **27**, 4426 (1962).
(7) G. Fodor and J. Kiss, *J. Am. Chem. Soc.*, **72**, 3495 (1950).
(8) F. G. Bordwell and E. W. Garbisch, Jr., *ibid.*, **82**, 3588 (1960).
(9) W. A. Bonner, J. A. Zderic, and G. A. Casalette, *ibid.*, **74**, 5086 (1952); W. A. Bonner and J. A. Zderic, *ibid.*, **78**, 3218 (1956).

(10) S. Mitsui and S. Imaizumi, *Bull. Chem. Soc. Japan*, **34**, 774 (1961), recently also have observed hydrogenolyses of benzyl acetates which occur with inversion of configuration, whereas the corresponding alcohols undergo hydrogenolysis with retention of configuration.

isomer may be attributed to a relatively greater steric hindrance to the approach of the base to the axial hydrogen atom α to the nitro group during carbanion formation.

Zimmerman[11] has found recently in a study of the protonation of a carbanion intermediate identical in structure to (A), except that the OAc group was replaced by H, that proton donors approached preferentially so as to place the proton in an equatorial rather than an axial position. One would then expect, by the principle of microscopic reversibility, that proton abstraction to form the carbanion would also occur so as to remove an equatorial hydrogen atom in preference to an axial hydrogen atom. This is what we have observed.

Elimination of acetic acid from the nitro acetates could be effected with either acid or base catalysis. With sulfuric acid in acetic anhydride, either I or II gave 6-nitro-1-phenylcyclohexene (IV), and 2-nitro-1-phenylcyclopentyl acetate gave 5-nitro-1-phenylcyclopentene. With one mole of sodium methoxide in methanol, I gave a mixture of about 85% of 2-nitro-1-phenylcyclohexene (III) and 15% of 6-nitro-1-phenylcyclohexene (IV), judging from an infrared analysis. In the presence of 15% alkali, IV was the sole product. 2-Nitro-1-phenylcyclopentyl acetate gave 2-nitro-1-phenylcyclopentene with triethylamine in dioxane. Equilibration of this nitroalkene with triethylamine in chloroform gave 5-nitro-1-phenylcyclopentene. In both the cyclohexene and cyclopentene series the more stable nitrocycloalkene is that of the type $-C{=}C(C_6H_5)-C(NO_2)-$. The lesser stability of the isomer containing the $-C-C(C_6H_5){=}C-NO_2$ system is noteworthy. Evidently the steric interference between the nitro group and the phenyl group in the latter system is such that *neither* can conjugate effectively with the carbon–carbon double bond. As a result the preferred position for the double bond is that where conjugation is with phenyl alone.

Experimental[12]

Nitration of 1-Phenylcyclohexene. β-Nitro Acetates I and II.—The nitration reagent was prepared by adding 4.5 g. (0.05 mole) of 70% nitric acid to 35 ml. of acetic anhydride at 25–30°.[2,3,8] The resulting reagent was cooled to −20° and then 4.0 g. (0.025 mole) of 1-phenylcyclohexene in 10 ml. of acetic anhydride was added. The temperature rose to 0°; the solution was then recooled to −20° and maintained at this temperature for 5 min. After this time, the solution was poured into 200 ml. of water and the resulting mixture was stirred until the excess of acetic anhydride was hydrolyzed. The product then was extracted with ether, the extract was washed with dilute sodium bicarbonate and water, and finally dried over calcium chloride. The ether was evaporated under reduced pressure. The crude nitration product (infrared analysis gave the ratio of I to II as approximately 3 to 1 with about 7% contamination by nitrate ester[2]) was dissolved in a minimum amount of chloroform and the solution placed on a 3 × 70 cm. silica gel column slurry packed with 4% of ether in hexane. The product was eluted with ether in hexane solutions: 6200 ml. of 4%, 3000 ml. of 5%, and 3000 ml. of 15%. First collected were fractions containing 0.53 g. (10%) of a mixture of unconjugated and conjugated nitroalkenes with the former predominating (by infrared). Next were collected fractions containing a total of 3.24 g. (49%) of isomer I (melting between 130° and 137°). Fractions containing 1.05 g. (19%) of isomer II (melting between 132° and 137°) were collected last.

1-Acetoxy-*trans*-2-nitro-1-phenylcyclohexane (I) melted at 137–137.5° after three recrystallizations from ether in hexane; infrared maxima (chloroform): 8.05 (s), 9.04 (m), 10.20 (s), 10.95 (m), 11.55 (w), and 11.90 (m) μ.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.48; H, 6.44; N, 5.55.

1-Acetoxy-*cis*-2-nitro-1-phenylcyclohexane (II) melted at 137–137.5° after three recrystallizations from ether in hexane; infrared maxima (chlorofrom): 8.80 (m), 10.24 (m), 10.34 (m), and 11.37 (m) μ.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.24; N, 5.57.

Reductions of I. (a) Palladium-on-Charcoal-Catalyzed Hydrogenation.—A mixture of 1.00 g. (0.0038 mole) of I, 35 ml. of methanol, 0.70 g. of concentrated sulfuric acid, and 0.60 g. of 10% palladium on charcoal was shaken under 40 p.s.i. of hydrogen at room temperature for 2.5 days. The mixture was then filtered into water (50 ml.) and the filtrate again filtered in order to remove a small amount of insoluble material. The resulting aqueous filtrate was extracted with 25 ml. of ether and the ether extract discarded. The aqueous layer was made basic with alkali and then extracted with 50 ml. of ether. The extract was dried over sodium sulfate and the ether then removed under reduced pressure to give 0.6 g. (86%) of *trans*-2-phenylcyclohexylamine melting at 54–56° (reported[13] m.p. 59–60°). The N-benzoyl derivative melted at 181° (reported[14] m.p. 181°).

(b) Electrolytic Reduction.—The procedure closely resembled that described by Bruckner and Fodor.[15] A solution of 2.63 g. 0.01 mole) of I in 20 ml. of acetic acid, and 40 ml. of absolute ethanol was placed in a 250-ml. beaker (7.5-cm. diameter), the bottom of which was covered with about 5 mm. of clean mercury (cathode compartment). Two and a half milliliters of concentrated hydrochloric acid was then added. A 4.5-cm. (inside diameter) porous cylinder was introduced and held about 1 cm. above the mercury surface. The porous cylinder was filled to approximately the level of the surrounding solution with 20% sulfuric acid. A lead plate 4.2 cm. wide was rested on the bottom of the cylinder and a current of 2.3 amp. was passed through the cell for 54 min., maintaining the reaction temperature at 50° by means of external cooling. After this time, the cathode solution was separated from the mercury. The reduction apparatus was washed with ethanol, and the washings added to the cathode solution. The solvent was removed under reduced pressure on the steam bath; the last traces of volatile material being removed under 1 mm. of pressure at 60°. The crude solid amine hydrochloride was digested with 20 ml. of ethyl acetate and then collected by filtration. The solid was washed with ethyl acetate and dried at 60° to give 2.01 g. (75%) of **1-acetoxy-*trans*-2-amino-1-phenylcyclohexane hydrochloride**, m.p 210–212° dec. After two recrystallizations, the amine hydrochloride melted at 215° dec.

Anal. Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19. Found: C, 62.26; H, 7.45; N, 5.29.

(c) Raney Nickel Hydrogenation.—A mixture of 1.32 g. (0.005 mole) of I, dissolved in 30 ml. of warm ethanol, and 4.0 g. of Raney nickel (W-2)[16] was shaken under 40 p.s.i. of hydrogen for 35 min. The mixture was then filtered and hydrochloric acid was added to the filtrate until acid to litmus. The solvent then was removed under reduced pressure and the semisolid residue digested with 15 ml. of ethyl acetate. Filtration gave 0.71 g. (53%) of 1-acetoxy-*trans*-2-amino-1-phenylcyclohexane hydrochloride, m.p. 208–209° dec. A mixture melting point with the amine hydrochloride of the electrolytic reduction was 208–209° dec.

1-Acetoxy-*trans*-2-acetamido-1-phenylcyclohexane.—Potassium bicarbonate (0.10 g.) was added to a stirred mixture of 0.27 g. (0.001 mol) of 1-acetoxy-*trans*-2-amino-1-phenylcyclohexane hydrochloride (dissolved in 5.0 ml. of water) and 6 drops of acetic anhydride. The oil which separated solidified slowly to give 0.25 g. (92%) of **1-acetoxy-*trans*-acetamido-1-phenylcyclohexane**, m.p. 60–63°. The melting point was not changed after three recrystallizations from ether–hexane.

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.74; H, 7.78; N, 5.29.

(11) H. E. Zimmerman and T. E. Nevins, *J. Am. Chem. Soc.*, **79**, 6559 (1957).

(12) Microanalyses were by Hilda Beck.

(13) R. T. Arnold and P. N. Richardson, *J. Am. Chem. Soc.*, **76**, 3649 (1954).

(14) D. V. Nightingale and W. Tweedie, *ibid.*, **66**, 1968 (1944).

(15) V. Bruckner and G. von Fodor, *Ber.*, **76**, 466 (1943); G. von Fodor, *ibid.*, **76**, 1216 (1943).

(16) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

2-Acetamido-*trans*-1-hydroxy-1-phenylcyclohexane.—A solution of 1.00 g. (0.0037 mole) of 1-acetoxy-*trans*-2-amino-1-phenylcyclohexane hydrochloride in 15 ml. of water was treated with an excess of potassmium carbonate and then left for 16 hr. After this time, the mixture was filtered and the solid recrystallized from ethyl acetate to give 0.56 g. (65%) of 2-acetamido-*trans*-1-hydroxy-1-phenylcyclohexane, m.p. 164–165°. Two further recrystallizations did not change the melting point (reported[4] m.p. 166.4–167°); infrared maxima (chloroform): 8.64 (m), 10.15 (m), and 11.27 (w) μ.

Treatment of 70 mg. of 1-acetoxy-*trans*-2-acetamido-1-phenylcyclohexane with 3.0 ml. of 90% methanol containing 2% of potassium hydroxide at 60° for 15 min. led to 2-acetamido-*trans*-1-hydroxy-1-phenylcyclohexane (60 mg.), m.p. 163.5–164° (crude).

1-Acetoxy-*trans*-2-benzamido-1-phenylcyclohexane.—This derivative was prepared from 1-acetoxy-*trans*-2-amino-1-phenylcyclohexane hydrochloride in 93% yield through treatment of a solution of the amine hydrochloride in pyridine with an excess of benzoyl chloride. The crude product melted at 168–168.5°, and the melting point was not changed by recrystallization from ethyl acetate–hexane.

Anal. Calcd. for $C_{29}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 75.07; H, 6.86; N, 4.32.

A mixture of 100 mg. of 1-acetoxy-*trans*-2-benzamido-1-phenylcyclohexane, 3 g. of W-2 Raney nickel,[16] and 10 ml. of ethanol was refluxed for 1 hr. The mixture was then filtered into water. The yield of *N*-*trans*-2-phenylcyclohexylbenzamide, m.p. 173–176°, was 72%. The melting point was raised to 178–179° after one recrystallization from methanol (reported[11] m.p. 181°).

2-Benzamido-*trans*-1-hydroxy-1-phenylcyclohexane.—This derivative was prepared by selective hydrolysis of the acetoxy function of 1-acetoxy-*trans*-2-benzamido-1-phenylcyclohexane through treatment with warm 90% methanol containing 2% of potassium hydroxide. The product melted at 155–156°. Repeated crystallizations did not raise the melting point (reported[4] m.p. 157–158°).

A mixture of 0.15 g. of 2-benzoylamino-*trans*-1-hydroxy-1-phenylcyclohexane, 3 g. of W-2 Raney nickel,[16] and 20 ml. of ethanol was refluxed for 25 min. The mixture was then filtered into water. The product which slowly solidified was collected by filtration to give 0.11 g. (78%) of *N*-*cis*-2-phenylcyclohexylbenzamide, m.p. 118–120°. Two crystallizations from aqueous methanol raised the melting point to 122.5–123.5° (reported m.p.[4] 126.5–127°).

Reduction of II. (a) **Electrolytic Reduction.**—The reduction, as described for I, did not lead to a product which could be characterized.

(b) **Raney Nickel Hydrogenation.**—A mixture of 0.66 g. (0.0025 mole) of II, 30 ml. of ethanol, and 3 g. of W-2 Raney nickel[16] was shaken under 40 p.s.i. of hydrogen for 1.5 hr. The mixture then was filtered and the ethanol removed under reduced pressure. The residue was dissolved in 10 ml. of ethyl acetate and the resulting solution filtered so as to remove a small amount of insoluble material. The ethyl acetate of the filtrate was evaporated and the residue solidified upon trituration with ether–hexane. Filtration gave 0.24 g. (59%) of 2-acetamido-*cis*-1-hydroxy-1-phenylcyclohexane, m.p. 130–131°. The melting point was not changed by three crystallizations from ether–hexane; infrared maxima (chloroform): 8.69 (m), 10.07 (m), 11.43 (w), and 11.81 (w) μ.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.01. Found: C, 72.76; H, 8.36; N, 6.20.

6-Nitro-1-phenylcyclohexene.—A solution of 15 ml. of acetic anhydride containing 20 drops of sulfuric acid was added to 0.50 g. of I and the mixture stirred until the β-nitro acetate had dissolved and for 10 min. thereafter. About 50 ml. of ice–water then was added and the mixture was stirred until the acetic anhydride had hydrolyzed. The β-nitroalkene solidified upon cooling and was collected by filtration to give, after washing with dilute potassium bicarbonate and water, 0.36 g. (93%) of 6-nitro-1-phenylcyclohexene, m.p. 33–35°. After three crystallizations from pentane, the melting point was 37.5°; λ_{max}^{EtOH} 238–239 mμ, ϵ 11,300.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.81; H, 6.22; N, 7.09.

Comparable results were obtained with isomer II; however, a longer reaction time was required (approximately fivefold).

The β-nitroalkene also was obtained by dissolving either I or II in an excess of 15% alcoholic alkali at room temperature and, after several minutes, acidifying with 20% acetic acid–alcohol. The resulting solution was left for several minutes and the product was then obtained after addition of water.

An attempt to prepare 1-nitro-2-phenylcyclohexene by titrating a warm methanolic solution of I with an equivalent amount of alcoholic sodium methoxide, led to an oily mixture of approximately 84% of 1-nitro-2-phenylcyclohexene and 16% of 6-nitro-1-phenylcyclohexene (by infrared). Chromatography failed to separate the isomers.

Equilibration of 6-Nitro-1-phenylcyclohexene.—A 2% (by weight) solution of both 6-nitro-1-phenylcyclohexene and triethylamine in chloroform was prepared and left at room temperature for 23 days. Periodically the infrared spectrum between 6.3 μ and 6.9 μ was measured. During this time, no absorption which could be attributed to 1-nitro-2-phenylcyclohexene was observed—the absorbance of the NO_2 absorption at 6.42 μ being the same after 23 days as compared with that initially.

Rates of Piperidine-Induced Elimination of Acetic Acid from I and II.—A solution of 105 mg. (4×10^{-4} mole) of I (or II) in 1.00 ml. of chloroform was prepared. To this was added 1.00 ml. of absolute ethanol followed by the addition of 1.00 ml. of freshly distilled piperidine. After mixing thoroughly, a sample of the resulting solution was transferred to a rock salt cell (73 μ) which then was placed in the sample beam of a Baird infrared spectrometer. A solution (in matched cell) of chloroform, ethanol, and piperidine (1:1:1 by volume) was placed in the reference beam. The absorbance at 5.07 μ was measured as a function of time. A plot of log (O.D. − O.D.$_\infty$) 5.70 μ against time gave linear plots for I and II from which approximate pseudo first-order rate constants of 0.030 min.$^{-1}$ and 0.12 min.$^{-1}$, respectively, were determined. The temperature of the cell compartment was 35 ± 2°. Both runs were followed to approximately 80% completion (13 min. for I and 50 min. for II from the time mixing).

Nitration of 1-Phenylcyclopentene. 1-Acetoxy-*trans*-2-nitrophenylcyclopentane.—To a nitration reagent prepared from 4.5 g. (0.05 mole) of 70% nitric acid and 45 ml. of acetic anhydride, and then cooled to −20° was added 2 drops of sulfuric acid followed by the addition of 4.3 g. (0.03 mole) of 1-phenylcyclopentene. After the initial temperature rise, the solution was recooled to −20° and then poured into an excess of water. The product was processed as described for the nitration of 1-phenylcyclohexene. Chromatography of the crude nitration product (see 1-phenylcyclohexene) led to the isolation of 1.90 g. (34%) of a mixture of conjugated and unconjugated nitroalkenes with the latter predominating (by infrared), and 2.97 g. (40%) of *trans*-β-nitro acetate, m.p. 125–127°. The only other material obtained was 70 mg. of resinous oil which was eluted last. The 1-acetoxy-*trans*-2-nitro-1-phenylcyclopentane was recrystallized twice from ether–hexane and melted at 127–127.5°; infrared maxima (chloroform): 8.50 (w) μ and 10.20 (m) μ.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.80; H, 6.12; N, 5.74.

Electrolytic Reduction of 1-Acetoxy-*trans*-2-nitro-1-phenylcyclopentane.—The procedure described for the reduction of I was followed with slight modification. A current of 2.3 amp. was passed through the electrolytic cell which contained in the cathode compartment a solution of 15 ml. of acetic acid, 30 ml. of ethanol, and 2.0 ml. of concentrated hydrochloric acid. The cell was cooled to 30° and then 1.25 g. (0.005 mole) of coarsely ground 1-acetoxy-*trans*-2-nitro-1-phenylcyclopentane was added to the cathode compartment. The temperature was maintained at 40–45° for 35 min., during which time the β-nitro acetate gradually dissolved. The cathode solution then was processed as described earlier to give 0.87 g. (68%) of 1-acetoxy-*trans*-2-amino-1-phenylcyclopentane hydrochloride, m.p. 197–199° dec. (trituration of the crude product with ethyl acetate induced crystallization of the amine hydrochloride). Two recrystallizations from ethyl acetate–ethanol raised the melting point to 198–199° dec.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.48. Found: C, 61.08; H, 7.19; N, 5.55.

Lower yields of amine hydrochloride were obtained when the reduction was conducted as described for I. This can be attributed to the apparent instability of 1-acetoxy-*trans*-2-nitro-1-phenylcyclopentane in the acidic reduction medium at 50°.

1-Acetoxy-*trans*-2-benzamido-1-phenylcyclopentane.—This derivative, m.p. 162.5–164°, was prepared from 1-acetoxy-*trans*-2-amino-1-phenylcyclopentane in 94% yield through the reaction with benzoyl chloride in pyridine.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.85; H, 6.73; N, 4.54.

A mixture of 100 mg. of the N-benzoyl, O-acetyl derivative, 3 g. of W-2 Raney nickel.[16] and 10 ml. of ethanol was refluxed for 30 min. The mixture was filtered into water and the resulting solid product collected by filtration to give 60 mg. (73%) of N-*trans*-1-phenylcyclopentylbenzamide, m.p. 150–152°. Two recrystallizations raised the melting point to 156–156.5°. A mixture melting point with an authentic sample[17] was not depressed.

2-Benzamido-*trans*-1-hydroxy-1-phenylcyclopentane.—An 0.52-g. sample of 1-acetoxy-*trans*-2-benzamido-1-phenylcyclopentane was treated with 5.0 ml. of 4% methanolic potassium hydroxide for 5 min. on the steam bath. After addition of ice–water and filtration, 0.41 g. (91%) of 2-benzamido-*trans*-1-hydroxy-1-phenylcyclopentane, m.p. 96°, was obtained. After crystallization from chloroform–hexane, the derivative melted at 97.5–98°, resolidifying at this temperature and then remelting at 109.5–110.5°. The material was dried at 110° for analysis.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.0; H, 6.63; N, 4.96.

1-Phenylcyclopentene Oxide.—The procedure was adopted from that of Curtin and Schmulker.[4] 1-Phenylcyclopentene, 24.5 g. (0.17 mole), was added to a solution of 23.2 g. (0.168 mole) of perbenzoic acid[18] in 280 ml. of chloroform at such a rate so as to maintain the reaction temperature below −15°. The reaction mixture was then left at −20° for 1 hr. and at −10° for 46 hr. After this time, iodometric titration showed only a trace of residual peroxide. The chloroform solution was then extracted with 11.0 g. of potassium hydroxide in 500 ml. of ice–water. The chloroform layer was dried over sodium sulfate and stored at −10°. Samples of the alkene oxide were obtained when needed by evaporation of the chloroform under reduced pressure at room temperature.

2-Amino-*trans*-1-hydroxy-1-phenylcyclopentane.—The procedure was patterned after that of Curtin and Schmulker.[4] A mixture of 10.0 g. (0.0575 mole) of 1-phenylcyclopentene oxide and 200 ml. of concentrated aqueous ammonia was heated at 145–150° for 19 hr. in a 450-ml. rotating autoclave (fitted with a glass liner) charged with 20 atm. of nitrogen. The reaction mixture then was cooled and slowly made acidic (to litmus) with concentrated hydrochloric acid. The solution was extracted four times with 300 ml. of ether and the ether extracts discarded. The aqueous layer was made basic with alkali and then extracted with three 300-ml. portions of ether. The ether extracts were combined and dried over sodium sulfate. The ether was evaporated under reduced pressure and the residue mixed with 15 ml. of ether and 5.0 ml. of hexane. The mixture was cooled, and scratching induced the crystallization of a mixture of amino alcohols. The solid was collected by filtration, and washed with 60% ether in hexane to give 5.86 g., m.p. 73–76°. An additional 0.83 g., m.p. 73–76°, was obtained from the filtrate and washings to bring the total of crude amino alcohols to 6.7 g. (62%).

The mixture of amino alcohols were partially separated by fractional crystallization from ether to give 0.56 g. of 2-amino-*trans*-1-phenylcyclopentane, m.p. 99–100°, and 0.18 g. of 2-amino-2-phenylcyclopentanol (?), m.p. 90°. The remaining material was chromatographed in a 2.5 × 70 cm. silica gel column slurry packed with 5% ether in hexane solution. The amino alcohols were eluted with 10% methanol–40% hexane in ether and 10% methanol in ether solutions. Fractions containing 1.09 g. of 2-amino-2-phenylcyclopentanol (?), m.p. 87–90°, were collected first. Fractions containing 0.51 g. of a mixture of amino alcohols, m.p. 69–73°, were collected next, and these were followed by fractions containing 0.79 g. of 2-amino-*trans*-1-hydroxy-1-phenylcyclopentane, m.p. 98–100°.

The 2-amino-*trans*-1-hydroxy-1-phenylcyclopentane, was recrystallized twice from ether and melted at 100.5°.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.40; H, 8.57; N, 8.17.

A mixture of 30 mg. of 2-amino-1-phenylcyclopentanol (?) and 10 drops of acetic anhydride was heated on the steam bath for 15 min. After this time, 5.0 ml. of saturated sodium bicarbonate was carefully added. The resulting mixture then was filtered and the solid washed with water and dried to give 38 mg. (86%) of 2-acetoxy-1-N-acetyl-1-phenylcyclopentylamine (?), m.p. 156.5–157°. One crystallization from ethyl acetate–hexane raised the melting point to 157.5–158°.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.33; N, 5.36. Found: C, 68.80; H, 7.15; N, 5.60.

A similar treatment of 2-amino-*trans*-1-hydroxy-1-phenylcyclopentane with acetic anhydride led to an oily material which exhibited strong infrared absorptions at 6.02 and 6.60 μ, but no absorptions at near 5.7 and 8.0 μ indicative of the acetoxy function.

N-Benzoylation of 2-amino-*trans*-1-hydroxy-1-phenylcyclopentane with benzoyl chloride in pyridine at room temperature led to 2-benzamido-*trans*-1-hydroxy-1-phenylcyclopentane in 61% yield, m.p. 96–97°, resolidifying at this temperature and remelting at 108–109.5° (crude). A mixture melting point of this material with the N-benzoyl amino alcohol obtained *via* the electrolytic reduction of 1-acetoxy-*trans*-2-nitro-1-phenylcyclopentane was 109–110°.

1-Nitro-2-phenylcyclopentene.—A solution of 1.0 g. of 1-acetoxy-*trans*-2-nitro-1-phenylcyclopentane in 15 ml. of dioxane was treated with 1.0 g. of triethylamine.[3] The resulting solution was left for 1.5 hr. at room temperature and then poured into an excess of dilute acetic acid. The product which slowly solidified was collected by filtration to give 0.70 g. (95%) of crude 1-nitro-2-phenylcyclopentene which melted at 51° after one crystallization from methanol. Recrystallizations from hexane raised the melting point to 51.5–52°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.64; H, 5.87; N, 7.70.

Comparable results were obtained by stirring a solution of the β-nitro acetate in dimethylformamide with catalytic amounts of sodium nitrite.[3]

5-Nitro-1-phenylcyclopentene.—To a solution of 15 ml. of acetic anhydride and 10 drops of sulfuric acid was added 0.50 g. of 1-acetoxy-*trans*-2-nitro-1-phenylcyclopentane. The β-nitro acetate dissolved rapidly and the resulting solution was stirred for 30 sec. at room temperature and then poured into an excess of water. The aqueous mixture was stirred until the acetic anhydride had hydrolyzed and, after being cooled to *ca.* 10°, the remaining oily material solidified. The solid was collected by filtration to give 0.35 g. (93%) of 5-nitro-1-phenylcyclopentene, m.p. 33–34°. After two recrystallizations from hexane, the melting point was 34.0°; λ_{max}^{EtOH} 248–249 mμ, ϵ 13,700.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.90; H, 5.85; N, 7.29.

Equilibration of 1-Nitro-2-phenylcyclopentene.—A solution of 24 mg. of 1-nitro-2-phenylcyclopentene, 0.6 ml. of chloroform, and 0.2 ml. of triethylamine was prepared and the infrared spectrum between 6.3 and 6.7 μ measured periodically over a period of 7 days. After this time, the initial conjugated nitro absorption at 6.60 μ had disappeared, being replaced by the unconjugated nitro absorption of 5-nitro-1-phenylcyclopentene at 6.42 μ. A sample of the 5-nitro-1-phenylcyclopentene, m.p. 29–32°, was obtained from the equilibration solution and a mixture melting point with a known sample was not depressed.

(17) Unpublished results of T. A. Whitney and F. G. Bordwell, Northwestern University.

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Derivatives of Pyromellitic Acid. 1,2,4,5-Tetrasubstituted Cyclohexanes[1]

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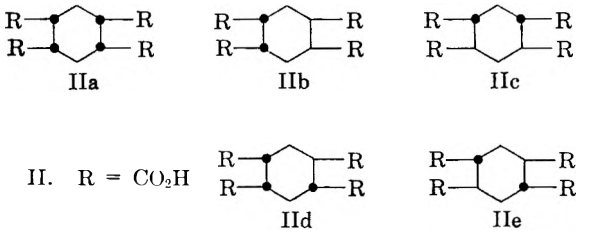
Catalytic hydrogenation of pyromellitic acid yields one of the five possible stereoisomeric 1,2,4,5-cyclohexanetetracarboxylic acids. The latter acid has been utilized as starting material for the preparation of a variety of tetrasubstituted cyclohexanes. 1,2,4,5-Tetrakis(iodomethyl)cyclohexane, precursor of 1,2,4,5-tetramethylenecyclohexane and its aromatized dimer tetramethyl[2.2]paracyclophane, has been derived from pyromellitic acid in an optimum over-all yield of 62%.

The commercial availability of pyromellitic acid (1,2,4,5-benzenetetracarboxylic acid, I) suggests the use of this compound for the preparation of tetrasubstituted cyclohexanes. We have utilized derivatives of pyromellitic acid as precursors of 1,2,4,5-tetramethylenecyclohexane[2] and its aromatized dimer tetramethyl[2.2]paracyclophane.[3] We wish to describe here the preparation of these precursors.

In an early attempt to reduce pyromellitic acid, Baeyer,[4] using sodium amalgam, obtained only a mixture of tetrahydro derivatives. We find that catalytic hydrogenation of this acid occurs with difficulty and that yields of completely reduced product are often erratic. However, in aqueous sodium carbonate solution utilizing W-2 Raney nickel catalyst and forcing conditions (3000 p.s.i. hydrogen at 150°), satisfactory yields (80–100%) of 1,2,4,5-cyclohexanetetracarboxylic acid (II) can be obtained. Less drastic conditions result in incomplete reduction or complete recovery of aromatic acid. Of the five possible stereoisomers of II (three *meso*, IIa, b, c; two *d,l*-pairs, IId, e) only one (m.p. 274–275° dec.) is formed under our hydrogenation conditions. Preliminary work[5] indicates that II is nonresolvable and is one of the three *meso* forms. There is no indication that II or its derivatives suffer isomerization when subjected to a variety of reaction media. While we suspect that II is the *trans–cis–trans*-tetraacid (IIc), a definitive assignment is not possible with the data presently available.[6]

It is pertinent to indicate that four other syntheses of II have been reported in the literature. Gregory and Perkin[7] described the preparation of a stable cyclohexane-1,1,2,2,4,4,5,5-octacarboxylic acid by condensation of the disodium salt of tetraethyl propane-1,1,3,3-tetracarboxylate with the α,α'-dibromo derivative of the same compound, followed by acid hydrolysis.



The octaacid decomposed above its melting point (218°) to yield a *"trans"* tetraacid (m.p. 175°) apparently assigned the *trans–trans–trans* structure IIe and a *"cis"* dianhydride whose hydrolysis product (m.p. 140°) was assigned the *cis–cis–cis* structure IIa.[8] Structural assignments were based on ease of formation of the *"cis"* dianhydride and the observation that the *"trans"* tetraacid gave only the *"cis"* dianhydride when treated with acetic anhydride.

Baker[9] reported the derivation of a 1,2,4,5-cyclohexanetetracarboxylic acid (m.p. 217° dec.) from a cyclohexanehexacarboxylic ester, the latter obtained by self-condensation of trimethyl 2-propene-1,1,2-tricarboxylate. The II thus obtained did not analyze well but was characterized by its tetramethyl ester (m.p. 88°) which did, and by subsequent dehydrogenation to pyromellitic acid.[10] Sieglitz and Horn hydrogenated pyromellitic acid (250° and 300 atmospheres) in aqueous sodium carbonate solution, utilizing an unspecified nickel catalyst.[11] Their reduced product II had m.p. 249–250° dec., after recrystallization from concentrated hydrochloric acid. Our crude II, formed under comparable hydrogenation conditions and precipitated from the aqueous medium by addition of concentrated hydrochloric acid, has m.p. 269–270° dec. On recrystallization from 50% ethanol we obtain analytically pure II with m.p. 274–275° dec.; however, if pure II is subsequently recrystallized from concentrated hydrochloric acid, the resulting sample has a decomposition range of *ca.* 250 to 270° and does not give a satisfactory analysis. That we obtain the same stereoisomeric tetraacid II as described by Sieglitz and Horn is further indicated by a comparison of the tetramethyl esters of II (III). The latter investigators obtain a III with m.p. 220°; our III, obtained from II in 70% yield by the method of Clinton and Laskowski,[12] has m.p. 223–225°.

Our interest in 1,2,4,5-tetramethylenecyclohexane[3] prompted the attempted conversion of the carboxylic acid groups in II to the dimethylaminomethyl groups in VI. Compound VI would serve as precursor of the tetramethylenecyclohexane *via* Hofmann degradation of the corresponding tetrakis-quaternary ammonium hydroxide. Previous work[13] has shown that the model exocyclic diene 1,2-dimethylenecyclohexane can be con-

(1) This work was supported in part by funds from the National Science Foundation (grant NSF-G-2626) and in part by the U. S. Army Research Office (Durham).

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(3) D. T. Longone and C. L. Warren, *J. Am. Chem. Soc.*, **84**, 1507 (1962).

(4) A. von Baeyer, *Ann., Suppl.*, **7**, 1 (1870); *Ann.*, **166**, 325 (1873).

(5) D. T. Longone and G. D. Mendenhall, unpublished results.

(6) We are investigating previously reported syntheses of II (*vide infra*) in order to verify somewhat tenuous structural assignments and to elucidate the stereochemistry of known 1,2,4,5-cyclohexanetetracarboxylic acids.

(7) T. W. D. Gregory and W. H. Perkin, Jr., *J. Chem. Soc.*, **83**, 780 (1903).

(8) In their structural assignments the investigators (ref. 7) considered the *"cis–trans"* isomer IId but made no mention of isomers IIb and IIc.

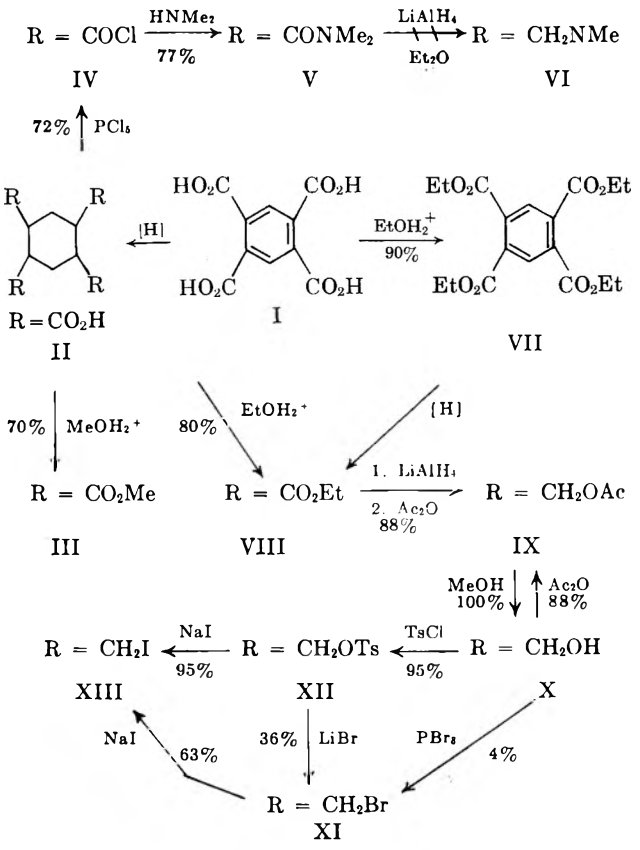
(9) J. W. Baker, *J. Chem. Soc.*, 188 (1935).

(10) Isolated as impure tetramethyl ester, "insufficient for further purification." Assignment of structure II to the aliphatic tetraacid has been questioned elsewhere (ref. 11).

(11) A. Sieglitz and O. Horn, *U. S. Dept. Comm., Office Tech. Serv., P. B. Rept.*, 777; German Patent 855,400 (1952); *Chem. Abstr.*, **47**, 4907 (1953).

(12) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

(13) A. T. Blomquist and D. T. Longone, *ibid.*, **79**, 3916 (1957).



veniently prepared by the Hofmann method. Reaction of acid II with phosphorus pentachloride in benzene gave the corresponding carbonyl chloride IV, m.p. 180–181°, in 72% yield. Aminolysis of IV in benzene solution with anhydrous dimethylamine produced the tetrakis-dimethylamide V, m.p. 296–298°, 77% yield. A single attempt to reduce V to VI with lithium aluminum hydride was unsuccessful. The infrared spectrum of the crude reaction mixture revealed the presence of large amounts of starting material and abnormal[14] reduction products. Strong absorption maxima occurred at 3400 (ROH), 1707 (RCHO), and 1633 cm.$^{-1}$ ($RCONMe_2$). If steric factors[14] determine the formation of abnormal products, they appear to be of the transannular type in this case. Both alicyclic *cis*- and *trans*-1,2-dimethylcarboxamides have given normal reduction products in relatively good yields.[15] Attempted reduction of V to VI was abandoned as it became apparent that the tetrakis-iodomethyl derivative XIII (*vide infra*) would serve as convenient progenitor of 1,2,4,5-tetramethylenecyclohexane.[3]

Azeotropic esterification of II affords tetraethyl 1,2,4,5-cyclohexanetetracarboxylate (VIII), m.p. 127–128° (80% yield). As a source of VIII we find catalytic hydrogenation of tetraethyl pyromellitate (VII) less satisfactory in that it yields a liquid mixture of stereoisomers.[16] Lithium aluminum hydride reduction of VIII, followed by acetylation with acetic anhydride,[18] gives the acetoxymethyl derivative IX, m.p. 102–103° (86% yield).[19] Methanolysis of IX affords, in quantitative yield, 1,2,4,5-tetrakis(hydroxymethyl)cyclohexane (X), m.p. 205–206°. Acetylation of X gives (88%) its precursor IX.

Reaction of tetraol X with phosphorus tribromide gave a poor yield (4%) of the bromomethyl compound XI. However, both XI and the corresponding iodomethyl derivative XIII can be derived from X *via* 1,2,4,5-tetrakis(tosyloxymethyl)cyclohexane (XII). Conversion of X to XII, m.p. 195–197° dec., was effected using *p*-toluenesulfonyl chloride (TsCl) in pyridine. Reaction of tetratosylate XII with sodium iodide in acetone gives 1,2,4,5-tetrakis(iodomethyl)cyclohexane (XIII), m.p. 245–246° (95% yield).[3] In like manner, XI, m.p. 207–208°, is obtained (36%) from XII using lithium bromide in acetone. Tetrabromide XI can be used to generate tetraiodide XIII (63% yield).

The over-all yield of tetraiodide XIII from tetraacid II (*via* XII) is 62%. The dehydroiodination of XIII to give 1,2,4,5-tetramethylenecyclohexane, tetramethyl-[2.2]paracyclophane,[3] and other products will be described in detail in a subsequent publication.

Experimental[20]

1,2,4,5-Cyclohexanetetracarboxylic Acid (II).—Neutral aqueous solutions (*ca.* 0.6 *M*) of tetrasodium pyromellitate were prepared from pyromellitic acid (or dianhydride) and the stoichiometric amount of sodium carbonate (or sodium hydroxide). As a representative hydrogenation, a volume of this solution containing 0.27 mole of acid salt and 6 g. W-2 Raney nickel was placed in a stainless steel hydrogenation bomb. The bomb, charged with hydrogen and heated to give 3000 p.s.i. at 150°, was kept at 150° for 3 days or until hydrogen consumption ceased. The resulting solution, filtered through Celite and a sintered glass filter to remove catalyst, exhibited no aromatic absorption in the ultraviolet. Addition of excess concentrated hydrochloric acid to a small portion of the solution gave a white precipitate which, after washing with cold water and drying *in vacuo*, had m.p. 269–270° dec. The remainder of the reaction solution was concentrated to incipient dryness (reduced pressure), 90 ml. of concentrated hydrochloric acid was added, and the resulting slurry (*ca.* pH 1.5) was filtered with suction. The filter cake was washed with cold water, broken up, and dried at 93° *in vacuo* to give a mixture of 69 g. (96%) II and 11 g. sodium chloride. Although the sodium chloride could be removed by careful recrystallization of the mixture from 50% ethanol, it was more convenient to remove it in a subsequent reaction (*e.g.*, esterification of II). Repetitive hydrogenations gave 81–99% yields of II.

Recrystallization of a portion of the acid–sodium chloride mixture from 50% ethanol gave analytically pure II, m.p. 274–275° dec.

Anal. Calcd. for $C_{10}H_{12}O_8$: C, 46.16; H, 4.65; N.E., 65.1. Found: C, 46.04; H, 4.72; N.E., 65.8, 65.9.

Tetramethyl 1,2,4,5-Cyclohexanetetracarboxylate (III).—Using the procedure of Clinton and Laskowski,[12] a mixture of 28.6 g. (0.110 mole) of II, 42.2 g. of methanol, 2 ml. of concentrated sulfuric acid, and 130 ml. of ethylene dichloride was refluxed for a total of 30 hr. During this time an aqueous layer developed and the suspended acid II was replaced by fine crystals of product ester. Water and chloroform were added to the mixture to dissolve all solids. The combined organic layer and chloroform extracts of the aqueous layer were washed successively with water, 5% sodium bicarbonate, and water. The resulting solution, after treatment with magnesium sulfate and

(14) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 544–546.

(15) *Cf.* A. T. Blomquist and D. T. Longone, *J. Am. Chem. Soc.*, **81**, 2012 (1959); K. Alder, S. Hartung, and O. Netz, *Ber.*, **90**, 1 (1957).

(16) Reported (ref. 17) b.p. 204° (2.5 mm.); H. I. X. Mager and W. Berends, *Rec. trav. chim.*, **76**, 28 (1957), obtained a single stereoisomer of III, m.p. 125°, on hydrogenation of tetramethyl pyromellitate.

(17) W. J. Bailey, E. J. Fetter, and J. Economy, *J. Org. Chem.*, **27**, 3479 (1962).

(18) W. J. Bailey and J. Economy, *J. Am. Chem. Soc.*, **77**, 1133 (1955).

(19) A liquid mixture of stereoisomers of IX has been used to generate 1,2,4,5-tetramethylenecyclohexane by the acetate pyrolysis method (ref. 17).

(20) Melting points are uncorrected.

Norit, was concentrated to give 17.3 g. of crystalline ester III, m.p. 223–225°. Two subsequent crops of crystals amounted to an additional 7.2 g. of product.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.19; H, 6.41.

1,2,4,5-Cyclohexanetetracarbonyl Chloride (IV).—A mixture of 22.7 g. (0.0873 mole) acid II, 83.3 g. (0.400 mole) phosphorus pentachloride, and 200 ml. of dry benzene was refluxed, protected from atmospheric moisture, until evolution of hydrogen chloride ceased (2 days). The resulting hot solution was treated with Norit, filtered, and concentrated to give 14.7 g. of analytically pure IV, m.p. 180–181°. A second crop, 6.3 g. and m.p. 178–180°, gave a total yield of 72%.

Anal. Calcd. for $C_{10}H_8O_4Cl_4$: C, 35.96; H, 2.41. Found: C, 36.18; H, 2.51.

1,2,4,5-Tetrakis(dimethylcarboxamide)cyclohexane (V).—Gaseous dimethylamine was passed into a solution of 18.6 g. (0.0557 mole) of the acid chloride IV in 500 ml. of dry benzene with continuous stirring and intermittent cooling with tap water. Introduction of the dimethylamine was interrupted from time to time when the reaction mixture was cooled. Reaction was considered to be complete when heat no longer was evolved upon further introduction of the amine. The reaction mixture was filtered hot and the filter cake washed with hot solvent. The solid residue, obtained by evaporating to dryness (diminished pressure) the combined filtrate and washings, was dissolved in excess water. Concentration of the aqueous solution gave, in five crops, 14.2 g. of product with m.p. 290–292° dec. to 296–298° dec., after drying over phosphorus pentoxide at 100° and 0.2 mm. for 16 hr. An additional 1.6 g. of product, m.p. 295–298°, was obtained in a similar manner from the original reaction mixture filter cake. Total yield was 77%. An analytical sample, m.p. 296–298° dec., was prepared by recrystallization (water) of a portion of the product and drying as described above. Product V has amide carbonyl absorption (Nujol) at 1635 $cm.^{-1}$.

Anal. Calcd. for $C_{18}H_{32}O_4N_4$: C, 58.67; H, 8.75. Found: C, 58.64, 58.87; H, 8.74, 8.71.

Tetraethyl 1,2,4,5-Cyclohexanetetracarboxylate (VIII). (A) From II.—An azeotropic esterification (6 days), essentially the procedure described elsewhere,[21] was carried out using 85.4 g. (0.328 mole) of tetraacid II, 245 ml. of absolute ethanol, 120 ml. of dry toluene, and 2 ml. of concentrated sulfuric acid. The reaction solution, on slow cooling, deposited colorless needles which, after drying *in vacuo* over phosphorus pentoxide at room temperature for 24 hr., amounted to 97.0 g. (80%) of analytically pure product VIII, m.p. 127–128°. Product VIII has strong ester-group absorptions (Nujol) at 1730 and 1190 $cm.^{-1}$.

Anal. Calcd. for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 57.88; H, 7.48.

(B) From Tetraethyl Pyromellitate (VII).—Azeotropic esterification[21] (16 days) of 260 g. (1.192 moles) of pyromellitic dianhydride was carried out using 835 ml. of absolute ethanol, 1500 ml. of dry benzene, and 5 ml. of concentrated sulfuric acid. Ethanol and benzene were removed under diminished pressure and the residual liquid slowly solidified to massive crystals on standing at room temperature for several days. The crystalline solid was dissolved in ether and the etheral solution washed successively with water, 1% sodium hydroxide, and water. After treatment with magnesium sulfate and Norit, the etheral solution was concentrated and chilled to give 345 g. of crystalline tetraethyl pyromellitate, m.p. 55–56° (reported[22] m.p. 52°). A second crop, 37.4 g., m.p. 54–56°, and a third crop, 8.4 g., m.p. 53–54°, gave a total yield of 90%.

The ultraviolet spectrum of product VII has λ_{max} (absolute ethanol) 292 mμ, log ε 3.38.

Catalytic hydrogenation of 61.2 g. (0.167 mole) of VII in 600 ml. of absolute ethanol was carried out using 5 g. of W-2 Raney nickel and 3000-p.s.i. hydrogen at 175°. The reduction charge was treated with Norit, heated to reflux, and filtered with suction through Celite and a sintered glass filter. The resulting clear solution was concentrated and cooled to give 1.5 g. of crystalline solid, m.p. 127–128°. This material was identical (infrared spectrum and mixture melting point) to reduced ester VIII previously obtained by esterification of acid II. Complete removal of solvent (reduced pressure) from the residual filtrate gave an oil which did not solidify. The oil exhibited no aromatic absorption in the ultraviolet and did not decolorize bromine or permanganate solutions. This material, apparently a mixture of stereoisomers of VIII, was not investigated further.

(C) From Acid Chloride IV.—To 323 mg. (0.968 mmole) acid chloride IV was added 5 ml. of absolute ethanol. The mixture was heated over steam and the resulting solution concentrated to *ca.* 1 ml. The colorless crystals which quickly formed on cooling were separated by filtration, washed with 1 ml. of cold absolute ethanol, and dried over phosphorus pentoxide *in vacuo* at room temperature for 16 hr. The resulting ester, 309 mg. (86%), had m.p. 127–128° and was identical (infrared spectrum and mixture melting point) to ester VIII previously obtained by esterification of acid II.

1,2,4,5-Tetrakis(acetoxymethyl)cyclohexane (IX).—Into a 5-l., three-necked flask, equipped with a large Soxhlet extraction assembly and Hershberg stirrer, were placed 1920 ml. of dry ether and 42.5 g. (1.12 moles) of lithium aluminum hydride. The extractor thimble was charged with 70.4 g. (0.189 mole) of tetraethyl ester VIII and the solvent then heated to reflux. The solid ester was extracted from the thimble over a period of several hours and the entire reaction mixture refluxed for a total of 26 hr. At the end of this time the reaction flask was cooled in an ice bath and 190 ml. of acetic anhydride was added dropwise, followed by 360 ml. of glacial acetic acid, and finally, an additional 190 ml. of acetic anhydride. Ether then was distilled from the mixture until a vapor temperature of 47° was reached (arbitrary); after 19-hr. reflux at this temperature the remaining ether was removed (vapor temp. above 100°) and the mixture refluxed an additional hour. The resulting mixture was filtered under reduced pressure while still hot and the filter cake washed well with hot acetic anhydride. Acetic acid and anhydride were distilled (reduced pressure) from the combined filtrate and washings to leave a moist solid. This solid was cooled to room temperature and repeatedly triturated with hot ether. Combined ether extracts were washed successively with water, 10% sodium bicarbonate, and water, treated with magnesium sulfate and Norit, filtered, and concentrated. The concentrate soon deposited 40.3 g. of colorless crystals, m.p. 101–102°. A second crop, 20.2 g., m.p. 100–102°, gave a total yield of 86% of product IX. An analytical sample, recrystallized from ether, had m.p. 102–103°. Product IX has strong acetate-ester absorptions at 1730 and 1245 $cm.^{-1}$.

Anal. Calcd. for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.20; H, 7.62.

An identical tetraacetate is obtained from acetylation of tetraol X (*vide infra*).

1,2,4,5-Tetrakis(hydroxymethyl)cyclohexane (X).—A solution of 15.1 g. (0.0406 mole) of IX and 0.3 g. of sodium methoxide in 55 ml. of absolute methanol was refluxed for 2 hr. During this time a white solid precipitated from solution. The mixture was then slowly distilled to remove methyl acetate as the methanol–methyl acetate azeotrope (b.p. 54°) and, subsequently, most of the remaining methanol. The resulting slurry was filtered with suction; the filter cake was washed with methanol and dried over phosphorus pentoxide at 0.2 mm. and room temperature for 24 hr. to give 8.4 g. (100%) of finely divided product X, m.p. 203–205°. The product is moderately soluble in cold water and quite soluble in hot water. An analytical sample was recrystallized from water and dried over phosphorus pentoxide at 100° and 0.2 mm. for 16 hr. to give m.p. 205–206°.

Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.52; H, 9.84.

Acetylation of X on a 0.98-mmole scale using acetic anhydride in pyridine regenerates (88%) its precursor, tetraacetate IX.

1,2,4,5-Tetrakis(tosyloxymethyl)cyclohexane (XII).—A solution–suspension of 4.9 g. (0.024 mole) of tetraol X in 65 g. of reagent pyridine (dried over barium oxide) was immersed in an ice bath and 20.2 g. (0.106 mole) of *p*-toluenesulfonyl chloride was added in small portions, with stirring, over 20 min. The resulting mixture was stirred at 0° for 3 hr., by the end of which time a thick white slurry had formed. The slurry was allowed to warm to room temperature and then poured into 200 ml. of chilled 6 *M* hydrochloric acid. The mixture was filtered with suction and the filter cake washed with dilute hydrochloric acid and water, and subsequently dried *in vacuo* at room temperature over phosphorus pentoxide. The resulting product XII weighed 18.8 g. (95%) and had m.p. 195–197° dec. after recrystallization

(21) V. M. Micovic, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 264.

(22) J. v. Braun, W. Leistner, and W. Münch, *Ber.*, **59**, 1950 (1926).

from chloroform (or dioxane). Product XII exhibited characteristic tosylate-group absorptions at 1362 and 1178 cm.$^{-1}$.

Anal. Calcd. for $C_{38}H_{44}O_{12}S_4$: C, 55.59; H, 5.40. Found: C, 55.29; H, 5.33.

1,2,4,5-Tetrakis(bromomethyl)cyclohexane (XI). (A) From Tetratosylate XII.—A glass-lined stainless steel bomb charged with 15.0 g. (0.0183 mole) of tetratosylate XII, 8.6 g. of lithium bromide, and 150 ml. of reagent acetone was heated at 110° for 14.5 hr. The resulting mixture, consisting of a fairly homogeneous solid phase and a discolored acetone phase, was filtered with suction. The filter cake, a mixture of product XI and tosylate salt, was triturated with four 100-ml. portions of carbon tetrachloride. The combined extracts were concentrated to give, in two crops (m.p. 207–208° and 205–207°), 3.0 g. (36%) of tetrabromide XI. The acetone filtrate from the original reaction mixture afforded no additional product. An analytical sample of XI, recrystallized from carbon tetrachloride, had m.p. 207–208°.

Anal. Calcd. for $C_{10}H_{16}Br_4$: C, 26.35; H, 3.54; Br, 70.12. Found: C, 26.56; H, 3.71; Br, 70.38.

(B) From Tetraol X.—Attempted bromination of X using phosphorus tribromide in carbon tetrachloride and carried out in the usual manner gave only 4% of tetrabromide XI as the sole isolable solid. This product was identical to XI derived from XII as described previously.

1,2,4,5-Tetrakis(iodomethyl)cyclohexane (XIII). (A) From Tosylate XII.[23]—A solution of 12.2 g. (0.0149 mole) of tosylate XII and 18.0 g. of dry sodium iodide in 80 ml. of reagent acetone was refluxed for 4 hr. During this time a white solid separated. The reaction mixture was cooled and filtered with suction. The filter cake, a mixture of product and sodium tosylate, was washed first with acetone, then thoroughly with water, and subsequently dried to give 95% crude iodide XIII, m.p. 244° dec. Product XIII is somewhat soluble in hot chloroform and moderately soluble in hot tetrahydrofuran.

An analytical sample, recrystallized from chloroform, had m.p. 245–246°.

Anal. Calcd. for $C_{10}H_{16}I_4$: C, 18.65; H, 2.50; I, 78.84. Found: C, 18.88; H, 2.54; I, 78.58.

(B) From Tetrabromide XI.—To a solution of 0.67 g. of XI (1.47 mmoles) in 75 ml. of hot acetone there was added, with stirring, 2.64 g. (17.6 mmoles) of dry sodium iodide. The resulting hot solution, initially clear, quickly became turbid and soon deposited a white solid. The mixture, after refluxing for 90 hr. (arbitrary), was cooled and filtered. To the filtrate was added an equal volume of chloroform and the resulting precipitate of inorganic salts was removed by filtration. The acetone–chloroform solution, hot, was used to triturate the filter cake from the original reaction mixture. The extract was concentrated to give, in two crops, 0.60 g. (63%) of tetraiodide XIII, m.p. 245–246° dec.

Acknowledgment.—The author is indebted to Dr. C. S. Marvel (National Science Foundation grant NSF-G-2626) with whose encouragement this work was initiated.

(23) The author is indebted to Mrs. C. L. Warren for initially carrying out this reaction.

Glycolic Acids and Esters From Cortisone[1]

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In methanolic cupric acetate the glyoxal from cortisone (20-keto-21-aldehyde) rearranges slowly to form the corresponding glycolic acids (20-hydroxy-21-acid) and methyl esters. Two 20-hydroxy acids (epimeric at C-20) and two epimeric 20-hydroxy esters are formed as main products. Reaction occurs slowly; 12% of starting material is present after two weeks. With alkali, rearrangement of the glyoxal to the same pair of epimeric 20-hydroxypregnenoic acids occurs rapidly. Acetylation of the epimeric acids under mild conditions gives the 17,20-diacetates whereas acetylation of the methyl esters under the same conditions gives the 20-monoacetates. Treatment of the methyl esters under vigorous acetylating conditions gives the 17,20-diacetates along with some of the corresponding C-3 enol acetates. The acetyl group is removed more readily from the 20α-acetate than from its 20β-epimer. The configurations at C-20 of the two series of epimers were determined.

In a previous paper it was shown that cupric acetate in methanol catalyzes the rearrangement of steroidal glyoxals to the methyl esters of steroidal glycolic acids.[3] From each glyoxal, two 20-epimeric 20-hydroxypregnan-21-oic esters were obtained. The rate of reaction of 17-hydroxy steroidal glyoxals was considerably less than that of the 17-deoxy analogs.

This paper describes the conversion of the glyoxal from cortisone into its 20-epimeric steroidal glycolates by catalysis with cupric acetate and with sodium hydroxide. Treatment of cortisone (I, Fig. 1) with methanolic cupric acetate for one hour[4] gave a good yield of glyoxal II. When this glyoxal was treated with methanolic cupric acetate at room temperature for two weeks, an 88% reduction in the Porter–Siber chromogenicity occurred. After the products of the reaction had been isolated, it was found that, in contrast to the analogous reaction with 3α-hydroxy-11,20-dioxo-5β-pregnan-21-al,[3] there was a significant acidic fraction (11%). This fraction was shown, by paper chromatography, to consist chiefly of the free glycolic acids (VIIIa[5] and VIIIb[5]) together with a small amount of the corresponding etienic acid (17-hydroxy-3,11-dioxoeti-4-enic acid).

The neutral fraction was acetylated and, after separation of a small amount of the 20α-acetoxy ester (IVa) by crystallization, the product was fractionated by column chromatography.[3] Small amounts of three compounds of unknown structure were obtained. The principal products were the 20α- and 20β-acetoxy esters (IVa and IVb) which were obtained in 27 and 22% yield, respectively.

Alkaline rearrangement of glyoxal II occurred much more rapidly and gave a higher yield of crystallizable product than did the cupric acetate-catalyzed rearrangement. Treatment of an aqueous suspension of glyoxal II at 0° under nitrogen with 1.25 equivalents of sodium hydroxide for thirty minutes resulted in almost complete disappearance of the glyoxal. Successive esterification and acetylation of the product, followed by

(1) Abridgment of thesis submitted by M. L. Lewbart to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biochemistry.

(2) This investigation was carried out during the tenure of a Fellowship from the Division of General Medical Sciences, Public Health Service.

(3) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).

(4) M. L. Lewbart and V. R. Mattox, *ibid.*, **28**, in press.

(5) "a" represents the 20 α-oxygen epimer; "b," the 20β-epimer.

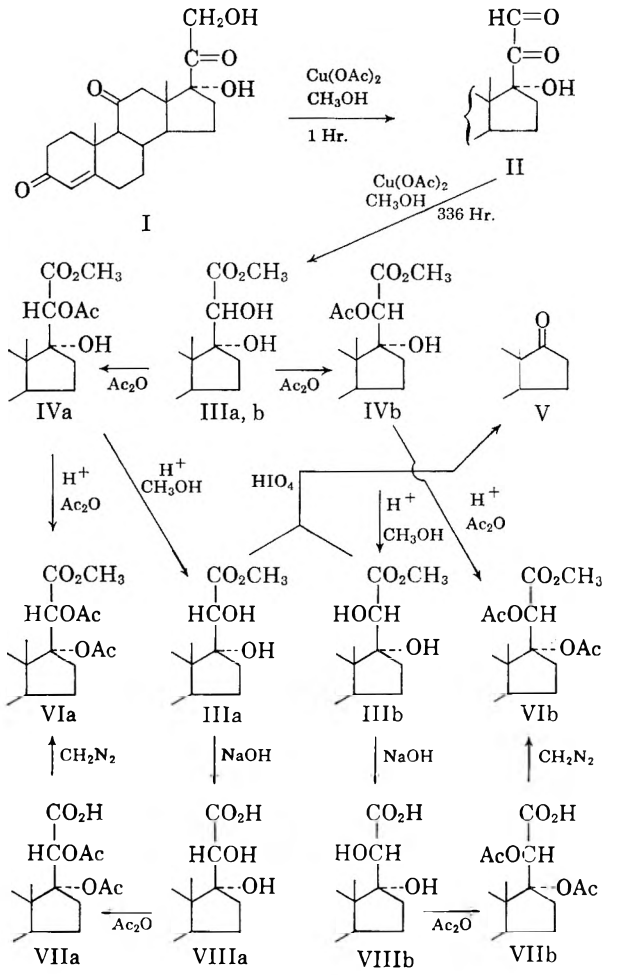

Figure 1

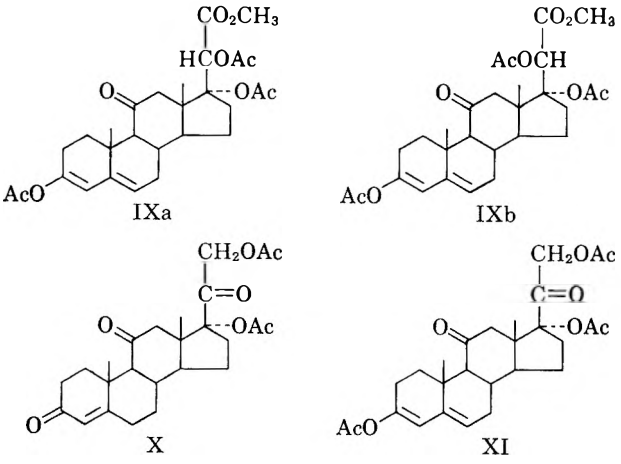

Figure 2

column chromatography, gave the 20α- and 20β-acetoxy methyl esters (IVa and IVb) in yields of 47 and 34%. These products were identical with the acetylated products obtained from reaction of the glyoxal II with methanolic cupric acetate.

The structures of IVa and IVb were anticipated from the studies on the glycolic acid derivates of 17-deoxy steroidal glyoxals[3] and were established from the transformations shown in Fig. 1. Treatment of the acetoxy esters (IVa and IVb) with methanolic hydrogen chloride removed the acetyl group from C-20 and gave the epimeric 20-hydroxy esters (IIIa and IIIb) in good yield. That these products contained vicinal hydroxyl groups was shown by their conversion to adrenosterone (V) by treatment with periodic acid. Attempts to convert the epimeric 20-hydroxy esters (IIIa and IIIb) to the corresponding 20-ketone by chromic acid oxidation under mild conditions were unsuccessful; adrenosterone was the only product detectable.

Saponification of the 20-hydroxy methyl esters (IIIa and IIIb) afforded the free 20-hydroxy acids (VIIIa and VIIIb) in about 80% yield. These acids had the same chromatographic mobility and gave the same color reactions as the major acidic artifact produced by the action of traces of copper on cortisone during paper chromatography.[6]

In an attempt to acetylate selectively the 20-hydroxyl group in the dihydroxy acids (VIIIa and VIIIb), these compounds were treated at room temperature with acetic anhydride and pyridine. The corresponding **17,20-diacetyl** derivatives (VIIa and VIIb) were obtained in yields of 51 and 44%, respectively. This result was unexpected since acetylation of 17-hydroxypregnanes ordinarily requires strenuous[7] conditions. It may have been due to formation of a mixed anhydride which served to bring an acetyl function into a position favorable for transfer to the 17-hydroxyl group by an intramolecular process.[8] From acetylation of corresponding dihydroxy esters (IIIa and IIIb) only the **20-monoacetates** (IVa and IVb) were obtained.

Proof of structure of the 17,20-diacetoxy acids (VIIa and VIIb) was obtained by esterification with diazomethane to give diacetoxy esters VIa and VIb. These products were prepared by acetylation at C-17 of the 20-acetyl methyl esters (IVa and IVb, respectively) with a mixture of acetic anhydride, acetic acid, and *p*-toluenesulfonic acid.[7]

From the acetylation at C-17 of each 20-acetyl methyl ester also was formed a less polar by-product. Only that product from the 20β-epimer could be obtained in crystalline form. Because of an ultraviolet absorption maximum at 234 mμ and the absence from the infrared spectrum of a band at 1669 cm.$^{-1}$ (characteristic for Δ^4-3-ketones), the substance was presumed to be the enol acetate (IXb, Fig. 2) of VIb (Fig. 1).

In describing the acylation at C-17 of 17-hydroxypregnanes, Turner[7] noted that, whereas yields from compounds saturated in ring A were nearly quantitative, those from Δ^4-3-ketones were less than 50%. Although Turner considered enol acetate formation as an explanation for the poor yields, he discounted such a possibility because of the absence in crude reaction mixtures of infrared absorption bands which are characteristic for such compounds.[9] Nevertheless, the crystalline by-product from forced acetylation of IVb was in fact the enol[10] acetate (IXb) as proven by elemental

(6) M. L. Lewbart and V. R. Mattox, *Nature*, **183**, 820 (1959).

(7) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953).

(8) We are indebted to R. M. Dodson for this suggestion.

(9) R. N. Jones and K. Dobriner, "Infrared Spectrometry Applied to Steroid Structure and Metabolism in Vitamins and Hormones," Vol. 7, Academic Press, Inc., New York, N. Y., 1949, p. 323.

(10) Further confirmation of the general formation of enol acetates from Δ^4-3-ketones was obtained when Turner's conditions were applied to cortisone in this laboratory. The 17,21-diacetate (X) and the 3,17,21-triacetate (XI) were each isolated in 37% yield. The (MDXI)-(MDX) of -796 units was of the expected magnitude. In addition, Ringold, *et al.*,[12] have also isolated an enol acetate as a by-product in the acetylation of 6-methyl-17-hydroxyprogesterone under Turner's conditions. The (MD $\Delta^{3,5}$-3-acetate) —(MDΔ^4-3-ketone) was -879 units. It was noted that shortening the reaction time reduced enol acetate formation, and afforded the 17-acetates in much better yield. Our findings are in agreement with this observation.

analysis and correlation of optical rotatory values. As shown by Westphal,[11] conversion of a Δ^4-3-ketone to the corresponding $\Delta^{3,5}$-3-acetate is associated with a strongly negative shift in the optical rotation. For example ($M_D\Delta^{3,5}$-3-acetate)-($M_D\Delta^4$-3-ketone) values for compounds derived from cholestenone, progesterone, and testosterone are −789, −756, and −855 units, respectively. In agreement with these values is (M_DIXb)-(M_DVIb) of −940 units.

The 20-acetoxy acids (XIIa and XIIb, Fig. 3), unsuccessfully sought by acetylation of the 20-hydroxy acids, could be obtained in low yields by partial hydrolysis of the 20-acetoxy esters (IVa and IVb). Treatment of these esters with one equivalent of sodium hydroxide in aqueous ethanol for fifteen minutes at room temperature gave a mixture of neutral and acidic products. Column chromatography of the mixture from the 20α-epimer gave the 20α-hydroxy acid (VIIIa), the 20α-acetoxy acid (XIIa), and the 20α-hydroxy ethyl ester (XIIIa), all of which could be crystallized. From the 20β-epimer (IVb) was obtained the 20β-hydroxy acid (VIIIb), the 20β-acetoxy acid (XIIb), the 20β-hydroxy ethyl ester (XIIIb), the 20β-acetoxy ethyl ester (XIVb), and the 20β-acetoxy methyl ester (IVb, starting material). The structures of the ethyl esters were established by independent preparation of them by treatment of the respective acids with diazoethane.

The isolation of significant amounts of ethyl esters of the acids indicates that, under the conditions employed, transesterification occurs rapidly. Also, in considering the hydrolysis of IVa and IVb, it is apparent that the 20β-acetyl group is removed less readily than is the 20α-acetyl group.

Values for the optical rotation of various derivatives of the 20-hydroxy epimers are given in Table I. It is apparent that values for molecular rotations of one epimeric series of 17-hydroxy-20-*acetoxy* compounds (pairs 3, 4, and 6) are uniformly greater than those of the other series. However, the acetylation increments[13] which can be calculated for compounds derived from one C-20 epimeric series are not uniformly larger (or smaller) than those derived from the other epimeric series. This can be seen by subtracting 1 from 3, 2 from 4, and 5 from 6 in the two epimeric series in Table I. Consequently, assignment of configuration at C-20 cannot be made with confidence from optical rotatory values.

TABLE I

MOLECULAR ROTATIONS[a] OF 3,11-DIOXOPREGN-4-ENE DERIVATIVES WITH SUBSTITUENTS AT C-17, C-20, AND C-21

Pair	Substituents			Epimers		Δ^b
no.	C-17	C-20	C-21	20α	20β	α-β
1	α-OH	OH	O_2H	+463	+467	−4
2	α-OH	OH	O_2CH_3	+453	+465	−12
3	α-OH	OAc	O_2H	+561	+548	+13
4	α-OH	OAc	O_2CH_3	+562	+493	+69
5	α-OH	OH	$O_2C_2H_5$	+562	+449	+113
6	α-OH	OAc	$O_2C_2H_5$	+621	+580	+41
7	α-OAc	OAc	O_2H	+253	+437	−184
8	α-OAc	OAc	O_2CH_3	+313	+451	−138

[a] Molecular rotations, M_D, are $[\alpha]_D \times$ mol. wt./100. [b] $\Delta = M_D^{20}\alpha - M_D^{20}\beta$.

(11) U. Westphal, *Ber.*, **70**, 2128 (1937).

(12) H. J. Ringold, J. P. Ruelas, E. Batres, and Carl Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959).

(13) L. F. Fieser, and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 612–618.

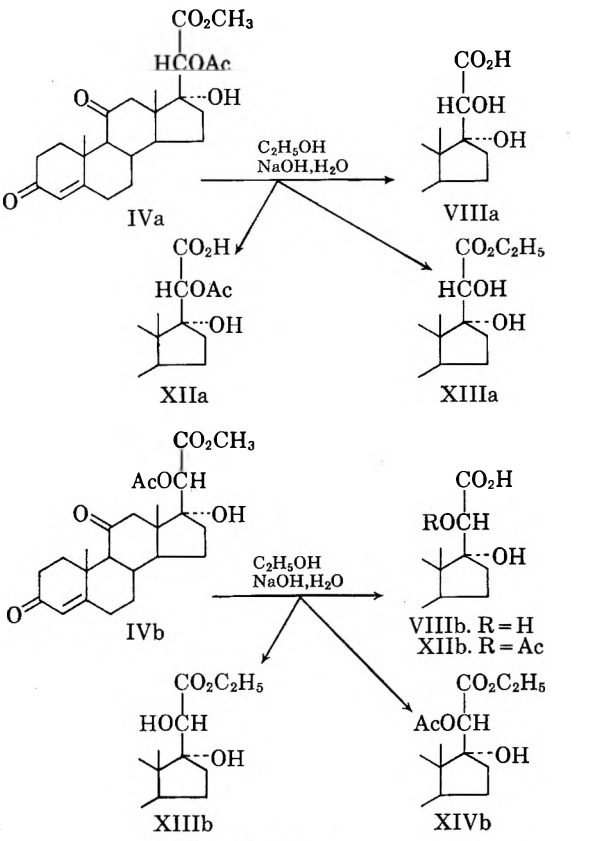

Figure 3

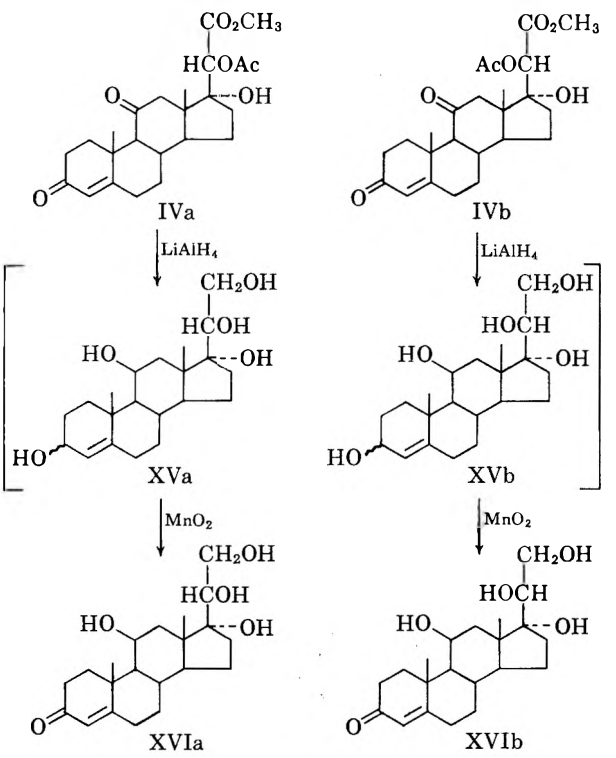

Figure 4

Configuration at C-20 was established definitively by lithium aluminum hydride reduction of the acetoxy methyl esters (IVa and IVb, Fig. 4) to their respective 3,11,17,20,21-pentols (XVa and XVb), followed by regeneration of the Δ^4-3-keto system with manganese

dioxide.[14] The configurations of the products, 11β,17,-20β,21 - tetrahydroxypregn - 4 - en - 3 - one[15,16] (XVIb) and its 20α-epimer[17] (XVIa), are known. Since lithium aluminum hydride reduction of α-hydroxy[18] acids proceeds without change of configuration[19] at the α-carbon[18] atom, this sequence of transformations establishes the configuration at C-20 in the two epimers (IVa and IVb).

The finding of greater dextrorotatory values for 17α-hydroxy-20α-acetoxy compounds than for the 17α-hydroxy-20β-acetoxy epimers (pairs 3, 4, and 6, Table I) parallels the findings[3] on six pairs of 20-epimeric 17-deoxy-20-hydroxy-5β-pregnan-21-oic acids and esters. However, when both C-17 and C-20 bear acetoxy groups (pairs 7 and 8, Table I) the 17α,20α-diacetoxy acid and ester are less dextrorotatory than the corresponding 17α,20β-diacetoxy acid and ester. From these findings, and others,[12] it is apparent that, in general, both the function at C-17 and the function at C-21 determine to a considerable extent whether an acetoxy group at C-20 is dextrorotatory or levorotatory in a particular configuration.

Experimental

Melting points were taken on a Fisher-Johns apparatus and are reported uncorrected. Optical rotations were measured in methanol at a concentration of about 1% and at 24 ± 2° unless otherwise indicated. Analyses were by J. F. Alicino, Metuchen, N. J.

A. Methyl 17-Hydroxy-20α(and 20β)-Acetoxy-3,11-dioxopregn-4-en-21-oates (IVa and IVb) and Two Unknown Compounds from Cortisone Glyoxal and Methanolic Cupric Acetate.—To a solution of 1.88 g. (4.82 mmoles) of cortisone glyoxal hemiacetal (17-hydroxy-3,11,20-trioxopregn-4-en-21-al 21-methyl hemiacetal)[4] in 125 ml. of methanol was added an equal volume of methanol containing 500 mg. (2.5 mmoles) of cupric acetate. After 14 days at room temperature, 11.6% of the original glyoxal remained. Disodium ethylenedinitrilotetraacetate (EDTA, 1 g.) in water (50 ml.) was added and the methanol was evaporated. The aqueous residue was extracted with methylene chloride which, after being washed with 5% sodium bicarbonate and water, was concentrated to dryness.

The combined aqueous washes were acidified with dilute hydrochloric acid and the resulting precipitate was extracted with ethyl acetate. The acidic residue from the ethyl acetate extract weighed 207 mg. (11.0%) and was shown by paper chromatography to consist of material with the same R_f and color reactions (periodate—Zimmermann,[20] ultraviolet absorption and sodium hydroxide-induced fluorescence) as the epimeric free 20-hydroxy acids (VIIIa and VIIIb, Fig. 1). A small amount of a substance with the mobility of **17-hydroxy-3,11-dioxoeti-4-enic acid** also was present.

After removal of residual glyoxal with sodium bisulfite,[4] the neutral fraction (methylene chloride extract) was treated with 3 ml. each of pyridine and acetic anhydride for 14 hr. at room temperature. The product gave **methyl 17-hydroxy-20α-acetoxy-3,11-dioxopregn-4-en-21-oate** (IVa) as colorless plates (378 mg., m.p. 196–202°) from acetone. Recrystallization from acetone gave 300 mg. (14.4%, m.p. 205.5–207°).

The residue from the mother liquor was fractionated on a 6 × 40 cm. column of Celite (350 g.) impregnated with 157.5 ml. of the heavier phase of benzene (1800), cyclohexane (1200), formamide (200). The flow rate was 130 ml./hr.; 22-ml. fractions were collected. Prior to collection of fraction 1, 800 ml. of effluent was discarded. The absorbance at 238 mμ of the residues from aliquots of selected fractions was determined and fractions were pooled after construction and evaluation of an elution diagram. Several unknown compounds emerged before the 20-acetoxy methyl esters.

Fractions 1–30.—Not investigated.

Unknown from Fractions 30–80.—The residue gave 38 mg. (m.p. 227–229°) of crystals from ethyl acetate.

Unknown from Fractions 90–120.—Crystallization from acetone–petroleum ether gave 30 mg., m.p. 225–226°.

Methyl 17-Hydroxy-20α-acetoxy-3,11-dioxopregn-4-en-21-oate (IVa). Fractions 124–170.—Crystallization from acetone–petroleum ether gave 257 mg. (m.p. 205–206°) and 11 mg. (m.p. 202–203°) of 20α-acetoxy methyl ester (IVa) for a total yield of 27%. A sample, recrystallized from acetone, melted at 208–209°; $[\alpha]_D$ +130° ± 1°; λ_{max}^{MeOH} 239 mμ, ε 15,800.

Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.62; H, 7.46; CH_3CO, 9.95; CH_3O, 7.17. Found: C, 66.44; H, 7.59; CH_3CO, 10.10; CH_3O, 7.33.

Methyl 17-Hydroxy-20β-acetoxy-3,11-dioxopregn-4-en-21-oate (IVb). Fractions 176–230.—Crystallization from acetone–petroleum ether gave the 20β-acetoxy methyl ester IVb in 22% yield (369 mg., m.p. 193–195°; and 85 mg., m.p. 192.5–194°). The analytical sample was recrystallized from acetone–ether; m.p. 195.5–197.5°; $[\alpha]_D$ +114° ± 1°; λ_{max}^{MeOH} 239 mμ, ε 16,100.

Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.62; H, 7.46; CH_3CO, 9.95; CH_3O, 7.17. Found: C, 66.61; H, 7.42; CH_3CO, 10.28; CH_3O, 7.27.

B. Methyl 17-Hydroxy-20α(and 20β)-acetoxy-3,11-dioxopregn-4-en-21-oates (IVa and IVb) from Cortisone Glyoxal and Sodium Hydroxide.—To a suspension of 3.0 g. (7.7 mmoles) of cortisone glyoxal hemiacetal in 150 ml. of water, 4.8 ml. of 2.09 *N* sodium hydroxide (10 mmoles) was added slowly, while stirring rapidly at 0° under nitrogen. After 1 hr., the reaction mixture contained less than 5% of starting material as indicated by analysis of an aliquot by the Porter–Silber reaction. The mixture was extracted promptly with two 50-ml. volumes of ethyl acetate. The organic phase was washed with water and discarded. The combined aqueous phases were acidified with *N* hydrochloric acid and re-extracted with ethyl acetate. The ethyl acetate extract was washed twice with water, dried, and concentrated to dryness. The residue was dissolved in 30 ml. of methanol and treated with an excess of diazomethane. After removal of the solvent, the residue was treated with 5 ml. each of pyridine and acetic anhydride for 15.5 hr. at room temperature. Crystallization of the product from acetone gave 1200 mg. (m.p. 200–205°) of crude 20α-acetoxy methyl ester (IVa). Recrystallization from the same solvent gave 1057 mg. (32%, m.p. 206–208°) of pure material.

The mother liquor was evaporated to dryness and the residue was fractionated on a column identical with the one used for the mixture obtained with methanolic cupric acetate.

Methyl 17-Hydroxy-20α-acetoxy-3,11-dioxopregn-4-en-21-oate (IVa). Fractions 166–221.—Crystallization from acetone–ether gave an additional 449 mg. (m.p. 206–208.5°) of product. The compound had an infrared spectrum identical with that of the more mobile acetylated epimer (IVa) obtained from cortisone glyoxal by reaction with methanolic cupric acetate.

Methyl 17-Hydroxy-20β-acetoxy-3,11-dioxopregn-4-en-21-oate (IVb). Fractions 236–318.—Crystallization from acetone–ether gave three crops of product (873 mg., m.p. 195–196°; 184 mg., m.p. 193–194°; and 57 mg., m.p. 186–188°). Recrystallization of the second and third crops gave 198 mg. (m.p. 194–197°) of pure 20β-epimer. The infrared spectrum of this compound was identical with that of the less mobile epimer acetate obtained with methanolic cupric acetate.

The residues from the mother liquors of both major fractions were combined with the residue from fractions 222–235 and rechromatographed on a small column in the same system used for the original mixture. An additional 55 mg. (m.p. 205–206°) of IVa and 58 mg. (m.p. 195–198°) of IVb was recovered from this column. The total yield of 20α-acetoxy methyl ester (IVa) was 1561 mg. (47.0%) and of 20β-aeetoxy methyl ester (IVb), 1129 mg. (33.8%).

Methyl 17,20α-Dihydroxy-3,11-dioxopregn-4-en-21-oate (IIIa) from IVa.—To a solution of 432 mg. (1 mmole) of methyl 17-hydroxy-20α-acetoxy-3,11-dioxopregn-4-en-21-oate in 25 ml. of methanol was added 25 ml. of 1.59 *N* hydrogen chloride in dry methanol. After 24 hr. at room temperature, the solution was

(14) Franz Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5930 (1953).

(15) L. F. Fieser and Mary Fieser "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 622.

(16) T. Reichstein and J. von Euw, *Helv. Chim. Acta*, **24**, 247E (1941).

(17) Shlomo Burstein and R. I. Dorfman, *J. Biol. Chem.*, **213**, 581 (1955).

(18) In this instance α denotes the position adjacent to the carboxyl group rather than its configuration.

(19) D. S. Noyce and D. B. Denney, *J. Am. Chem. Soc.*, **72**, 5743 (1950).

(20) Constance de Courcy, and J. J. Schneider, *J. Biol. Chem.*, **223**, 865 (1956).

diluted with an equal volume of methylene chloride and added to 100 ml. of water. After two additional extractions with the organic solvent, the combined methylene chloride extracts were washed with water, dried, and concentrated to dryness. Crystallization from acetone–ether gave two crops (295 mg., m.p. 195.5–197° and 43 mg., m.p. 192–194°) of dihydroxy ester (IIIa) for a yield of 86.7%. A sample, recrystallized from acetone–ether, melted at 197–198.5°; $[\alpha]_D$ +116° ± 2°; λ_{max}^{MeOH} 239 mμ, ε 16,100.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.86; H, 7.75.

Methyl 17,20β-Dihydroxy-3,11-dioxopregn-4-en-21-oate (IIIb) from IVb.—To a solution of 158 mg. (0.366 mmole) of methyl 17-hydroxy-20β-acetoxy-3,11-dioxopregn-4-en-21-oate in 10 ml. of methanol was added 10 ml. of 1.59 *N* hydrogen chloride in dry methanol. Paper chromatography of an aliquot removed after 24 hr. at room temperature revealed the presence of approximately 10% of starting material. After an additional 24 hr., the product was recovered in the same manner as the 20α-epimer. Crystallization from acetone–ether gave two crops (108 mg., m.p. 208–210°; and 17 mg., m.p. 202–204°) of dihydroxy ester IIIb; yield 87.5%. A sample for analysis was obtained by recrystallization from acetone–ether; m.p. 212–214°; $[\alpha]_D$ +119° ±2 °; λ_{max}^{MeOH} 239 mμ, ε 15,800.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.91; H, 7.65.

Androst-4-ene-3,11,17-trione (V, Adrenosterone) from IIIa and IIIb.—To 50 mg. each of the epimeric diols (IIIa and IIIb) in 5 ml. of methanol and 2 ml. of water was added 3 ml. of 4% periodic acid in 0.2 *N* sulfuric acid. After 3.5 hr. at room temperature, the reaction mixtures were diluted with 50 ml. of water and extracted with methylene chloride. The methylene chloride extracts were washed with dilute sodium bicarbonate solution and then water, dried, and concentrated to dryness. Crystallization from ethyl acetate gave 26 and 21 mg. of plates (m.p. 220–223° in each case) from the 20α- and 20β-epimers, respectively. The products did not depress the melting point of authentic adrenosterone (V) and their infrared spectra were identical with that of the reference compound.

17,20α-Dihydroxy-3,11-dioxopregn-4-en-21-oic Acid (VIIIa) from IIIa.—To 156 mg. (0.4 mmole) of methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate in 2 ml. of methanol was added 10 ml. of water and 0.4 ml. of 2 *N* sodium hydroxide (0.8 mmole). The turbid solution became clear in a few minutes, and, after 10 min. at room temperature, it was diluted with water and extracted with ethyl acetate. The organic phase was discarded. The aqueous phase was acidified with *N* hydrochloric acid and re-extracted with ethyl acetate. The extract was washed with water, dried, and concentrated to dryness. Crystallization from acetone gave 117 mg. (78.0%, m.p. 244.5–245° dec.) of 20α-hydroxy acid (VIIIa). A sample, recrystallized from acetone, melted at 245–246° dec.; $[\alpha]_D$ +123° ± 2°; λ_{max}^{MeOH} 239 mμ, ε 15,700.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.49. Found: C, 66.89; H, 7.48.

17,20β-Dihydroxy-3,11-dioxopregn-4-en-21-oic Acid (VIIIb) from IIIb.—Hydrolysis of 156 mg. (0.4 mmole) of methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate was performed in the same manner as for the 20α-epimer. Crystallization from acetone gave 117 mg. (78.0%, m.p. 223–225° dec.) of dihydroxy acid (VIIIb). For the analytical sample, m.p. 224–225° dec.; $[\alpha]_D$ +124° ± 2°; λ_{max}^{MeOH} 239 mμ, ε 15,700.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.49. Found: C, 66.98; H, 7.66.

17,20α-Diacetoxy-3,11-dioxopregn-4-en-21-oic Acid (VIIa) from VIIIa.—Acetylation of 200 mg. of 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oic acid was performed with 1 ml. each of pyridine and acetic anhydride for 19 hr. at room temperature. The solution was mixed with ice and water, and the product was extracted with ethyl acetate. The extract was washed with *N* hydrochloric acid, with water until neutral, and then dried, and evaporated to dryness. The residue was dissolved in a minimal volume of methanol and the solution was diluted with water to give a milky suspension. The mixture was made slightly alkaline by addition of 5% sodium bicarbonate solution, and extracted with ethyl acetate. The ethyl acetate extract was washed with water and concentrated to dryness. This neutral fraction weighed 80 mg. (40%) and gave crystals from ethyl acetate–petroleum ether. The crystalline material had a wide melting range (120–140°) and was a mixture of three compounds—R_f 0.5, 0.83, and 0.88 in toluene (275), isooctane (225), methanol (400), water (100). Its composition was not determined.

The acidic fraction was recovered by addition to the aqueous layer of slightly more than one equivalent of hydrochloric acid followed by extraction with ethyl acetate. Crystallization of the residue from acetone–ether gave 116 mg. (48%, m.p. 202–204°) of the diacetoxy acid (VIIa) as rosettes. For the analytical sample; m.p. 203–204° dec.; $[\alpha]_D$ +55° ± 2°; λ_{max}^{MeOH} 238 mμ, ε 15,700.

Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.19; H, 7.01; CH_3CO, 18.68. Found: C, 65.45; H, 7.09; CH_3CO, 17.92.

17,20β-Diacetoxy-3,11-dioxopregn-4-en-21-oic Acid (VIIb) from VIIIb.—Acetylation of 250 mg. of 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oic acid was carried out with 1 ml. each of pyridine and acetic anhydride for 21 hr. at room temperature. The product was recovered and separated into neutral and acidic fractions by the same procedure used for the 20α-epimer. The neutral fraction gave crystals from acetone–ether; this fraction was not homogeneous. Crystallization of the acidic fraction from acetone afforded 145.5 mg. (48%, m.p. 154–155°) of diacetoxy acid (VIIb) as well formed prisms. For the analytical sample, m.p. 154–155°; $[\alpha]_D$ +95° ± 2°; λ_{max}^{MeOH} 238 mμ, ε 15,900.

Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.19; H, 7.01; CH_3CO, 18.68. Found: C, 65.73; H, 6.84; CH_3CO, 18.15.

Methyl 17,20α-Diacetoxy-3,11-dioxopregn-4-en-21-oate (VIa) from IVa.—Acetylation of 250 mg. of methyl 17-hydroxy-20α-acetoxy-3,11-dioxopregn-4-en-21-oate in a mixture of acetic anhydride (2 ml.) and glacial acetic acid (10 ml.) containing *p*-toluenesulfonic acid (200 mg.) was carried out in the manner described by Turner.[7] After 4 hr. at room temperature, the reaction mixture was diluted with methylene chloride and washed successively with 5% sodium bicarbonate solution and water, dried, and concentrated to dryness. The acidic fraction was not investigated. The residue from the neutral fraction was chromatographed on a 1.8 × 47 cm. column prepared by treating 50 g. of Celite with 22.5 ml. of formamide. The mobile phase was a 2:1 mixture of cyclohexane–benzene saturated with formamide. Five-milliliter fractions were collected after the first 50 ml. of effluent was discarded.

Methyl 3,17,20α-Triacetoxy-11-oxopregna-3,5-dien-21-oate (IXa). Fractions 5–11.—The residue (81 mg., 27%) could not be crystallized. It was provisionally identified as the $\Delta^{3,5}$-enol acetate (IXa, Fig. 2) by its intense ultraviolet absorption (λ_{max}^{MeOH} 234 mμ).

Methyl 17,20α-Diacetoxy-3,11-dioxopregn-4-en-21-oate (VIa). Fractions 22–36.—The residue gave prisms (93 mg., m.p. 197.5–199°; and 8 mg., m.p. 195–197°) from acetone and acetone–petroleum ether, respectively, in 36.9% yield. When the acetylation reaction went for 15 instead of 4 hr. at room temperature, the yield of diacetoxy methyl ester (VIa) was only 26.5%. Recrystallization from acetone–ether gave the analytical sample; m.p. 197–199.5°; $[\alpha]_D$ +66° ± 2°; λ_{max}^{MeOH} 238 mμ, ε 16,000.

Anal. Calcd. for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, C, 65.85; H, 7.12.

Treatment of the 17,20α-diacetoxy acid (VIIa) with diazomethane gave a product which did not depress the melting point of VIa and which had an infrared spectrum identical with that of VIa.

Methyl 3,17,20β-Triacetoxy-11-oxopregna-3,5-dien-21-oate (IXb) from IVb.—Acetylation of 250 mg. of methyl 17-hydroxy-20β-acetoxy-3,11-dioxopregn-4-en-21-oate was performed in the same manner as for the 20α-epimer. Direct crystallization from methanol gave needles (80 mg., m.p. 190–192°) of IXb. The residue from the mother liquor was fractionated on the same column and under the same conditions used for the 20α-epimer.

Fractions 5–11.—Crystallization from methanol gave 23 mg. (m.p. 189–190°) of material identical with that crystallized directly. The total yield of enol acetate was 103 mg. (34.6%). The yield after a reaction time of 15 hr. was 120.5 mg. (48.5%). A sample, recrystallized from methanol, melted at 190–192°; $[\alpha]_D$ −95° ± 2°; λ_{max}^{MeOH} 234 mμ, ε 19,300.

Anal. Calcd. for $C_{28}H_{36}O_9$: C, 65.09; H, 7.03. Found: C, 65.04; H, 7.14.

Methyl 17,20β-Diacetoxy-3,11-dioxopregn-4-en-21-oate (VIb) from IVb. Fractions 21–40.—Crystallization from acetone–ether gave fine needles (77 mg., m.p. 190–191°; and 19 mg., m.p. 189.5–191°) in 35% yield. The analytical sample was

recrystallized from acetone–petroleum ether; m.p. 191–191.5°; $[\alpha]D$ +95° ± 1°; λ_{max}^{MeOH} 238 mμ, ε 16,200.

Anal. Calcd. for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.87; H, 7.19.

Treatment of the 17,20β-diacetoxy acid (VIIb) with diazomethane gave a product with an infrared spectrum identical with that of VIb.

17,21-Diacetoxypregn-4-ene-3,11,20-trione (X) and 3,17,21-Triacetoxypregna-3,5-diene-11,20-dione (XI) from Cortisone.—Acetylation of 250 mg. of cortisone for 18 hr. was carried out under the same conditions used for acetylation of IVa and IVb. Paper chromatography of an aliquot from the reaction mixture was carried out in isooctane (140), toluene (60), methanol (160), water (40). Two ultraviolet-absorbing compounds (R_f 0.32 and 0.66) were present in approximately equal amounts. The mixture was fractionated on a 1.8 × 38 cm. column prepared by treating 40 g. of Celite with 20 ml. of stationary phase from the system cyclohexane (480), benzene (320), formamide (25). Numbering of the 5-ml. fractions was begun after 40 ml. of effluent had been discarded.

3,17,21-Triacetoxypregna-3,5-diene-11,20-dione (XI). Fractions 5–9.—Precipitation from methanol solution with water gave 125 mg. (37%, m.p. 113–115°) of a white solid. A sample for analysis was reprecipitated from aqueous methanol and dried for 2.5 hr. at 78° and 0.1 mm. over P_2O_5; m.p. 115–120°; $[\alpha]D$ −57° ± 2°; λ_{max}^{MeOH} 234 mμ, ε, 17,200.

Anal. Calcd. for $C_{27}H_{34}O_8 \cdot {}^1/_2H_2O$: C, 65.44; H, 7.12. Found: C, 65.23; H, 6.44.

17,21-Diacetoxypregn-4-ene-3,11,20-trione (X). Fractions 49–61.—Crystallization from methanol gave X (97 mg., m.p. 224.5–226.5°; 15 mg., m.p. 222–223°; and 2.5 mg., m.p. 212–215°) in a yield of 37%. For the analytical sample, m.p. 222–223°; $[\alpha]D$ +117° ± 2°; λ_{max}^{MeOH} 238 mμ, ε 16,400. Reported[7] m.p. 223.5–224.5°; $[\alpha]D$ +113° (dioxane).

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.54; H, 7.25. Found: C, 67.45; H, 6.86.

Treatment of Methyl 17-Hydroxy-20α-acetoxy-3,11-dioxopregn-4-en-21-oate (IVa) with One Equivalent of Sodium Hydroxide.—To a solution of 432 mg. (1 mmole) of acetoxy ester (IVa) in 40 ml. of 95% ethanol was added 20 ml. of water and 0.5 ml. of 2.03 *N* sodium hydroxide (1 mmole). After 20 min. at room temperature, the clear solution was carefully acidified with slightly more than one equivalent of hydrochloric acid, added to 250 ml. of water, and extracted with 100 ml. of ethyl acetate. The extract was washed twice with water, dried, and concentrated to dryness. The residue, which consisted of both neutral and acidic products, was fractionated on a 1.8 × 36 cm. column of Celite (50 g.) impregnated with 25 ml. of the heavier phase of benzene (250), cyclohexane (250), methanol (250), acetic acid (75), water (175). After 44 ml. of effluent had been discarded, 5-ml. fractions were collected. Beginning with fraction no. 83, the top phase of benzene (500), methanol (250), acetic acid (75), water (175) was used as the mobile phase. The absorbance of selected fractions at 238 mμ was used to determine the elution diagram and indicate which fractions were to be pooled.

Ethyl 17,20α-Dihydroxy-3,11-dioxopregn-4-en-21-oate (XIIIa, Fig. 3). Fractions 32–55.—Crystallization from ether gave rosettes in two crops (85 mg., m.p. 155.5–157° with softening at 106°; and 3 mg., m.p. 152–154°); yield was 22%.

Treatment of 100 mg. of 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (VIIIa) with diazoethane[21] gave 96 mg. (89%; m.p. 155–157°) of crystals from ether. The product was proven identical with the compound from fractions 32–55 by a mixture melting point determination and by comparison of their infrared spectra. The analytical sample, recrystallized from ether, melted at 156–156.5°; $[\alpha]D$ +139° ± 2°; λ_{max}^{MeOH} 238 mμ, ε 15,900.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.36; H, 7.88.

Ethyl 17-Hydroxy-20α-acetoxy-3,11-dioxopregn-4-en-21-oate.—Ethyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (XIIIa) (50 mg.) was dissolved in 0.2 ml. each of pyridine and acetic anhydride. After 12 hr. at room temperature, the solvent was removed in a stream of nitrogen. Crystals (46 mg., m.p. 175.5–176°; and 3.5 mg., m.p. 174–175°) were obtained from ether; $[\alpha]D$ +139° ± 2°; λ_{max}^{MeOH} 238 mμ, ε 16,100.

(21) Prepared from N-ethyl-N′-nitro-N-nitrosoguanidine (Aldrich Chemical Co., Inc. Milwaukee, Wis.). *Cf.* A. F. McKay, W. L. Ott, G. W. Taylor, M. N. Buchanan, and J. F. Crooker, *Can. J. Res., Sect. B*, **28**, 683 (1950).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.20; H, 7.38.

17-Hydroxy-20α-acetoxy-3,11-dioxopregn-4-en-21-oic Acid (XIIa). Fractions 106–130.—Crystallization from acetone afforded XIIa in 18% yield (65.5 mg., m.p. 187–188° dec.; and 10 mg., m.p. 185–186° dec.). A sample was recrystallized from ethyl acetate and dried in air. On further drying for 2.5 hr. at 100° and 0.2 mm., it lost 8.25%; calcd. for loss of 0.5 mole of ethyl acetate, 9.5%; m.p. 190° dec.; $[\alpha]D$ +134° ± 2°; λ_{max}^{MeOH} 238 mμ ε 16,000.

On exposure to air the sample rapidly gained weight. When redried to constant weight at 100° and 0.2 mm. it lost 4.10%; calcd. for loss of 1 mole of water, 4.12%. On re-exposure to air the sample gained 4.21% after 41 hr.

Anal. Calcd. for $C_{23}H_{30}O_7 \cdot H_2O$: C, 63.29; H, 7.39. Found: C, 63.39, 63.41; H, 7.06, 7.11.

Treatment of the compound with diazomethane yielded a product which did not depress the melting point of the 20α-acetoxy methyl ester (IVa).

17,20α-Dihydroxy-3,11-dioxopregn-4-en-21-oic Acid (VIIIa). Fractions 180–223.—Crystallization from acetone gave 80 mg. (21.3%, m.p. 245.5–246° dec.) of a product which did not depress the melting point of the 20α-hydroxy acid (VIIIa) prepared directly from IIIa.

Treatment of Methyl 17-Hydroxy-20β-acetoxy-3,11-dioxopregn-4-en-21-oate (IVb) with One Equivalent of Sodium Hydroxide.—Treatment of 432 mg. (1 mmole) of IVb with aqueous ethanolic sodium hydroxide was carried out in exactly the same manner as for the 20α-epimer (IVa). The mixture of neutral and acidic products, similarly obtained, was fractionated by chromatography in benzene (300), cyclohexane (200), methanol (250), acetic acid (75), water (175) on 50 g. of Celite plus 25 ml. of lower phase in a 1.8 × 3.6 cm. column. Fraction 1 (5 ml./fraction) was collected after 45 ml. of effluent had been discarded. After fraction 56 had been collected, the mobile phase was changed to the top phase of benzene (500), methanol (250), acetic acid (75), water (175). From appropriate fractions 100-μl. aliquots were removed and taken to dryness. The residues were dissolved in 3.00 ml. of methanol and the absorbance at 238 mμ was determined and plotted against fraction number to determine the elution pattern.

Ethyl 17-Hydroxy-20β-acetoxy-3,11-dioxopregn-4-en-21-oate (XIVb). Fractions 8–14.—The residue gave needles from acetone–petroleum ether (29 mg., 6.5%, m.p. 166–168°). A purified sample had m.p. 169–170°; $[\alpha]D$ +130° ± 1°; λ_{max}^{MeOH} 238 mμ, ε 16,200.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.15; H, 7.49.

Treatment of 50 mg. of the 20β-acetoxy acid (XIIb) with diazoethane and crystallization from acetone–petroleum ether gave needles of XIVb (45 mg., 85%, m.p. 169.5–170.5°). This product did not depress the melting point of the chromatographed sample of XIVb.

Fractions 15–35.—This fraction consisted of a mixture of 20β-acetoxy methyl (IVb) and 20β-hydroxy ethyl (XIIIb) esters. The mixture was rechromatographed in a less polar system consisting of benzene (500), cyclohexane (200), formamide (30). Fifty grams of Celite plus 22.5 ml. of stationary phase was packed in a glass cylinder to give a 1.8 × 47 cm. column. Fifty milliliters of effluent was discarded prior to collection of fraction 1 (5 ml./fraction).

Methyl 17-Hydroxy-20β-acetoxy-3,11-dioxopregn-4-en-21-oate (IVb). Fractions 55–81.—Crystallization from acetone–ether gave needles (26 mg., 6.0%, m.p. 197–199°) which did not depress the melting point of starting material (IVb).

Ethyl 17,20β-Dihydroxy-3,11-dioxopregn-4-en-21-oate (XIIIb). Fractions 130–170.—Crystallization from acetone–ether gave plates (60 mg., 14.9%, m.p. 193–195°). Recrystallization from ether gave the analytical sample; m.p. 195–196°; $[\alpha]D$ +111° ±1°; λ_{max}^{MeOH} 238 mμ, ε 16,000.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.19; H, 7.79.

Treatment of 40 mg. of the 20β-hydroxy acid (VIIIb) with diazoethane afforded 35 mg. (84%, m.p. 193–195.5°) of plates from acetone–ether. The product was identical with the chromatographed compound (XIIIb) as shown by a mixture melting point determination and by comparison of their infrared spectra.

Methyl 17,20β-Dihydroxy-3,11-dioxopregn-4-en-21-oate IIIb). Fractions 46–67.—The compound in this fraction had the same R_f value and gave the same color reactions as the dihydroxy ester

IIIb previously described. Because of the small amount present, no attempt was made to recover it in crystalline form.

17-Hydroxy-20β-acetoxy-3-,11-dioxopregn-4-en-21-oic Acid (XIIb). Fractions 83–110.—Crystallization from acetone–ether gave 125 mg. (30%, m.p. 194.5–196° dec.) of acetoxy acid. A purified sample melted at 198–198.5° dec.; $[\alpha]_D$ +131° ± 2°; λ_{max}^{MeOH} 238 mμ, ε 16,000.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.69; H, 7.30.

Treatment of the acid with diazomethane gave a product which did not depress the melting point of starting material (IVb).

17,20β-Dihydroxy-3,11-dioxopregn-4-en-21-oic Acid (VIIIb). Fractions 150–215.—Crystallization from acetone–ether gave two crops (38.5 mg., m.p. 225–226° dec.; and 6 mg., m.p. 222.5–223° dec.) of product which did not depress the melting point of the dihydroxy acid (VIIIb) prepared directly from IIIb. The yield was 12.0%.

Proof of Configuration at C-20 in the Epimeric 20-Hydroxy-21-oic Acids Derived from Cortisone Glyoxal. 11β,17,20α,21-Tetrahydroxypregn-4-en-3-one (XVIa, Fig. 4) from IVa.—To a solution of 216 mg. (0.5 mmole) of methyl 17-hydroxy-20α-acetoxy-3,11-dioxopregn-4-en-21-oate in 5 ml. of tetrahydrofuran (redistilled from lithium aluminum hydride) was added 190 mg. (5 mmoles) of lithium aluminum hydride in 20 ml. of tetrahydrofuran. After being refluxed for 30 min., the mixture was cooled and the excess reducing agent was decomposed with ethyl acetate. After the addition of a small volume of concentrated sodium sulfate solution and 10 g. of solid sodium sulfate, the mixture was filtered and the precipitate was washed well with tetrahydrofuran. Paper chromatography of an aliquot in toluene (120), ethyl acetate (80), methanol (100), water (100) showed the presence of six or seven compounds, all of which gave pink spots[22] with 10% phosphomolybdic acid in methanol at room temperature.

The tetrahydrofuran was evaporated and the residue was dissolved in 25 ml. of ethyl acetate. After addition of 2.5 g. of manganese dioxide, prepared according to Mancera, *et al.*,[23] the mixture was agitated on a mechanical shaker for 48 hr. at room temperature. The manganese dioxide was filtered off and washed repeatedly with hot methanol. The combined filtrates were concentrated to dryness. The absorption by the residue at 242 mμ was equivalent to 49 mg. of 11β,17,20α,21-tetrahydroxypregn-4-en-3-one (XVIa).

The mixture was chromatographed on a 1.8 × 48 cm. column prepared by treating 50 g. of Celite with 25 ml. of lower phase from the system benzene (375), ethyl acetate (125), methanol (250), water (250). Numbering of the 5-ml. fractions was begun after 65 ml. of effluent had been discarded. The fractions were analyzed by measurement of ultraviolet absorption at 242 mμ. The residue from fractions 25–42 crystallized from ethyl acetate as rosettes (16 mg., m.p. 242–246°). The reported[17] melting point for 11β,17,20α,21-tetra-hydroxypregn-4-en-3-one (XVIa) is 239–243°.

11β,17-Dihydroxy-20α,21-diacetoxypregn-4-en-3-one from XVIa.—The residue from the mother liquor (7.6 mg.) plus 9.7 mg. of the crystalline material was treated with 0.1 ml. each of pyridine and acetic anhydride for 4 hr. at room temperature. The product crystallized as needles (10 mg., m.p. 204.5–205.5°) from petroleum ether. The infrared spectrum in chloroform was identical with that for authentic 11β,17-dihydroxy-20α,21-diacetoxypregn-4-en-3-one.[24]

11β,17,20β,21-Tetrahydroxypregn-4-en-3-one (XVIb) from IVb.—Methyl 17-hydroxy-20β-acetoxy-3,11-dioxopregn-4-en-21-oate (216 mg., 0.5 mmole) was reduced and selectively re-oxidized in the same manner as its 20α-epimer. The product of the final reaction mixture weighed 149 mg. The extinction at 242 mμ indicated the equivalent of 67 mg. of Δ⁴-3-ketopregnenetetrol (XVIb). The product was chromatographed under the same conditions used for the reaction mixture from the 20α-epimer. Fractions 20–47 gave 47 mg. of rosettes (m.p. 120–126°) from ethyl acetate. This product did not depress the melting point (m.p. 122–126°) of an authentic sample of 11β,17,20β,21-tetrahydroxypregn-4-en-3-one (XVIb).

11β,17-Dihydroxy-20β,21-diacetoxypregn-4-en-3-one from XVIb.—Acetylation of XVIb (17 mg.) gave 13.5 mg. (m.p. 232.5–233.5°) of needles from ethyl acetate. The infrared spectrum of this compound in chloroform was identical with that of an authentic sample of 11β,17-dihydroxy-20β,21-diacetoxypregn-4-en-3-one (Reichstein's substance E diacetate).

Acknowledgment.—We wish to thank Dr. H. L. Mason for several helpful suggestions. We are indebted to Merck & Co., Inc., Rahway, New Jersey, for a generous supply of cortisone.

(22) This color reaction was found to be characteristic of steroids with a Δ⁴-3-hydroxy grouping. Steroids with an analogous system (Δ⁵-7-hydroxy) in ring B give a bright blue color under the same conditions.

(23) O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(24) K. Dobriner, E. R. Katzenellenbogen, E. R. Jones, G. Roberts, and B. S. Gallagher, "Infrared Absorption Spectra of Steroids, an Atlas," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1958.

Conversion of Steroid-17-yl Glyoxals to Epimeric Glycolic Esters[1]

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Methanolic cupric acetate catalyzes the rearrangement of a steroidal glyoxal (20-keto-21-aldehyde) to the corresponding methyl glycolate (20-hydroxy-21-acid ester). The reaction is general for steroidal glyoxals and may be conducted in various alcohols, each alcohol giving a different ester. Glyoxals from 17-deoxy steroids react much more rapidly than do those from 17-hydroxy analogs. The presence of water retards the rearrangement. The principal products from the reaction of methanolic cupric acetate and 3α-hydroxy-11,20-dioxo-5β-pregnan-21-al are the 20α- and 20β-epimers of methyl 3α,20-dihydroxy-11-oxo-5β-pregnan-21-oate. Hydrolysis of these esters gives the corresponding 20-hydroxypregnan-21-oic acids. This same pair of epimeric 20-hydroxy acids also is obtained by treatment of 3α-hydroxy-11,20-dioxo-5β-pregnan-21-al with aqueous sodium hydroxide. The mono- and diacetates of both epimeric acids and both esters were made and the absolute configuration at C-20 was established by comparison with a substance of known configuration. Optical rotations of the various derivatives were determined and correlated. In every instance, the compound with a 20α-oxygen function was more dextrorotatory than its 20β-epimer. This finding indicates that the rule which states that a 20β-acetoxypregnane is more dextrorotatory than its 20α-epimer is not applicable to 20-acetoxy-5β-pregnan-21-oic acids and esters.

The 21-hydroxyl group of an α-ketolic steroid can be oxidized to an aldehyde by treatment with methanolic cupric acetate.[3–6] During studies on the preparation[5] of a glyoxal (3α-hydroxy-11,20-dioxo-5β-pregnan-21-al)

(1) Abridgment of thesis submitted by M. L. Lewbart to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biochemistry.

(2) This investigation was carried out during the tenure of a Fellowship from the Division of Medical Sciences, Public Health Service.

(3) J. P. Conbere, U. S. Patent 2,733,077 (1956).

(4) J. Weijlard, U. S. Patent 2,773,078 (1956).

(5) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, in press.

(6) M. L. Lewbart and V. R. Mattox, *Anal. Chem.*, **33**, 559 (1961)

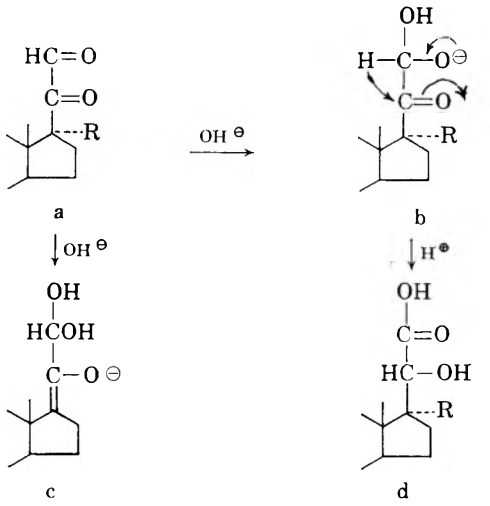

Fig. 1.—R = H or OH. 17-Hydroxy steroidal glyoxals cannot enolize to give structure c.

by this procedure it was found that the amount of glyoxal formed was maximal in fifteen to thirty minutes but decreased slowly at longer reaction periods. After seventy-two hours, only 15% of the glyoxal remained, as indicated by measurement[5] by the Porter–Silber procedure. A plot of the logarithm of the concentration of glyoxal against time gave a straight line. Approximate half-lives, when the methanolic solution was 0.02 *M* in glyoxal and the molar ratios of copper to steroid were 1:20, 1:8, 1:2, and 1:1, were fifty-seven, thirty, twenty-one, and twenty-one hours, respectively.

The major products of the reaction of 3α-hydroxy-11,-20-dioxo-5β-pregnan-21-al (II, Fig. 2) with copper acetate in methanol were the methyl esters (IIIa[7] and IIIb[7]) of the 20-epimeric 20-hydroxypregnan-21-oic-acids. Three by-products of unknown structure were obtained in low yield. This complex reaction mixture was separated readily by partition-type chromatography on a column of Celite.

That copper salts are capable of catalyzing, under neutral conditions, the rearrangement of α-keto aldehydes to α-hydroxy (glycolic) acids is not generally recognized. The only mention of this type of reaction that has been located in the literature is by Nef,[8] describing the conversion of acetol and benzoylcarbinol, in aqueous solutions, to lactic acid and mandelic acid, respectively, by treatment with aqueous cupric acetate or cupric sulfate. His presumption that the α-keto aldehydes were intermediates was confirmed by Evans[9] who showed that benzoylformaldehyde was convertible to mandelic acid under the same conditions.

The use of alkali or alkoxides to achieve this type of transformation is well known and, in effect, represents an intramolecular Cannizzaro reaction.[10] In the steroid field, Wendler and Graber[11] obtained a mixture of 20-epimeric glycolic acids (VIIa + VIIb) after treatment of 3α,17,21-trihydroxy-5β-pregnane-11,20-dione with dilute methanolic potassium hydroxide in an atmosphere of nitrogen. The diacetates of the corresponding methyl esters also were prepared, but the epimers were not separated. The amorphous 20-epimeric 11β,20-dihydroxy-3-oxopregna-1,4-dien-21-oic acids were obtained by Hirschmann, *et al.*,[12] from prednisolone as by-products in the reaction of 21-iodoprednisolone with silver dihydrogen phosphate.

Franzen[13] has shown that the rearrangement of methylglyoxal and phenylglyoxal to the glycolic acids is catalyzed by compounds which contain thiol and amino groups either in the same or in different molecules. By conducting the reaction in heavy water, he obtained evidence that a hydride ion transfer is involved in the rearrangement.

Although we have not investigated the mechanism of the conversion of glyoxals to methyl glycolates by copper acetate in methanol, we present the following speculation. The yellow anhydrous glyoxal II becomes colorless when it is dissolved in methanol. It is assumed that a hemiacetal is formed since the methyl and ethyl hemiacetals[5] of the aldehyde from cortisone have been crystallized from aqueous solutions of the corresponding alcohols. If the rearrangement of the glyoxal hemiacetal involves a transfer of a hydride ion from C-21 to C-20, which seems probable, any process which would increase the electron density at C-21 or tend to produce a positive charge on C-20 would promote the reaction.[14]

Copper acetate is a Lewis-type acid and is known to form complexes with many substances. It is postulated that the hemiacetal of the glyoxal forms a complex with copper acetate involving the carbonyl oxygen at C-20 and the hydroxyl oxygen at C-21. It is assumed that copper acetate acts as an acceptor for a pair of electrons from the carbonyl oxygen at C-20, and that the positive charge so induced on C-20 provides the driving force for the reaction. After the rearrangement occurs, the regenerated catalyst is available for reaction with another molecule of glyoxal hemiacetal.

In methanolic cupric acetate, steroidal glyoxals with a hydroxyl group at C-17 rearrange much more slowly than do 17-deoxy glyoxals. Whether this phenomenon is due to inhibition of formation of a reactive complex with cupric acetate because of hindrance by or combination with the hydroxyl group at C-17 or to an electronic effect exerted on C-20 by the hydroxyl group at C-17 is not known. It is noteworthy that no significant amount of acidic material[15] is obtained from the 17-deoxy steroidal glyoxals whereas the acidic fraction from a 17-hydroxy glyoxal[16] (derived from cortisone) amounts to 11%.

Treatment of both the 17-deoxy glyoxal II and the 17-hydroxy glyoxal from cortisone with alkali gives mixtures of the corresponding glycolic acids. With glyoxal II in 4 *N* alkali, about eight hours is required for complete reaction, whereas with the glyoxal from cortisone in 1.25 *N* alkali, the reaction is complete within thirty minutes.[16] If the rearrangement occurs by the type of mechanism[13] which has been suggested for this process (a → b → d for 20α-epimer in Fig. 1), the slower reaction of the 17-deoxy glyoxal may be due to 17(20)-enolization to give intermediate c, or the equivalent, which competes with the reaction that leads to the gly-

(7) "a" represents the 20α-oxygen epimer; "b," the 20β-oxygen epimer.
(8) J. U. Nef, *Ann. Chem.*, **335**, 247 (1904).
(9) W. L. Evans, *Am. Chem. J.*, **35**, 115 (1906).
(10) T. A. Geissman, *Org. Reactions*, **2**, 94 (1944).
(11) N. L. Wendler and R. P. Graber, *Chem. Ind.* (London), 549 (1956).
(12) R. Hirschmann, G. Bailey, and J. M. Chemerda, *ibid.*, 682 (1958).
(13) V. Franzen, *Chem. Ber.*, **88**, 1361 (1955); **89**, 1020 (1956).
(14) N. C. Deno, H. J. Peterson, and G. S. Saines, *Chem. Rev.*, **60**, 7 (1960).
(15) A small amount of acidic product is formed when glycolic esters IIIa and IIIb are prepared by treatment of ketol I with cupric acetate. The acidic material is formed during oxidation of ketol I rather than during rearrangement of glyoxal II.
(16) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1773 (1963).

colic acid mixture. A 17-hydroxyl group precludes a structure of type c. The Cannizzaro reaction ordinarily is associated with substances that have no enolizable hydrogen in the function undergoing reaction.

To study the scope and rate of this rearrangement, the steroidal glyoxals listed in Table I were treated with copper acetate in methanol. The half-lives of the glyoxals, as indicated by rate of disappearance of Porter–Silber chromogenicity, were determined.

TABLE I

RATE OF DISAPPEARANCE OF GLYOXALS IN 0.01 *M* METHANOLIC CUPRIC ACETATE[a]

Glyoxal from	Half-life[b]
3α,21-Dihydroxy-5β-pregnane-11,20-dione	17
3α-21-Dihydroxy-5β-pregnan-20-one	19
3α,21-Dihydroxy-16α,17α-epoxy-5β-pregnane-11,20-dione	20
3α,11β,21-Trihydroxy-5β-pregnan-20-one	23
11-Deoxycorticosterone	23
Corticosterone	30
Cortisone	128
3α,17,21-Trihydroxy-5β-pregnane-11,20-dione	170

[a] Molar ratio of copper to steroid, 1:2. [b] Half-life refers to time in hours required for a 50% decrease of absorbance in the Porter–Silber reaction. Initial absorbancies were obtained after treatment of the respective α-ketols for one hour.

The approximate half-life of 3α-hydroxy-11,20-dioxo-5β-pregnan-21-al in various alcohols, with a copper to steroid ratio of 1:2, is shown in Table II. The reaction was more rapid in *n*-propyl alcohol than in methyl alcohol, but in *t*-butyl alcohol, was considerably slower than in methyl alcohol. That different products were formed from the glyoxal with the different alcohols was shown by the fact that paper chromatography gave R_f values varying from 0.38 for methyl alcohol to 0.62 for *t*-butyl alcohol, as shown in Table II. The half-lives of the glyoxal derivatives from cortisone in methyl, ethyl, propyl and butyl alcohols containing copper acetate also are given in the table.

TABLE II

RATE OF DISAPPEARANCE OF GLYOXALS IN 0.01 *M* CUPRIC ACETATE[a] IN VARIOUS ALCOHOLS

	Glyoxal from 3α,21-dihydroxy-5β-pregnane-11,20-dione			Glyoxal from cortisone	
Alcohol	Half-life[b]	R_fa[c]	R_fb[c]	Half-life[b]	R_fa[c]
CH_3OH	17.5	0.38	..	128	0.20
C_2H_5OH	11.0	.52	..	170	.42
n-C_3H_7OH	8.5	.65	0.35	144	.58
n-C_4H_9OH	10.0	.74	.48	143	.71
n-$C_5H_{11}OH$	10.5	..	.59		
n-$C_6H_{13}OH$	9.0	..	.65		
n-$C_7H_{15}OH$	10.0	..	.71		
i-C_3H_7OH	19.0	0.52	..		
i-C_4H_9OH	21.5	.58	..		
sec-C_4H_9OH	18.0	.64	..		
t-C_4H_9OH	31.0	.62	..		

[a] Copper to steroid ratio, 1:2. [b] Half-life denotes time in hours required for a 50% reduction of the original color in the Porter–Silber reaction. [c] R_f, ratio of movement of major spot to movement of solvent front; a, isooctane–toluene–methanol–water, 90:110:160:40; and b, isooctane–toluene–methanol–water, 140:60:160:40.

The structures of the two main products (IIIa and IIIb) from the reaction between methanolic cupric acetate and 3α-hydroxy-11,20-dioxo-5β-pregnan-21-al (II) were deduced from the following observations. Substances IIIa and IIIb were neutral and had the same per cent composition. They contained no carbonyl groups active toward 2,4-dinitrophenylhydrazine. Oxidation of IIIa and IIIb with chromic acid gave a single compound (VI). Substances IIIa and IIIb contained two acylable hydroxyl groups, as shown by formation of the isomeric diacetoxy esters (IVa and IVb). Hydrolysis of dihydroxy esters IIIa and IIIb gave two dihydroxy acids (VIIa and VIIb) which were convertible to 3α-hydroxy-11-oxo-5β-etianic acid (V) by treatment with potassium permanganate in acetic acid. Neither the esters (IIIa and IIIb) nor the free acids (VIIa and VIIb) were altered by treatment with periodic acid. From these results it follows that substances IIIa and IIIb are 20-epimeric 20-hydroxypregnan-21-oic esters.

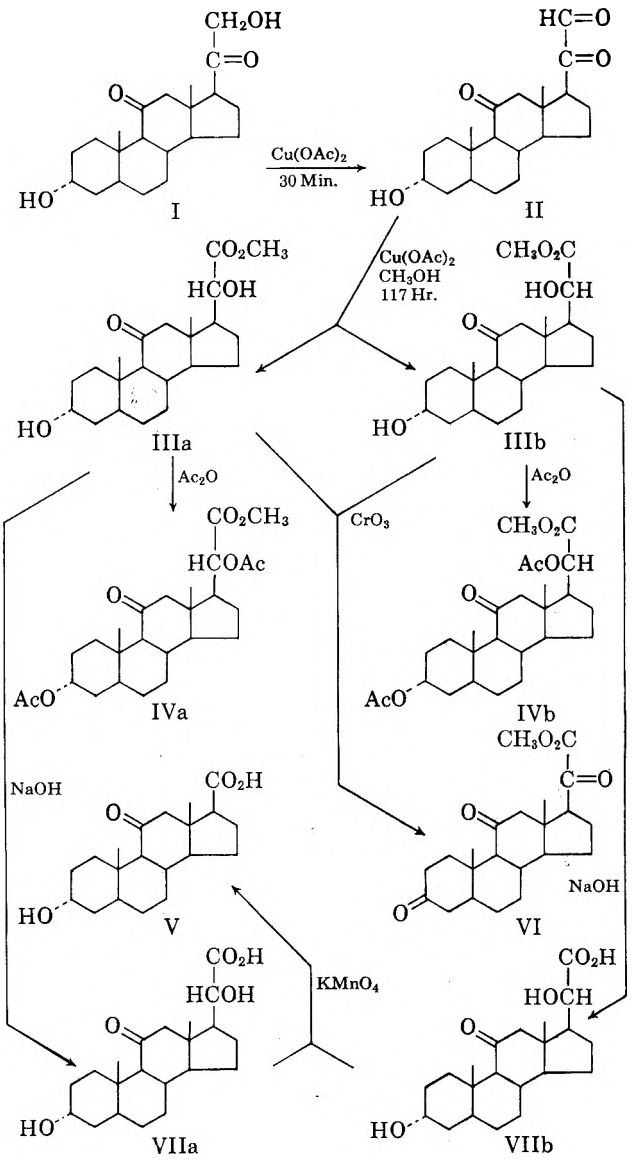

Figure 2

Acetylation of the dihydroxy acids (VIIa and VIIb) gave the corresponding diacetoxy acids (VIIIa and VIIIb, Fig. 3). The 3α-acetyl group was selectively removed from each of these compounds by mild treatment of the diacetoxy acids (VIIIa and VIIIb) with a slight excess of alkali. More vigorous treatment of the diacetates (VIIIa and VIIIb) produced the dihydroxy acids (VIIa and VIIb).

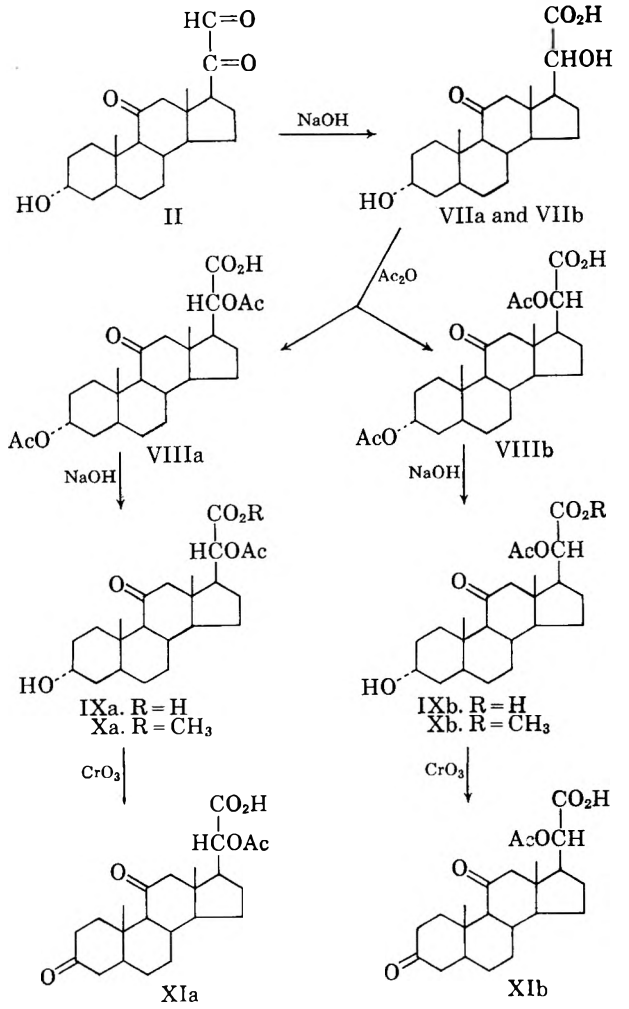

Figure 3

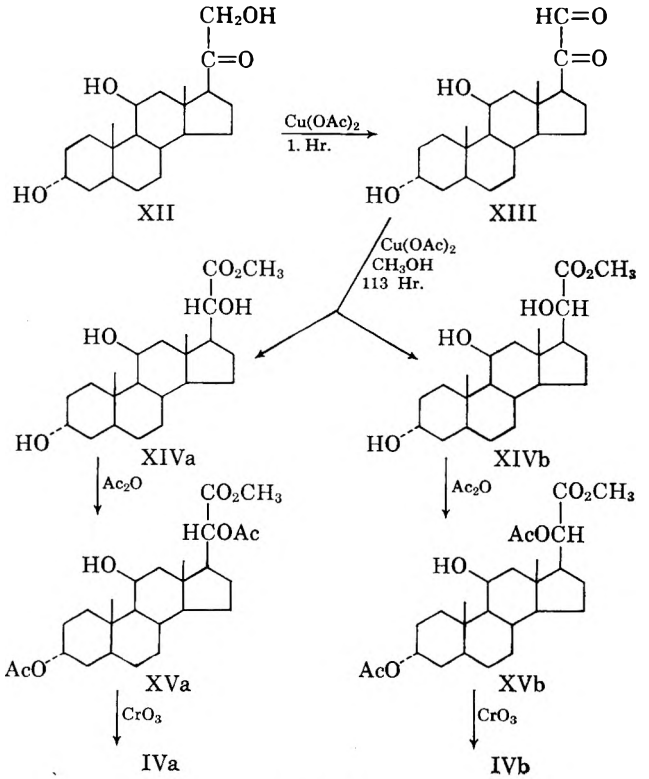

Figure 4

The 20-acetyl group is removed more easily from the 20α-acetate than from its 20β-epimer. This fact was demonstrated by treating the diacetoxy epimers (VIIIa and VIIIb) with four equivalents of sodium hydroxide under identical conditions and analyzing, by paper chromatography,[17] serial aliquots of the mixtures. After forty minutes at room temperature the 20β-acetoxy acid (IXb) was essentially the only product present in the reaction mixture from the 20β-epimer (VIIIb). From the 20α-epimer (VIIIa), a 1:1 mixture of 20α-acetoxy acid (IXa) and 3α,20α-dihydroxy acid (VIIa) was obtained. Esterification of the 20-acetoxy acids (IXa and IXb) with diazomethane produced the corresponding methyl esters (Xa and Xb). Oxidation of the 3α-hydroxy-20α- and 20β-acetoxy acids (IXa and IXb) with chromic acid yielded the corresponding 3-keto compounds (XIa and XIb).

The conversion of 3α-hydroxy-11,20-dioxo-5β-pregnan-21-al (II) to the mixture of glycolic acids (VIIa and VIIb) could be obtained more quickly by treatment with alkali than the corresponding esters could be obtained by treatment with cupric acetate (eight *vs.* 117 hours). After acetylation of the mixture of acids, the 20α- and 20β-acetoxy compounds (VIIIa) and VIIIb) could be obtained in 42 and 34% yield by fractional crystallization from ethyl acetate.

Treatment of 3α,11β-dihydroxy-20-oxo-5β-pregnan-21-al (XIII, Fig. 4) with methanolic cupric acetate gave the 20α- and 20β-epimers of the glycolic acid methyl esters (XIVa and XIVb) in yields of 26 and 35%, respectively. Mild acetylation of these products gave the corresponding diacetates (XVa and XVb). Proof of structure of these products was established by chromic acid oxidation of the 11β-hydroxyl group to give corresponding 11-ketones (IVa and IVb).

The configuration at C-20 of a pair of epimeric 20-acetoxy pregnanes can be established by comparing their molecular optical rotations. A simple rule, formulated by Fieser and Fieser,[18] states that a 20β-acetoxy compound of any type is more dextrorotatory than its 20α-acetoxy epimer. The rule holds for pregnan-20-ols which are unsubstituted at C-17 and C-21 as well as for pregnane-20,21-diols, pregnane-17,20-diols and pregnane-17,20,21-triols.[19]

This rule was considered in assigning configurations[20] to the 20-epimeric 20-hydroxypregnan-21-oic derivatives listed in Table III. Its application would designate those compounds with the more positive rotations as having a 20β-oxygen function. However, on this basis the 20α-acetate should be the more difficult epimer to hydrolyze; in the acetylated glycolic acids from cortisone, the 20β-acetate[16] is more difficult to hydrolyze than is its 20α-epimer. Furthermore, with the 20-epimeric 17,20-dihydroxypregnen-21-oic derivatives

(17) Solvent system: isooctane (100), toluene (100), methanol (100), acetic acid (30), water (70). R_f values of the diacetoxy, monoacetoxy, and dihydroxy acids were 0.7, 0.11, and 0.01. There was no significant difference in the mobilities of the 20α- and 20β-epimer pairs.

(18) L. F. Fieser, and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 612.

(19) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1165 (1949).

(20) Data in Table III are sufficient for determining C-20 acetylation increments for only two pairs of epimers (pairs 7 and 8 in Table III). The acetylation increments of the 20α-hydroxy compounds are positive and those of the 20β-hydroxy epimers are negative. This finding is at variance with results from acetylation of epimeric 20-hydroxy-pregnanes which are unsubstituted at C-21 or bear a hydroxyl group. With these compounds, acetylation increments for 20β-ols are strongly positive and those for 20α-ols are negative or very slightly positive.

from cortisone, neither the acetylation increments[18] nor the optical rotations of the 20-acetates of one series were consistently greater than those of the other.[16] Thus it was obvious that the generalizations concerning rotation and configuration at C-20 were not valid[21] for assigning C-20 configuration to 17,20-dihydroxypregn-4-en-21-oic acids and it seemed probable that they would not be valid for the 17-deoxy-20-hydroxypregnanoic derivatives in Table III.

TABLE III

MOLECULAR ROTATIONS[a] OF 5β-PREGNANES WITH SUBSTITUENTS AT C-3, C-11, C-20 AND C-21

Pair	Substituents				Epimers		Δ[b]
no.	C-3	C-11	C-20	C-21	20α	20β	α-β
1	α-OH	=O	OH	O_2H	+182	+91	+91
2	α-OH	=O	OH	O_2CH_3	+148	+95	+53
3	α-OH	β-OH	OH	O_2CH_3	+197	+102	+95
4	α-OAc	=O	OAc	O_2H	+350	+188	+162
5	α-OAc	=O	OAc	O_2CH_3	+351	+152	+199
6	α-OAc	β-OH	OAc	O_2CH_3	+366	+162	+204
7	α-OH	=O	OAc	O_2H	+248	+85	+163
8	α-OH	=O	OAc	O_2CH_3	+256	+63	+193
9	=O	=O	OAc	O_2H	+281	+93	+188

[a] Molecular rotations, MD, are $[\alpha]_D \times$ mol. wt./100. [b] Δ = MD 20α − MD 20β.

Because of these considerations, 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oic acid of known absolute configuration at C-20[22] was synthesized. With this compound available, it was possible to establish the 20β-configuration for the acetoxy group in the 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid which melts at 199–200°, and to assign formula VIIIb to this substance. Since VIIIb is already correlated configurationally at C-20 with the various other 20-asymmetric compounds which are described, it follows that their configurations are as indicated in the figures.

Experimental

General Procedures.—Melting points were taken on a Fisher-Johns apparatus and are reported uncorrected. Optical rotations were measured in methanol at a concentration of about 1% and at a temperature of 24 ± 2° unless otherwise designated. Analyses were by J. F. Alicino, Metuchen, N. J.

Paper chromatography was used extensively for evaluating complex reaction mixtures, developing solvent systems for chromatography on columns, and judging homogeneity of purified samples. Chromatography on columns was employed to separate preparative quantities of pure products. In general, the procedures discussed in detail by Neher[23] were followed.

For detection of Δ⁴-3-ketones on paper chromatograms, ultraviolet absorption and sodium hydroxide-induced fluorescence were employed. Alkaline blue tetrazolium was used for α-ketols and the Porter–Silber reagent was employed[6] for detection of dihydroxyacetone or glyoxal groupings. For several other classes of compounds phosphomolybdic acid, which is nonspecific and relatively insensitive, was used. With this reagent, the methyl esters of the 20-epimeric 3α,20-dihydroxy-11-oxo-5β-pregnan-21-oic acids gave very little color, even at levels of 100 μg., whereas the 11β-hydroxy analogs gave intense spots with as little as 10 μg. Acids were detected by dipping the paper chromatograms into a 0.01% alcoholic solution of chlorophenol red and then holding the paper over a mild current of steam to drive off the residual acetic acid; steroidal acids gave yellow spots on a purple background. The test was sensitive to 2 μg. of carboxyl group in the steroidal acids examined.

Columns were prepared for chromatography with either Bush- or Zaffaroni-type solvent systems by pretreating Celite 545 (100–200 mesh) with an excess of mobile phase mixed with approximately 50% (v./w.) of stationary phase. For the preparation of columns greater than 2 cm. in diameter, the use of a conventional close-fitting Martin packer did not result in uniform packing of the supporting medium. Chromatography of sudan III indicated that the center of the column was packed more loosely than was the periphery. When a close-fitting packer was used in conjunction with a packer of small diameter, which was used to tamp the center of the column, satisfactory uniformity of the supporting medium was achieved. A column was judged suitable for use if a test sample of sudan III was eluted in less than 20% of the effluent collected after applying sudan III to the column. Rates of flow of the solvents through the columns were in the range of 4 to 16 ml./sq. cm. surface area/hr.

Methyl 3α,20α-(and 20β)-Dihydroxy-11-oxo-5β-pregnan-21-oates and Three Unknown Compounds from I and Methanolic Cupric Acetate.—A solution of 3.48 g. (10 mmoles) of 3α,21-dihydroxy-5β-pregnane-11,20-dione[5] (I) in 250 ml. of methanol was mixed with 1.0 g. (5 mmoles) of cupric acetate in an equal volume of methanol at room temperature. After 117 hr., only 7% of the glyoxal remained, as indicated by analysis[6] with the Porter–Silber reagent. After addition of 2.0 g. of disodium ethylenedinitrilotetraacetate (EDTA) in 50 ml. of water, the methanol was evaporated *in vacuo*, and the aqueous residue was extracted with methylene chloride. The extract was washed with 5% sodium bicarbonate and then water, and concentrated to dryness. To remove unchanged glyoxal II, the residue in 20 ml. of methanol was heated on a steam bath with 500 mg. of sodium bisulfite in 50 ml. of water. The cooled mixture was extracted with methylene chloride, and the organic layer, after being washed with water, was concentrated to dryness. The residue gave 1500 mg. (m.p. 190–195°) of fine needles from 5 ml. of benzene. Recrystallization from acetone gave 1170 mg. (31%, m.p. 200–203°) of pure **methyl 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oate (IIIb)** as prisms.

The residue (2127 mg.) from the benzene and acetone mother liquors was chromatographed in benzene (1800), cyclohexane (1200), formamide (200) on a 6-cm. diameter column packed to a height of 40 cm. with 350 g. of Celite plus 57.5 ml. of stationary phase. Before fraction no. 1 was collected 800 ml. of effluent was discarded. Each fraction contained 20 ml. Weight of the residue from every fifth fraction was obtained and plotted against the corresponding fraction number. Fractions were pooled and the solvent was removed. Three compounds of unknown structure, X_1, X_2, and X_3, emerged before the dihydroxy esters.

Compound X_1. Fractions 17–40.—The residue gave long needles from methyl ethyl ketone (288 mg., m.p. 164–165°). A sample for analysis prepared from the same solvent melted at 167–168.5°; $[\alpha]_D$ +112° ± 2°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; CH_3O, 8.24. Calcd. for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05; CH_3O, 8.20. Found: C, 70.35; H, 8.63; CH_3O, 8.19.

Compound X_2. Fractions 48–80.—The residue gave crystals (84 mg., m.p. 189–190°) from acetone. Recrystallization from acetone did not alter the melting point; $[\alpha]_D$ +139° ± 1°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.99; H, 9.38; CH_3O, 0.0.

Compound X_3. Fractions 116–164.—Crystals (121 mg., m.p. 198–198.5°; and 9 mg., 196–198°) were obtained from acetone–ether. The sample for analysis was recrystallized from acetone–ether; m.p. 200–201°; $[\alpha]_D$ +15° ± 2°.

Anal. Calcd. for $C_{24}H_{38}O_6 \cdot CH_3COCH$: C, 67.47; H, 9.23; $3CH_3O$, 19.40. Found: C, 67.46; H, 9.19; CH_3O, 19.17.

Compound X_3 Acetate.—Acetylation at room temperature in acetic anhydride–pyridine and crystallization from ether–petroleum ether gave a product with m.p. 124.5–125°; $[\alpha]_D$ +47° ± 1°.

Anal. Calcd. for $C_{28}H_{42}O_8$: C, 66.38; H, 8.36; 2 CH_3CO, 17.00. Found: C, 66.24; H, 8.34; CH_3CO, 17.88.

Methyl 3α,20α-Dihydroxy-11-oxo-5β-pregnan-21-oate (IIIa). Fractions 210–280.—Rosettes (580 mg.) were obtained from acetone–petroleum ether. Recrystallization from methyl ethyl ketone gave 436 mg. (11.5%, m.p. 175–178°) of pure IIIa. The sample for analysis was recrystallized from acetone–ether; m.p. 177.5–178°; $[\alpha]_D$ +39° ± 1°.

(21) We are indebted to R. M. Dodson who, in view of these findings, emphasized the chance of being in error when using molecular rotations to assign configurations to the 17-deoxy-20-acetoxy-5β-pregnan-21-oic compounds described in this paper.

(22) V. R. Mattox, unpublished data.

(23) R. Neher, "Chromatographie von Sterinen, Steroiden und Verwandten Verbindungen," Elsevier Publishing Co., New York, N. Y., 1958, 100 pp.

Anal. Calcd. for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.89; H, 9.05.

Saponification of the mother liquor with aqueous methanolic sodium hydroxide followed by acetylation of the acidic fraction gave an additional 5.8% (260 mg., m.p. 259–261°) of the 20α-epimer as **3α,20α-diacetoxy-11-oxo-5β-pregnan-21-oic acid (VIIIa)** and brought the total yield of 20α-epimer from I to 17.3%.

Methyl 3α,20β-Dihydroxy-11-oxo-5β-pregnan-21-oate (IIIb). Fractions 284–344.—Crystallization from acetone gave 170 mg. (4.5%, m.p. 198–200°) of 20β-epimer IIIb. The total yield of IIIb, obtained by direct crystallization and after chromatography, was 35.5%. Recrystallization from acetone gave the analytical sample; m.p. 202.5–204°; $[\alpha]_D$ +25° ± 2°.

Anal. Calcd. for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05; CH_3O, 8.20; mol. wt., 378. Found: C, 70.12, 70.21; H, 8.59, 9.10; CH_3O, 8.17; mol. wt., 373.

3α,20α- (and 20β)-Diacetoxy-11-oxo-5β-pregnan-21-oic Acids (VIIIa and VIIIb) from II and Sodium Hydroxide.—To 3.64 g. (10 mmoles) of 3α,21,21-trihydroxy-5β-pregnane-11,20-dione[5] (hydrate of II) suspended in 100 ml. of water was added slowly, while stirring vigorously, 20 ml. of 2 *N* sodium hydroxide. After being stirred for 8 hr. at room temperature, the mixture was acidified with *N* hydrochloric acid and extracted three times with 20-ml. portions of ethyl acetate. The ethyl acetate extract was washed four times with a total volume of 60 ml. of 5% sodium bicarbonate. The combined alkaline washes were extracted with ethyl acetate which, along with the original organic phase, was discarded. Acidification of the aqueous phase and extraction with ethyl acetate gave 3.75 g. of crude acidic material. This product was acetylated with 5 ml. each of pyridine and acetic anhydride for 11 hr. at room temperature. The acetylated product, recovered in the usual fashion except for omission of the bicarbonate wash, was subjected to fractional crystallization and gave 1.91 g. (42.6%, m.p. 260–262°) of pure **3α,20α-diacetoxy-11-oxo-5β-pregnan-21-oic acid (VIIIa)** from ethyl acetate. The analytical sample was prepared by recrystallization from acetone; m.p. 261.5–262°; $[\alpha]_D$ +78° ± 1°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.77; H, 8.04.

The addition of petroleum ether to the mother liquor from VIIIa gave 1.76 g. (39.3%, m.p. 189–192°) of impure **3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oic acid (VIIIb)**. This fraction, after recrystallization from acetone, saponification with aqueous methanolic alkali, and esterification with diazomethane, afforded 822 mg. (21.8% over-all from II, m.p. 202–203.5°) of pure **methyl 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oate (IIIb)**. This product did not depress the melting point of IIIb which was prepared from I by treatment with cupric acetate.

A sample of pure **3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oic acid (VIIIb)** was obtained by acetylation of the 3α,20β-dihydroxy acid (VIIb) with acetic anhydride and pyridine for 3 hr. at room temperature. From 250 mg. of VIIb were obtained three crops of crystals (185 mg., m.p. 197–199°; 84 mg., m.p. 195.5–197°; and 8 mg., m.p. 194–195.5°) from acetone in a yield of 90%. A sample for analysis was prepared by recrystallization from acetone and drying for 2 hr. at 100° and 5–10 μ; m.p. 199–200°; $[\alpha]_D$ +41° ± 1°.

Anal. Calcd. for $C_{25}H_{36}O_7 \cdot {}^1/_2H_2O$: C, 65.62; H, 8.18. Found: C, 65.66, 65.73; H, 8.11, 8.19.

3α,20β-Dihydroxy-11-oxo-5β-pregnan-21-oic Acid (VIIb) from IIIb.—To a solution of 400 mg. of methyl 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oate (IIIb) in 3 ml. of methanol was added 12 ml. of water, then 4 ml. of 2 *N* sodium hydroxide. The milky suspension became clear in about 1 min. After 15 min. at room temperature, the solution was acidified with dilute hydrochloric acid. The product was extracted with ethyl acetate and crystallized from acetone–ether in a yield of 87% (300 mg., m.p. 244–245°; and 37 mg., m.p. 243–245°). Recrystallization from acetone–ether did not elevate the melting point; $[\alpha]_D$ +25° ± 2°.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.19; H, 8.85. Found: C, 69.28; H, 9.17.

Treatment of acid VIIb with diazomethane gave an ester which melted at 202.5–203.5°; it did not depress the melting point of IIIb that was obtained from II by treatment with cupric acetate.

3α,20α-Dihydroxy-11-oxo-5β-pregnan-21-oic Acid (VIIa) from VIIIa.—To a solution of 1260 mg. (2.8 mmoles) of 3α,20α-diacetoxy-11-oxo-5β-pregnan-21-oic acid in 45 ml. of methanol was added 100 ml. of water and 16.2 ml. of 1.72 *N* sodium hydroxide (28 mmoles). The solution was heated on a steam bath for 1.5 hr., cooled, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water, dried, and concentrated to dryness. Crystals were obtained from acetone (813 mg., m.p. 237–238°; and 75 mg., m.p. 231–232°) in 87% yield. A sample for analysis was crystallized from acetone; m.p. 239–241°, $[\alpha]_D$ +50° ± 1°.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.19; H, 8.85. Found: C, 69.07; H, 8.71.

3α,20α-Dihydroxy-11-oxo-5β-pregnan-21-oic Acid (VIIa) from IIIa.—Treatment of 100 mg. of methyl 3α,20α-dihydroxy-11-oxo-5β-pregnan-21-oate under the conditions described for preparation of VIIb from IIIb gave 82 mg. (m.p. 237–237.5°) of VIIa; it did not depress the melting point of VIIa that was obtained by hydrolysis of VIIIa. The infrared spectra of the two samples of VIIa were identical.

Treatment of acid VIIa with diazomethane gave an ester, m.p. 175–177°; it did not depress the melting point of IIIa that was obtained by the action of cupric acetate on II.

3α-Hydroxy-11-oxo-5β-etianic Acid (V) from VIIa and VIIb.—To separate solutions of 46 mg. each of 3α,20α-dihydroxy-11-oxo-5β-pregnan-21-oic acid and 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oic acid in 3 ml. of glacial acetic acid was added 40 mg. of potassium permanganate in 3 ml. of water. A precipitate of manganese dioxide formed rapidly. After 1 hr. at room temperature, excess oxidizing agent was decolorized with sodium bisulfite solution and the mixtures were extracted with ethyl acetate. The extracts were washed with water and concentrated to dryness. Crystallization from acetone gave 25 mg. (60%, m.p. 290–292°) of needles from each extract. The infrared spectra of the acids were identical with that of authentic 3α-hydroxy-11-oxo-5β-etianic acid[24] (V) prepared by periodate oxidation of 3α,21-dihydroxy-5β-pregnane-11,20-dione (I).

3α-Hydroxy-20β-acetoxy-11-oxo-5β-pregnan-21-oic Acid (IXb) from VIIIb.—To a solution of 921 mg. (2.05 mmoles) of 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oic acid in 15 ml. of methanol was added 50 ml. of water and 4.62 ml. of 1.72 *N* sodium hydroxide (8 mmoles). After 20 min. at room temperature, the solution was acidified with hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried, and taken to dryness. Crystallization from acetone gave three crops (658 mg., 80%) of 20β-acetoxy acid (IXb) which melted in the range 254.5–256.5°. A purified sample melted at 259.5–261°; $[\alpha]_D$ +21° ± 1°.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.99; H, 8.35.

Methyl 3α-Hydroxy-20β-acetoxy-11-oxo-5β-pregnan-21-oate (Xb) from IXb.—Treatment of 100 mg. of 3α-hydroxy-20β-acetoxy-11-oxo-5β-pregnan-21-oic acid (IXb) with diazomethane gave 99 mg. (96%, m.p. 220–222°) of crystals from acetone. Recrystallization from acetone gave the analytical sample; m.p. 224.5–226°; $[\alpha]_D$ +15° ± 1°.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.28; H, 8.96.

20β-Acetoxy-3,11-dioxo-5β-pregnan-21-oic Acid (XIb) from IXb.—To 406 mg. (1.0 mmole) of 3α-hydroxy-20β-acetoxy-11-oxo-5β-pregnan-21-oic acid in 20 ml. of acetic acid was added 1.2 ml. of 1.0 *M* aqueous chromic acid. The solution was heated on a steam bath for 20 min., cooled, and added to 100 ml. of water. The suspension was extracted with ethyl acetate, the organic phase was washed with water, and taken to dryness. Crystallization from acetone gave 337 mg. (83.4%, m.p. 255.5–257°) of 20β-acetoxy-3,11-dioxo acid (XIb). The product gave a positive test for a carbonyl group with Brady's reagent and depressed the melting point of starting material by more than 100°. A sample of XIb, recrystallized from acetone and dried in air, lost 13.0% after further drying at 100° and 1–2 mm.; calcd. for loss of one mole of acetone, 12.6%; m.p. 256–257°; $[\alpha]_D$ +23° ± 1°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.42; H, 8.27.

3α-Hydroxy-20α-acetoxy-11-oxo-5β-pregnan-21-oic Acid (IXa) from VIIIa.—To a solution of 1.34 g. (3.0 mmoles) of 3α, 20α diacetoxy-11-oxo-5β-pregnan-21-oic acid in 45 ml. of methanol was added 100 ml. of water and 3.64 ml. of 1.72 *N* sodium hydroxide (6.25 mmoles). After 1.5 hr., the solution was acidified with hydrochloric acid and extracted with ethyl acetate. The

(24) J. Von Euw, A. Lardon, and T. Reichstein, *Helv. Chim. Acta*, **27**, 1287 (1944).

extract was washed with water, dried, and taken to dryness. Crystallization from acetone gave 963 mg. (79%, m.p. 261.5–263°) of IXa. A sample, purified from the same solvent, melted at 263.5–265°; $[\alpha]_D$ +61° ± 1°.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.73; H, 8.37.

Methyl 3α-Hydroxy-20α-acetoxy-11-oxo-5β-pregnan-21-oate (Xa) from IXa.—Treatment of 150 mg. of 3α-hydroxy-20α-acetoxy-11-oxo-5β-pregnan-21-oic acid with diazomethane gave 133 mg. (86%, m.p. 178–180°) of methyl ester Xa, which, after recrystallization from acetone–ether, had m.p. 179.5–181.5°; $[\alpha]_D$ +61° ± 1°.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.35; H, 8.58.

20α-Acetoxy-3,11-dioxo-5β-pregnan-21-oic Acid (XIa) from Xa.—To a solution of 406 mg. (1.0 mmole) of 3α-hydroxy-20α-acetoxy-11-oxo-5β-pregnan-21-oic acid in 20 ml. of glacial acetic acid was added 1.2 ml. of 1.0 *M* aqueous chromic acid. After being heated on a steam bath for 20 min., the mixture was added to 125 ml. of water and extracted with methylene chloride. The extract was washed repeatedly with 5% sodium bicarbonate, then discarded. The combined alkaline washes were acidified with hydrochloric acid and extracted with methylene chloride. The methylene chloride extract was washed with water and evaporated. The residue gave 267 mg. (66%, m.p. 122–124°) of the dioxo acid (XIa) from aqueous methanol. It gave a positive test with Brady's reagent. A sample was recrystallized from 95% ethanol and dried for 1 hr. at 100° and 1–2 mm. It exhibited dual melting points at 120–122° and 198–200°; $[\alpha]_D$ +62° ± 1° (not corrected for solvent of crystallization).

Anal. Calcd. for $C_{23}H_{32}O_6 \cdot C_2H_5OH$: C, 66.64; H, 8.53. Found: C, 66.16, 67.04; H, 8.18, 8.71.

When a portion of the sample was dried for 2 hr. at 121° and 10–20 μ, it lost 9.60%; calcd. for loss of 1 mole of ethanol, 10.22%. This sample melted at 198–200° without previous softening.

Methyl 3,11,20-Trioxo-5β-pregnan-21-oate (VI) from IIIa.—To 113 mg. (0.25 mmole) of methyl 3α, 20α-dihydroxy-11-oxo-5β-pregnan-21-oate in 2.85 ml. of glacial acetic acid was added 0.16 ml. of aqueous 5 *M* chromic acid. The solution was heated on the steam bath for 20 min., cooled, diluted with water, and extracted with methylene chloride. The extract was washed with 5% sodium bicarbonate and then water, dried, and taken to dryness. Crystallization from methanol gave the trioxo ester (VI) in two crops (52 mg., m.p. 164.5–166.5°; and 5 mg., m.p. 162–164°). A sample, recrystallized from methanol, melted at 167.5–170.5°; $[\alpha]_D$ +119° ± 2°.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07; CH_3O, 8.29. Found: C, 70.04; H, 8.24; CH_3O, 8.53.

Methyl 3,11-20-Trioxo-5β-pregnan-21-oate (VI) from IIIb.—A solution of 378 mg. (1.0 mmole) of methyl 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oate in 9.5 ml. of glacial acetic acid and 0.50 ml. of aqueous 5 *M* chromic acid was heated on a steam bath for 90 min. and worked up as described in the previous paragraph. The product (170 mg., m.p. 163–165°; and 31 mg., m.p. 159–161°) did not depress the melting point of VI obtained from IIIa. Their infrared spectra in Nujol were identical and contained no band for an OH group.

Methyl 3α,20α-Diacetoxy-11-oxo-5β-pregnan-21-oate (IVa) from IIIa.—Treatment of methyl 3α,20α-dihydroxy-11-oxo-5β-pregnan-21-oate with acetic anhydride and pyridine gave the diacetoxy ester (IVa) as needles from ether; m.p. 194–194.5°; $[\alpha]_D$ +76° ±2°.

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.50; H, 8.28. Found: C, 67.35; H, 8.19.

Methyl 3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-oate (IVb) from IIIb.—Acetylation of methyl 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oate with acetic anhydride–pyridine and crystallization from ether gave the diacetoxy ester (IVb) as long needles; m.p. 204–205°; $[\alpha]_D$ +33° ± 1°.

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.50; H, 8.28; CH_3CO, 18.59. Found: C, 67.97; H, 8.09;. CH_3CO, 18.59.

Methyl 3α,20α-Diacetoxy-11-oxo-5β-pregnan-21-oate (IVa) from VIIIa.—Treatment of 3α,20α-diacetoxy-11-oxo-5β-pregnan-21-oic acid (derived from glyoxal II through treatment with alkali and acetylation) with diazomethane gave a product with an infrared spectrum identical with that from IVa (derived from glyoxal II through treatment with copper acetate followed by acetylation).

Methyl 3α,11β,20α(and 20β)-Trihydroxy-5β-pregnan-21-oate (XIVa and XIVb) and Two Unknown Compounds from XII and Methanolic Cupric Acetate.—To a solution of 1.75 g. (5 mmoles) of 3α, 11β,21-trihydroxy-5β-pregnan-20-one in 125 ml. of methanol was added 500 mg. (2.5 mmoles) of cupric acetate in an equal volume of methanol (glyoxal XIII is formed *in situ* in less than an hour). After 113 hr. at room temperature, 9.7% of the original glyoxal was present. One gram of EDTA in 25 ml. of water was added and the methanol was evaporated *in vacuo*. The aqueous residue was extracted with methylene chloride and the organic phase, after being washed with water, was concentrated to dryness. After removal of the residual glyoxal in the manner described under the preparation of III from II, there was obtained 590 mg. (m.p. 170–180°) of needles from acetone. Recrystallization from acetone gave 528 mg. (27.8%, m.p. 185–188°) of **methyl 3α,11β,20β-trihydroxy-5β-pregnan-21-oate (XIVb).**

The residue from the acetone mother liquors was chromatographed on a 4.6-cm. diameter column packed to a height of 38 cm. with 200 g. of Celite plus 80 ml. of formamide. The solvent system was benzene (2000), formamide (100). Prior to collection of fraction no. 1, 450 ml. of effluent was discarded. Each fraction contained 15 ml. Appropriate fractions were combined after the weight of the residues had been determined and an elution diagram had been made.

Two compounds of unknown structure, X_4 and X_5, emerged before the trihydroxy esters.

Compound X_4. Fractions 8–20.—Crystallized from acetone–petroleum ether as needles (165 mg., m.p. 147–148.5°).

Compound X_5. Fractions 32–45.—Crystallized from acetone (48 mg., m.p. 233–235°).

Methyl 3α,11β,20β-Trihydroxy-5β-pregnan-21-oate (XIVb). Fractions 85–110.—Crystallization from acetone gave 142 mg. (m.p. 186–188°) of XIVb which, when added to that crystallized before chromatography, brought the yield to 670 mg. (35.5%). The analytical sample melted at 189–189.5°; $[\alpha]_D$ +27° ± 2°.

Anal. Calcd. for $C_{22}H_{36}O_5$: C, 69.43; H, 9.53. Found: C, 69.24, 69.19; H, 9.19, 9.02.

Methyl 3α,11β,20α-Trihydroxy-5β-pregnan-21-oate (XIVa). Fractions 121–165.—The residue from these fractions weighed 489 mg. (25.7%) and was homogeneous by chromatography. Initial attempts to crystallize the trihydroxy ester were unsuccessful. After approximately 4 months the compound, which was stored as a glass, crystallized spontaneously. In the meantime one-half of the residue had been removed for further treatment. Crystallization of the remaining half from ether gave prisms (170 mg., m.p. 163–164°; and 14 mg., 160.5–162°) which, after recrystallization from ether, had m.p. 161–163°; $[\alpha]_D$ +52° ± 2°.

Anal. Calcd. for $C_{22}H_{36}O_5$: C, 69.43; H, 9.53. Found: C, 69.29, 69.35; H, 9.28, 9.17.

Methyl 3α,20β-Diacetoxy-11β-hydroxy-5β-pregnan-20-oate (XVb) from XIVb.—To 380 mg. (1.0 mmole) of methyl 3α,11β, 20β-trihydroxy-5β-pregnan-21-oate was added 1.0 ml. each of pyridine and acetic anhydride. After 11 hr. at room temperature, the product was recovered and crystallized from ether [390 mg. (84%), m.p. 174–176°]. Several recrystallizations from ether–petroleum ether raised the m.p. to 176.5–177.5°; $[\alpha]_D$ +35° ± 1°.

Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 66.81; H, 8.63.

Methyl 3α,20α-Diacetoxy-11β-hydroxy-5β-pregnan-21-oate (XVa) from XIVa.—Acetylation of 245 mg. of amorphous methyl 3α,11β,20α-triacetoxy-5β-pregnan-21-oate (from fractions 121–165) under the conditions used for acetylation of the corresponding 20β-epimer (XIVb) gave 252 mg. (84%, m.p. 142–145°) of XVa. A sample recrystallized from ether–petroleum ether melted at 143.5–144°; $[\alpha]_D$ +79° ± 2°.

Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 66.83; H, 8.59.

Methyl 3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-oate (IVb) from XVb.—To 92.8 mg. (0.20 mmole) of methyl 3α, 20β-diacetoxy-11β-hydroxy-5β-pregnan-21-oate in 4.76 ml. of glacial acetic acid was added 0.24 ml. of aqueous 1.0 *M* chromic acid. The solution was heated on a steam bath for 15 min. and the product was recovered and crystallized from ether (83 mg., m.p. 203–204°). This product did not depress the melting point of

IVb which had been prepared from IIIb. The infrared spectra of the two samples of IVb were identical.

Methyl 3α,20α-Diacetoxy-11-oxo-5β-pregnan-21-oate (IVa) from XVa.—Treatment of 92.8 mg. (0.20 mmole) of methyl 3α,20α-diacetoxy-11β-hydroxy-5β-pregnan-21-oate with chromic acid as described in the previous paragraph (except that the reaction period was 45 min.) gave 64 mg. (m.p. 194–195°) of product. Its infrared spectrum was identical with that of IVa which had been prepared from IIIa.

Acknowledgment.—We wish to acknowledge several helpful suggestions from Dr. H. L. Mason during the course of this investigation.

The Muconomycins. I. Studies on the Structure of Muconomycin A, a New Biologically Active Compound[1]

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The chemistry of Muconomycin A has been investigated. This compound can be reduced catalytically to what appears to be a hexahydro derivative and may be acetylated to a diacetate. Basic hydrolysis yields three products. The structure of two of these is discussed.

During a search for new fungicides from natural sources, a crystalline compound was isolated from the cultures of the mold *Myrothecium verrucaria*.[2] This substance, which has been designated as Muconomycin A, proved to be quite interesting because of its high antifungal activity, its extreme toxicity (0.5–0.75 mg./kg.) to albino mice,[3] and the fact that it possesses allergic properties which result in skin irritation on contact. Recent studies by Guarino showed that some of the toxic properties are manifested by severe creatinurea in vitamin E deficient albino rats, a fact which is indicative of a possible interference with oxidative phosphorylation.[3]

This paper describes some studies on the chemistry of this biologically active compound.

Muconomycin A (I), when purified either by repeated recrystallization from acetone–water or by chromatography on alumina, yielded clear, colorless plates which turned yellow at 240° and slowly decomposed over a wide temperature range. An infrared spectrum of the antibiotic shows a main carbonyl peak at 1725 cm.$^{-1}$ with shoulders at 1710 and 1740 cm.$^{-1}$, a hydroxyl peak at 3557 cm.$^{-1}$, and double bond bands at 1637 and 1591 cm.$^{-1}$. The antibiotic is characterized by a single peak in the ultraviolet spectrum at 258.5 mμ (ε 21,200). A molecular weight determination by boiling point elevation in acetone showed the molecular weight to be 496 ± 15. A formula of $C_{27}H_{34}O_9$ (mol. wt., 502.5) was assigned based on this molecular weight and its elemental analysis. A methyl determination was found to be 8.34% methyl, which corresponds to at least three methyl groups for a compound with a molecular weight of 502.5. The molecule contains one active hydrogen and no methoxyl or ethoxyl groups. No derivative could be obtained with carbonyl reagents; thus it was concluded that the main carbonyl peak of I is that of an ester group, a conclusion which was supported by titration with base. The saponification equivalent of Muconomycin A was found to be 168 as compared with an expected value of 167 based on three ester groups.

When I was hydrogenated over Adam's catalyst, a compound was isolated which recrystallized from ether as colorless crystalline clusters, m.p. 145–146.5°. Elemental analysis suggested that the reduced material is most likely a hexahydro derivative, though the possibility that it is a tetrahydro derivative could not be eliminated on the basis of this analysis alone. In one experiment in which I was reduced with hydrogen at atmospheric pressure over palladium on charcoal, 2.80 moles of hydrogen were absorbed per mole of I.

An infrared spectrum of the reduced material shows a single carbonyl peak at 1742 cm.$^{-1}$ and no evidence of unsaturation. It was concluded from these observations that I contains at least one double bond in conjugation with an ester carbonyl.

Muconomycin A formed an acetate readily when treated with acetic anhydride and pyridine at steam bath temperatures. It is interesting to note that though I contains only one active hydrogen, it forms a diacetate.

When the antibiotic was subjected to hydrolysis with dilute base, three principal fragments were isolated from the reaction mixture. One of these was a dicarboxylic acid which was identified as one of the geometrical isomers of muconic acid by analysis, the infrared and ultraviolet spectra, and the fact that it consumed two moles of hydrogen on catalytic reduction with the formation of adipic acid. The preparation of the benzhydryl ester showed it to be the *cis–trans* isomer (II) (m.p. 142.5–143° as reported[4]), a conclusion which was confirmed by synthesis by conventional methods.[4,5]

In addition to *cis,trans*-muconic acid, two alcohols were isolated from the hydrolysis reaction of I. These were designated as alcohol A (III) and alcohol C (IV).

Alcohol A crystallized from ether in the form of flat needles, m.p. 156–157°. The infrared spectrum shows

(1) The research on elucidation of the structure of Muconomycin A, herein reported, was carried out for the most part at the laboratories of the Rohm and Haas Company, Bristol, Pa. Further characterization of the physical properties of degradation products and derivatives of Muconomycin A was carried out at the University of Rhode Island, supported in part by P.H.S. research grant E-4352 from the National Institutes of Health, Public Health Service.

(2) Patent application allowed, Smythe-Kraskin, assigned to the Rohm and Haas Co. The organism has been deposited with the American Type Culture Collection, Washington, D. C., and has been assigned the number ATCC 13667.

(3) A. Guarino, Chemistry Department, University of Rhode Island, unpublished data. This value is in confirmation of the LD_{50} previously determined under Rohn and Haas sponsorship.

(4) J. A. Elvidge, R. P. Linstead, P. Sims, and B. A. Orkin, *J. Chem. Soc.*, 2235 (1950).

(5) J. Pospisbil and V. Ettel, *Chem. Prumysl*, **7**, 244 (1957).

hydroxyl bands at 3550 and 3300 cm.$^{-1}$, a weak double bond band at 1690 cm.$^{-1}$, and a band at 1381 cm.$^{-1}$ assignable to the vibrations of a C–CH_3 group. No significant ultraviolet absorption was noted in the range 220–350 mμ. A molecular formula of $C_{15}H_{22}O_4$ was assigned based on its elemental analysis and molecular weight determination. The molecule contains two active hydrogens and three or four methyl groups as determined by analysis.

Alcohol A when treated with acetic anhydride and pyridine formed an acetate, m.p. 147–148°. Assuming a molecular weight of about 270 for the alcohol, a molecular formula of $C_{19}H_{26}O_6$ was calculated for the acetate based on its elemental analysis. The per cent acetate calculated as CH_3CO– was found to be 24.20 which is in good agreement with the expected value of 24.56% for a diacetate. The infrared spectrum of the acetate showed no hydroxyl bands and led to the conclusion that the remaining oxygen atoms are in the form of ethers.

Alcohol C is soluble in water and most organic solvents. It crystallizes from ether in the form of long needles, though an analytical sample is best prepared by sublimation, m.p. 102.5–103°. In the alkaline hydrolysis of Muconomycin A, IV is isolated by extraction with chloroform only after the reaction mixture has been made strongly acidic, a fact which indicates the presence of a lactone ring. The most prominent features of the infrared spectrum of alcohol C are strong bands at 3350 cm.$^{-1}$ (potassium bromide) or 3460 cm.$^{-1}$ (bromoform) (hydroxyl band) and at 1730 cm.$^{-1}$ (potassium bromide or bromoform) (ester). Only end absorption was observed in the ultraviolet spectrum.

No carbonyl derivative was obtained with either *p*-nitrophenylhydrazine or semicarbazide hydrochloride, and ammoniacal silver was not reduced in the Tollens test.

The titration curve of IV is similar to that reported[6] for mevalonic acid lactone and indicates an equivalent weight of 128 which was used with the elemental analysis to calculate a formula of $C_6H_{10}O_3$. Following the titration, the starting material was isolated unchanged providing further evidence that the alcohol and carboxyl groups are present in the same molecule. The infrared spectrum of alcohol C in morpholine was taken at intervals over a period of two hours and changes in the carbonyl region noted. During this time the band at 1742 cm.$^{-1}$ (lactone) disappeared and a new band simultaneously formed at 1640 cm.$^{-1}$ (tertiary amide) and became intensified. These observations clearly indicate the presence of a lactone ring system. A δ-lactone rather than a γ-lactone is more consistent with the infrared spectrum.

A similar morpholinolysis experiment has been described for the isomeric mevalonic acid lactone, and it was reported that at least forty-eight hours was required to open this lactone ring.[7] We found that approximately the same length of time was necessary for the morpholinolysis of δ-valerolactone.

In an attempt to prepare a solid derivative, IV was treated with various amines. A crystalline amide, however, was obtained only with benzhydrylamine.

(6) D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright, and K. F. Folkers, *J. Am. Chem. Soc.*, **79**, 1486 (1957).

(7) D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright, and K. Folkers, *ibid.*, **78**, 4499 (1956).

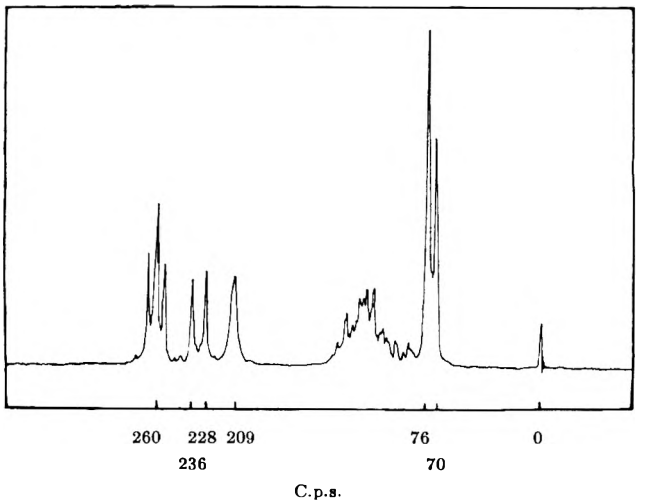
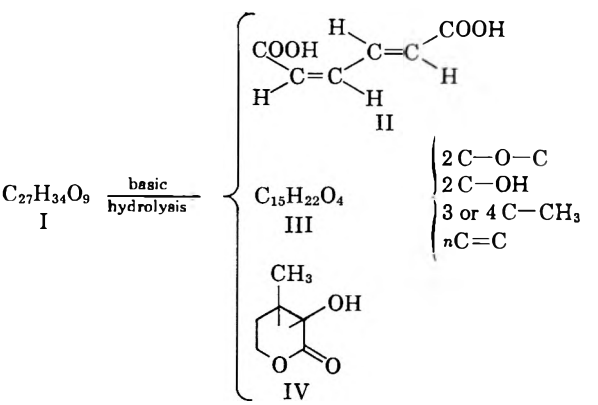


Fig. 1.—Nuclear magnetic resonance spectrum of alcohol C at 60 Mc. with tetramethylsilane as internal standard.

Methyl analysis of IV was indicative of the presence of at least one methyl group. The position of the methyl and hydroxyl groups on the δ-lactone ring of alcohol C remained to be determined. IV gave a negative iodoform reaction and hence the methyl group would not be expected to be in the δ-position. The periodate reaction was inconclusive.

Based on the reactivity of the carbonyl group of alcohol C, the hydroxyl group was tentatively assigned to the α-position. The final assignment for the positions of the methyl and hydroxyl groups was based on the nuclear magnetic resonance (n.m.r.) spectrum of the compound.



The 60-Mc. n.m.r. spectrum of IV (Fig. 1) shows signals from the methyl group at 76 and 70 c.p.s. relative to tetramethylsilane as internal standard. The doublet signal is produced by spin coupling of the methyl group with a single proton on the adjacent carbon atom and confirms the presence of the grouping CH_3–CH in the molecule. Since the methyl and hydroxyl groups must be on different carbon atoms there would be statistically twelve different position isomers of hydroxymethyl-δ-valerolactone. An examination of the expected low field pattern for each isomer reveals that the pattern for β-methyl-α-hydroxy-δ-valerolactone seems to fit the spectrum of IV the best. The signal at 209 c.p.s. is from the hydroxyl group. The doublet signal at 228 and 236 c.p.s. is from the proton on the α-carbon containing the hydroxyl group and is split into bands by spin coupling with the single proton on the β-carbon atom. The triplet signal cen-

tered around 260 c.p.s. is from the $-CH_2-$ group in the δ-position α to the ring oxygen. The remaining three protons are found in the multiplet between 209 and 76 c.p.s. A 40-Mc. spectrum taken before and after adding benzenesulfonic acid to the solution facilitated the location of the hydroxyl proton band and showed that this proton exchanges sufficiently fast so that it does not spin couple with any neighboring protons. Furthermore, the triplet–doublet pattern assumed for the α-hydroxyl-β-methyl-δ-valerolactone structure was confirmed by comparison of the coupling constants from the 40- and 60-Mc. spectra.

In an early experiment in which Muconomycin A was subjected to basic hydrolysis with 20% sodium hydroxide in aqueous ethanol, two compounds were isolated. One of these was *cis,trans*-muconic acid. The other was a white, crystalline solid melting at 151–151.5° and was designated as alcohol B. Infrared analysis indicates the presence of a primary alcohol and a *gem*-dimethyl group. No carbonyl bands are present in the spectrum. Alcohol B was obtained from only one reaction and attempts to isolate this compound from subsequent reaction mixtures were not successful.

Further efforts are being made to elucidate the structure of Muconomycin A and other closely related compounds and additional reports are forthcoming.

Experimental[8-10]

Muconomycin A.[11]—Muconomycin A was obtained as a semipure crystalline solid which was purified further by chromatography on alumina. Recrystallization from acetone–water yielded small colorless plates which decomposed slowly over a wide range above 240° with $[\alpha]^{19}D$ +184°, λ_{max} 258.5 mμ (ε 21,200).

The infrared spectrum of the antibiotic shows a main carbonyl peak at 1725 cm.$^{-1}$ with shoulders at 1710 and 1740 cm.$^{-1}$, a hydroxyl peak at 3557 cm.$^{-1}$, and double bond absorption at 1637 and 1591 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{34}O_9$: C, 64.53; H, 6.82; O, 28.65. Found: C, 64.40; H, 6.77; O, 28.79.

Reduction of Muconomycin A.—A solution of 993.9 mg. (1.98×10^{-3} mole) of Muconomycin A in 150 ml. of absolute ethanol was placed in a hydrogenation flask. A small quantity of Adam's catalyst was added and the mixture reduced in a Parr apparatus at room temperature and 35-lb. pressure. The reduction was stopped at the end of 1 hr. The catalyst was removed by filtration and the solvent by evaporation at reduced pressure at about 45°. A colorless amorphous solid remained as residue. The residue was taken up in acetone and induced to crystallize by the addition of water. Small plates were obtained, yield 420.1 mg., m.p. 106–108.5°. After many recrystallizations from acetone–water the melting point was not improved. The solid was then recrystallized from ether. Crystalline clusters were obtained which after two further recrystallizations melted at 145–146.5°, $[\alpha]^{18}D$ +19°, wt., 100 mg.

Anal. Calcd. for $C_{27}H_{40}O_9$: C, 63.76; H, 7.93. Found: C, 63.80; H, 7.76.

In one experiment in which I was reduced quantitatively with hydrogen over palladium on charcoal at atmospheric pressure, 2.80 moles of hydrogen were absorbed per mole of I.

The infrared spectrum of this reduced material shows a single carbonyl peak at 1742 cm.$^{-1}$. No double bond bands appear in the 1600-cm.$^{-1}$ region. Only end absorption appeared in the ultraviolet spectrum.

Acetylation of Muconomycin A.—Muconomycin A (243.7 mg., 4.85×10^{-4} mole) was placed in a 50-ml. round-bottomed flask with 7 ml. of anhydrous pyridine and 5.0 ml. of acetic anhydride. The solution was heated on a steam bath for 15 min. and then evaporated at reduced pressure at about 50°. The viscous oil that remained as residue was taken up in chloroform and the solution washed with dilute (3 *N*) sulfuric acid and then with water. The chloroform layer was separated and dried over anhydrous magnesium sulfate. After removal of the drying agent and solvent, a colorless amorphous solid remained as residue. This material was purified by chromatography on alumina followed by recrystallization from ethanol–water. The acetate was obtained in low yield as small needles which decomposed slowly on heating above 230°.

Acetate analysis showed 13.78% acetate to be present indicating that a diacetate had formed (calculated for two acetates, 14.67%).

Anal. Calcd. for $C_{31}H_{38}O_{11}$: C, 63.47; H, 6.53; mol. wt., 586.6. Found: C, 63.24; H, 6.68; mol. wt., 593, 581.

The infrared spectrum of Muconomycin A diacetate had carbonyl peaks at 1752 cm.$^{-1}$ due to the acetate and at 1726 cm.$^{-1}$ assignable to a conjugated ester.

Infrared and elemental analysis of other fractions from the chromatogram indicated that other acetates were formed in the reaction, though as yet none of these have been obtained in pure form.

Hydrolysis of Muconomycin A with Sodium Hydroxide.—Muconomycin A (959.9 mg., 1.91×10^{-3} moles) was placed in a 100-ml. flask with 15 ml. of 3% aqueous sodium hydroxide and 3 ml. of ethanol. A reflux condenser was attached and the mixture heated on a steam bath gently for 30 min. The reaction mixture was then cooled to room temperature and was extracted thoroughly with chloroform. The combined extracts were dried over anhydrous magnesium sulfate and the drying agent and solvent removed as usual. A colorless, clear amorphous solid remained as residue which crystallized immediately on standing at room temperature. The residue was dissolved in chloroform and recrystallized from ether–chloroform solution, yield 401.2 mg. of flat needles, m.p. 155.5–156°. A highly purified sample melted at 158–158.5°, $[\alpha]^{19}D$ −55°.

The infrared spectrum (potassium bromide) shows hydroxyl bands at 3550 and 3300 cm.$^{-1}$, a weak double bond band at 1690 cm.$^{-1}$, and a band at 1381 cm.$^{-1}$ assignable to the vibrations of a $C-CH_3$ group. No significant absorption appeared in the ultraviolet spectrum.

The molecular weight (Rast) of III was found to be 270 and 280 in two determinations.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.67; H, 8.33; O, 24.03; mol. wt., 266.3. Found: C, 67.38; H, 8.38; O, 23.93.

The basic reaction mixture was made strongly acidic (about pH 2) and extracted with ether several times. The combined extracts were dried over anhydrous magnesium sulfate. After removal of the drying agent and solvent, a powder with a yellow tint remained as residue. The yellow tint was removed by washing with chloroform, yield 184 mg., m.p. 187–188° dec. A highly purified sample was obtained by dissolving the powder in 0.1 *N* sodium hydroxide and reisolating the free acid from the

(8) All melting points are corrected. The infrared spectra were determined in part by Walter Smith and Vincent Pierro of the Rohm and Haas Company, Bristol, Pa. The microanalyses were performed by Clyde Nash, Rohm and Haas Company, Bristol, Pa., Clark Microanalytical Laboratory, Urbana, Ill., Pascher and Pascher Microanalytical Laboratory, Bonn, Germany, and Micro-analysis, Inc., Wilmington, Del. The molecular weight of Muconomycin A was determined by Harry Mason, Rohm and Haas Co., Philadelphia, Pa.

(9) The infrared spectra were obtained on either a Perkin-Elmer Model 21 spectrophotometer or on a Baird-Atomic Model KM-1 recording spectrophotometer and were taken in carbon tetrachloride unless otherwise indicated; the ultraviolet spectra were obtained on a Beckman DK-2 recording spectrophotometer. Rotations were taken on a Rudolph Precision polarimeter.

(10) All rotations and ultraviolet spectra were taken in methanol solution.

(11) The following procedure for obtaining Muconomycin A was described in a personal communication from C. Smythe, Rohm and Haas Co., Bristol, Pa. The organism was grown in a medium containing 1.0% glucose, 0.5% rolled oats, 0.1% Bacto-peptone, 0.1% Difco yeast extract, 0.05% K_2HPO_4, and 0.02% $MgSO_4 \cdot 7H_2O$. The medium was adjusted to pH 7.0 with sodium hydroxide, dispensed in 100-ml. portions into 1-l. wide-mouthed erlenmeyer flasks and sterilized at 15 p.s.i. for 30 min. After inoculation with 1.0% of aqueous spore suspension derived from a well sporulated potato–dextrose–agar slant of ATCC 13667, incubation was carried out on a shaker rotating at 260 r.p.m. at 26° for 72 hr. The concentration of Muconomycin was about 100 μg./ml.

The mycelia was then removed by filtration with the aid of diatomaceous earth and the filtrate treated with about 0.3% of Darco G60. The Darco adsorbate was collected on a filter, dried in air, and the activity eluted with benzene in a Soxhlet extractor. After evaporation of the benzene, a yellow oil remained which was taken up in acetone and induced to crystallize by the addition of water.

acidified solution. In this way a sample melting at 190.5–191°, λ_{max} 259 (ϵ 24,600) was obtained.

The neutralization equivalent was found to be 72.5 as determined by titration with 0.1 *N* sodium hydroxide. Assuming two equivalents to be present in the molecule, a molecular formula of $C_6H_6O_4$ was calculated on the basis of its elemental analysis.

Anal. Calcd. for $C_6H_6O_4$: C, 50.71; H, 4.26. Found: C, 50.59; H, 4.35.

The infrared spectrum (potassium bromide) of this material shows broad absorption in the 3000-cm.$^{-1}$ region, a carbonyl band at 1680 cm.$^{-1}$, double bond bands at 1625 and 1600 cm.$^{-1}$, and is superimposable on a spectrum of a synthetic sample of *cis,-trans*-muconic acid.

The acidified reaction mixture was then extracted many times with chloroform until no more material could be removed. The extracts were combined and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent by distillation at reduced pressure. A colorless, clear oil remained which crystallized immediately on standing at room temperature. This residue was purified by sublimation at 65° at 15-mm. pressure, yield 98.8 mg., m.p. 98–101°. A highly purified sample melts at 102.5–103°, $[\alpha]^{18}D$ −17.2°.

The infrared spectrum of this material shows strong bands at 3350 cm.$^{-1}$ (potassium bromide) or 3460 cm.$^{-1}$ (bromoform) (hydroxyl band) and at 1730 cm.$^{-1}$ (potassium bromide or bromoform) (ester). No evidence of unsaturation is present in the 1600–1700-cm.$^{-1}$ region of the spectrum.

The equivalent weight of this material was found to be 128 by potentiometric titration.

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75; O, 36.88. Found: C, 55.12; H, 7.78; O, 36.82.

Catalytic Reduction of the Dicarboxylic Acid (II).—The dicarboxylic acid (57.4 mg.) was reduced over palladium on charcoal in ethanol. Two moles of hydrogen were absorbed per mole of acid. The product was a white solid (35.4 mg.) which melted at 152–153° after one recrystallization from ether.

The infrared spectrum of the reduced material is superimposable on that of adipic acid. A mixture melting point determination with an authentic sample of adipic acid showed no depression.

Synthesis of *cis,trans*-Muconic acid.—*cis,cis*-Muconic acid was prepared by a procedure adapted from that of Pospishil and Ettel.[5] Acetic anhydride (50 g.) and glacial acetic acid (51 g.) were placed in a 1-l., four-necked flask fitted with reflux condenser and drying tube, mechanical stirrer, dropping funnel, and thermometer. Then while the temperature was kept at 30°, 40 g. of 90% hydrogen peroxide was added rapidly, and the solution stirred for 10 min. Pyrocatechol (50 g.) was dissolved in acetic anhydride (100 g.) and the resulting solution was added to the reaction mixture dropwise over a period of 60 min. The temperature was maintained at 30° with an ice bath. After 1 hr. 10 ml. of a concentrated solution of manganous acetate and cupric acetate (1:1 ratio) in acetic anhydride was added. Stirring at 30° was continued for another 3 hr. The mixture was stored in the dark for 4 days and the *cis,cis*-muconic acid collected by filtration, yield 24.8 g. of product, m.p. 184–185° (reported[12] m.p. 184°). Recrystallization from methanol did not improve the melting point.

cis, trans-Muconic acid was prepared from *cis,cis*-muconic acid by recrystallization from water. *cis,cis*-Muconic acid (15 mg.) was placed in a small flask with 5 ml. of distilled water. The mixture was heated under reflux on a steam bath for 1 hr. The acid dissolved rapidly on heating. When the reaction mixture was cooled, a white granular solid separated, m.p. 181–182.5° (reported[12,13] m.p. 184 or 190–191°). The infrared spectrum of this material is consistent with that expected for *cis,trans*-muconic acid.

(12) J. A. Elvidge, R. P. Linstead, B. A. Orkin, P. Sims, H. Baer, and D. B. Pattison, *J. Chem. Soc.*, 2228 (1950).

(13) The melting point has been found to vary with the rate of heating.

Benzhydryl Ester of *cis,trans*-Muconic Acid (II).—The benzhydryl ester of the dicarboxylic acid (II) was prepared according to the method described by J. A. Elvidge, *et. al.*[4] Yellow mercuric oxide (2.23 g.) was placed in a vial with 2.19 g. of benzophenone hydrazone and 20 ml. of a 1:1 solution of pentane–hexane added. A wet cloth was placed around the vial and then it was shaken for 6.5 hr. After this time, the mercury and any unchanged benzophenone hydrazone was removed by filtration. To 10 ml. of the filtrate was added a solution of 0.20 g. of *cis,-trans*-muconic acid in 2 ml. of methanol and the mixture was kept in the dark for 65 hr. After this time the solvent was removed by evaporation at reduced pressure and the residue washed with methanol. After one recrystallization from methanol, a white powder was obtained, yield 0.6 g., m.p. 142.5–143.5°. One further recrystallization yielded a white powder melting at 144.5–145° (reported[4] m.p. 143.5°).

Anal. Calcd. for $C_{32}H_{26}O_4$: C, 80.99; H, 5.52. Found: C, 81.02; H, 5.47.

Acetylation of Alcohol A.—In a small one-necked flask was placed 71.5 mg. of Alcohol A. To this was added 4 ml. of anhydrous pyridine and 3 ml. of acetic anhydride and the mixture heated on a steam bath for 10 min. The solution was then cooled to near room temperature and 2 ml. of water added. The solvent then was removed by distillation at reduced pressure. The oil which remained as residue was taken up in chloroform and the solution washed twice with dilute sulfuric acid and twice with water. The organic layer was separated and dried over anhydrous magnesium sulfate. When the drying agent and solvent were removed, an oil remained as residue. The residue was taken up in a benzene–hexane (4:1) solution and the acetate purified by chromatography on alumina. The fractions containing product were combined and dissolved in chloroform. The chloroform was replaced by ethanol from which the product was induced to crystallize by the addition of water. Small prisms were obtained, yield 45 mg., m.p. 145–146°. After one further recrystallization a sample melting at 147–148° was obtained.

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48; mol. wt., 350.4. Found: C, 65.19; H, 7.27; mol. wt., 335 (Rast). The per cent acetate was found to be 24.40.

The infrared spectrum of the acetate contains strong bands at 1749 and 1241 cm.$^{-1}$ attributable to vibrations of the acetate group. No hydroxyl band is evident in the spectrum.

Benzhydryl Amide of Alcohol. C.—Alcohol C (16 mg.) was placed in a vial with 0.5-1 ml. of benzhydrylamine. The vial was stoppered and the solution was heated on a steam bath for 1 hr. The reaction mixture was then dissolved in 10 ml. of chloroform and the resulting solution washed with a 0.1 *N* hydrochloric acid solution and then with water until the washings were nearly neutral to litmus. The chloroform solution was then dried over anhydrous magnesium sulfate and the drying agent and solvent removed as usual. An oil with a yellow tint remained as residue which crystallized on standing at room temperature. The crystalline residue was dissolved in benzene and the product was induced to crystallize by the addition of hexane and cooling. Clusters of crystals formed, yield 20 mg., m.p. 117.5–118°.

Infrared analysis (chloroform) showed the presence of a monosubstituted amide (1510 and 1662 cm.$^{-1}$) and a hydroxyl group (3350 cm.$^{-1}$).

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.96; H, 7.43; N, 4.38. C-Methyl analysis indicated the presence of one methyl group (4.80%).

Acknowledgment.—The author is indebted to Dr. Keith McCallum of the Rohm and Haas Company for his valuable assistance in the interpretation of the nuclear magnetic resonance spectra and to the Rohm and Haas Company for the generous supply of Muconomycin A.

The Constituents of *Ecballium elaterium* L. XVI. Stereochemical Problems in the Cucurbitacins[1,2]

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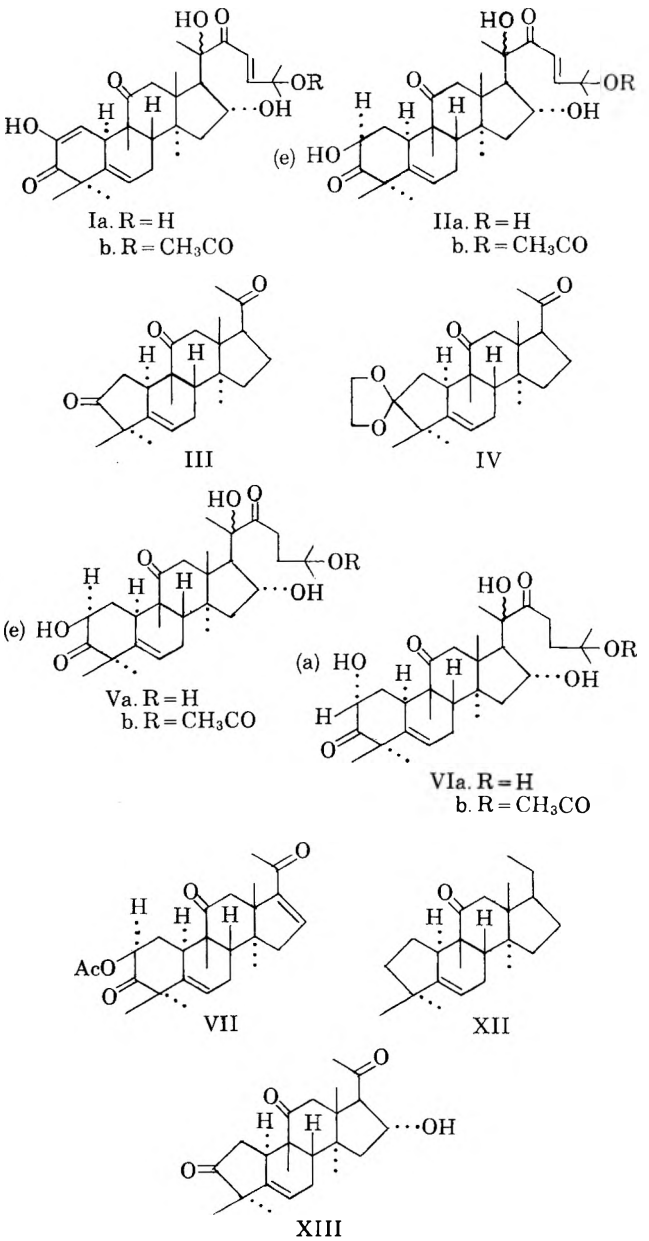
The configuration of the various asymmetric centers of elatericin A and cucurbitacin B as well as the hydrogenated derivatives of elatericin B and elaterin (cucurbitacin E) are presented and discussed.

In the preceding paper[2b] of this series, complete structures were proposed for elatericin B (Ia), elaterin (cucurbitacin E) (Ib), elatericin A (IIa), and cucurbitacin B (IIb). In the present paper experiments are described which contribute toward the elucidation of the stereochemistry of several asymmetric centers in these tetracyclic triterpenes and their derivatives.[4]

In order to determine the stereochemistry at carbon atom 10, the contribution of the ketone group in ring A of compound III[2b] to the optical rotatory dispersion was determined by drawing the difference curve of the two substances III and IV. The latter substance was obtained through the preparation of the bisethylene ketal of the ketone groups at 3 and 20 of compound III by the usual procedure[2b] and the subsequent selective hydrolysis of the C-20 ketal, using a dilute solution of acetic acid during a limited period of time. By substracting the optical rotatory dispersion curve of IV from III, the contribution of the two carbonyl groups at C-11 and C-20 were eliminated and the resultant curve ($[\alpha]_{320}$ −3837°, $[\alpha]_{280}$ +4710°) showed a strong negative Cotton effect whose large amplitude, due to the strain of the five-membered ring bearing the ketone group in ring A, was comparable but opposite in sign to that found in the curve obtained with 4,4-dimethyl-A(2)-nor-cholestenone.[5] Since the latter has a β-substituent at the C-10 position, it was concluded that the corresponding hydrogen in compounds III, IV, and elatericin A, from which they derive, has the α-orientation. The substitution in the latter products of a hydrogen by a methyl group should not influence the sign of the curve. In view of the presence of the methyl group at C-9, this α-orientation could have been anticipated biogenetically in the cucurbitacins. With this observation in mind, the previous stereochemical assignments of the C-2 hydroxyl groups in elatericin A (IIa) and in cucurbitacin B (IIb) should be revised.[6]

In our previous studies we erroneously had assumed a β-oriented methyl group at C-10.[7] The relationship existing between dihydroelatericin A (Va) (double bond of the side chain reduced) and tetrahydroelatericin B (VIa) (double bonds in side chain and ring A reduced) has now to be clarified. These two derivatives have already been reported to differ in physical properties (melting points, optical rotations, and solubilities); they are epimers at C-2.[7]



The conformations of the hydroxyl group at C-2 in the compounds possessing a 1,2-hydroxy ketone were determined using several spectroscopic measurements.

A. In the infrared spectra it was found that dihydroelatericin A (Va) and dihydrocucurbitacin B (Vb)

(1) This investigation was supported by a research grant CY-2810 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) (a) A previous version of this paper which was already in print, June, 1960, was withdrawn from publication in order to avoid misinterpretations in the literature. Various subsequent communications have been published meanwhile; however, for the sake of continuity, we have kept the numbering of the original version; (b) Part XV, D. Lavie, Y. Shvo, O. R. Gottlieb, and E. Glotter, *J. Org. Chem.*, **27**, 4546 (1962).

(3) On leave of absence from the Instituto de Química Agrícola, Ministério da Agricultura, Rio de Janeiro; O. R. G. acknowledges support from the Conselho Nacional de Pesquisas, Brazil.

(4) Presented in part before the 2nd International Symposium on the Chemistry of Natural Products, Prague, 1962; *cf. Bull. Res. Council Israel*, **11A**, 34 (1962).

(5) R. Hanna and G. Ourisson, *Bull. soc. chim. France*, (**5**), 1945 (1961).

(6) D. Lavie, Y. Shvo, and O. R. Gottlieb, *Tetrahedron Letters*, No. **22**, 23 (1960).

(7) D. Lavie and O. R. Gottlieb, *Chem. Ind.* (London), 929 (1960).

as well as elatericin A (IIa) and cucurbitacin B (IIb), have bands at 1125 cm.$^{-1}$, while in tetrahydroelatericin B (VIa) and in tetrahydroelaterin (VIb) that band is at 1100 cm.$^{-1}$. The frequency of the C–OH stretching band for secondary alcohols is at about 990–1065 cm.$^{-1}$, and it has been found to be *higher* for the equatorial hydroxyl than for the axial partner.[8] The effect of a neighboring carbonyl is to displace these bands in both cases to higher frequencies. The hydroxyl group then should be equatorial in substances Va and Vb and axial in VIa and VIb. A careful study of the spectrum of the carbonyl region using a calcium fluoride prism, corroborated these findings. A band at 1712 cm.$^{-1}$ was observed in the two dihydroderivatives (V) as well as in elatericin A (IIa) and cucurbitacin B (IIb). We correlate this band to the increased stretching frequency of the carbonyl at C-3, an increase which is due to the adjacent equatorial hydroxyl at C-2. In the two tetrahydroderivatives (VI) the band was recorded at about 1705 cm.$^{-1}$, it was somewhat lower due to the smaller effect of the vicinal axial hydroxyl. Such a relative lowering effect of an axial hydroxyl on the frequency of the carbonyl has been described previously.[8]

B. The ultraviolet spectra were consistent with these observations,[9] acetylation of the equatorial hydroxyl at C-2 of V shifted the weak carbonyl maximum to longer wave lengths, while acetylation of the axial hydroxyl of VI resulted in a shift to shorter wave lengths.

C. Part of the n.m.r. spectrum of elatericin A diacetate[10] shown in Fig. 1a indicates a series of signals which are due to the two protons at C-2 and C-16. They are composed of a triplet of lines in higher field originating from the C-16 proton and of a quartet in lower field which is due to the C-2 proton. There is an overlapping of two neighboring signals resulting in the appearance of the first higher peak. The pattern of four signals related to the C-2 proton is clearly visible in Fig. 1b, for 16-desoxyhexanorelatericin A monoacetate (VII).[11] This pattern is the result of a large coupling constant due to axial–axial interaction (13.6 c.p.s.) and of a small coupling constant due to axial–equiatorial interaction (4.2 c.p.s.). This characteristic pattern[12] of the C-2 hydrogen implies an axial conformation for this hydrogen. The acetoxy group has therefore an equatorial conformation in this derivative of elatericin A. The similarity of the two quartet patterns of lines in Fig. 1a and 1b ascertains the unaltered nature of the stereochemistry at carbon 2 in 16-desoxyhexanorelatericin A monoacetate which is obtained following a series of reactions from elatericin A diacetate.

It can be deduced from the various evidences presented, that in elatericin A (IIa) and cucurbitacin B (IIb) (as well as in their dihydroderivatives V) the conformation of the hydroxyl group at C-2 is equatorial, while in tetrahydroelatericin B (VIa) and tetrahydroelaterin (VIb) this group is axial. In view of the α-

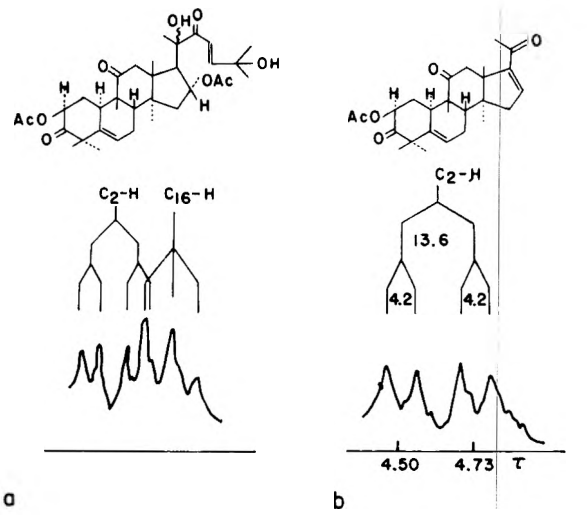


Fig. 1.—Part of n.m.r. spectra in chloroform-*d* of: a, elatericin A diacetate; b, 16-desoxyhexanorelatericin A acetate.

orientation of the hydrogen at C-10, determined earlier in this presentation, the configuration at C-2 should be β for the equatorial and α for the axial epimer. In the tetrahydro derivatives (VI) the α-axial configuration is, therefore, the result of a frontal approach to the molecule during the process of hydrogenation of the enolic double bond of ring A in I.

It is noteworthy that in agreement with these observations, the optical rotatory dispersion curves measured on dihydroelatericin A (Va) and tetrahydroelatericin B (VIa), which are both positive, display a remarkable difference in amplitude. It has been reported[13] that in steroids, as well as in triterpenes, the contribution to the size of the optical rotation in 1,2-hydroxy ketones is stronger for an axial than for an equatorial hydroxyl. In a β-configuration at C-10, the 2,β-axial hydroxyl group falls in a positive octant (lower right) and its contribution is, therefore, positive. When the configuration at C-10 is α the contribution of the 2-α-axial hydroxyl falling in a negative octant (lower left) is negative. Indeed, we have observed that in tetrahydroelatericin B (2,α-axial OH) the Cotton effect is smaller at the peak $[\alpha]_{325}$ +1550° than in dihydroelatericin A (2,β-equatorial OH) $[\alpha]_{325}$ +2200°.

With the stereochemistry of the asymmetric centers in ring A determined, a study of the various optical rotation values of several cucurbitacins and their derivatives leads to some novel and interesting observations. These values are reported in Table I. It can be seen that the substances possessing a 1,2-hydroxy ketone in ring A, as for example elatericin A, cucurbitacin B, and their dihydro derivatives as well as tetrahydroelatericin B and tetrahydroelaterin, have positive optical rotation values, while the cucurbitacins in which a diosphenol system occurs in ring A, *e.g.* elatericin B, elaterin, and their respective dihydro derivatives, have negative rotations. The sign of the optical rotations of the cucurbitacins is thus consistent with their structures, and it can, therefore, be used to make a distinction between the two major groups, differing in the nature of the substituents in ring A. This fact fitted conclusively for the substances obtained during the hydrogenation of the substances with the diosphenol

(8) The carbonyl absorption in the infrared of epimeric 1,2-hydroxy ketones was reported by A. R. H. Cole and G. T. A. Müller, *J. Chem. Soc.*, 1224 (1959), and by R. B. Bates, G. Büchi, T. Matsuura, and R. R. Shaffer, *J. Am. Chem. Soc.*, **82**, 2327 (1960).

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

(10) D. Lavie and Y. Shvo, *J. Am. Chem. Soc.*, **81**, 3058 (1959).

(11) D. Lavie and Y. Shvo, *ibid.*, **82**, 966 (1960).

(12) K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4623 (1961).

(13) W. Klyne, *Tetrahedron*, **13**, 29 (1961).

TABLE I

OPTICAL ROTATIONS, $[\alpha]_D$, OF THE CUCURBITACINS ARRANGED ACCORDING TO THE FUNCTIONAL GROUPS OF RING A

Diosphenols		1,2-Hydroxy ketones		1,2-Diols
Elaterin[a] (Ib) −58°	Dihydroelaterin −46°	2-Epicucurbitacin B[b] +41°	Tetrahydroelaterin (VIb) +21°	Hexahydroelaterin +54°
		Cucurbitacin B (IIb)[c] +87°	Dihydrocucurbitacin B (Vb)[c] +57°	
Elatericin B (Ia)[d] −52°	Dihydroelatericin B −44°		Tetrahydroelatericin B (VIa) +59°	Hexahydroelatericin B[c] +49°
		Elatericin A (IIa)[e] +48°	Dihydroelatericin A (Va)[e] +83°	Tetrahydroelatericin A[e] +31°

[a] See ref. 14. [b] See ref. 16. [c] See ref. 17. [d] See ref. 15. [e] See ref. 10.

in ring A, namely elatericin B and elaterin, the sign of the optical rotation becoming positive when a 1,2-hydroxy ketone was formed. This was true for tetrahydroelatericin B[15], which has now been prepared in a carefully purified form, as well as for tetrahydroelaterin.[18] Furthermore it can be seen that in each pair of epimeric 1,2-hydroxy ketones, those possessing an equatorial hydroxyl group show higher rotation values than the axial partner. Thus cucurbitacin B > 2-epicucurbitacin B, dihydrocucurbitacin B > tetrahydroelaterin, and dihydroelatericin A > tetrahydroelatericin B.

We report in Table I, for further reference, the cucurbitacin derivatives in which the carbonyl functions in ring A have been converted to 1,2-diols. Their optical rotations are all positive.

The occurrence of 2-epicucurbitacin B has been recently[16] reported in *Luffa echinata*. In this naturally occurring substance the conformation of the hydroxyl group at C-2 has been found to be identical with the conformation of this group in tetrahydroelaterin; it is, therefore, *α-axial*. This is the first instance of an α-axial 2-alcohol occurring in nature in this series of substances. Furthermore the optical rotation of 2-epicucurbitacin B is positive as expected, and finds its place among the 1,2-hydroxy ketones in Table I.

(14) D. Lavie and S. Szinai, *J. Am. Chem. Soc.*, **80**, 707 (1958).

(15) D. Lavie and D. Willner, *ibid.*, **80**, 710 (1958).

(16) D. Lavie, Y. Shvo, O. R. Gottlieb, R. B. Desai, and M. L. Khorana, *J. Chem. Soc.*, 3259 (1962).

(17) W. O. Eisenhut and C. R. Noller, *J. Org. Chem.*, **23**, 1984 (1958); A. Meleta, W. Schlegel, and C. R. Noller, *ibid.*, **24**, 291 (1959).

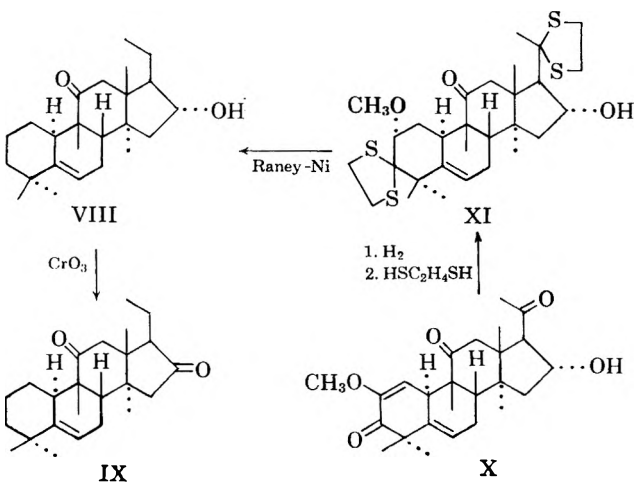
(18) The catalytic hydrogenation of elaterin (Ib) has led to controversial results.[19] A reinvestigation of the reduction sequence was therefore undertaken. Elaterin (Ib) in tetrahydrofuran solution, with palladium on carbon as catalyst, was reduced very rapidly to dihydroelaterin, the double bond of the side chain being saturated. For this purpose, the reaction had to be discontinued when one mole of hydrogen was absorbed. That only the double bond of the side chain had been reduced, was shown by the spectroscopical and chemical evidences. When the hydrogenation was allowed to proceed, a second mole of hydrogen was absorbed at a much lower rate, to yield tetrahydroelaterin. During this process, the diosphenol system in ring A (I) was reduced to the 1,2-hydroxy ketone (VI). Chemically this transformation was indicated by a negative reaction with ferric chloride, and a positive reaction with triphenyltetrazolium chloride (red precipitate of formazan). With bismuth oxide in acetic acid solution, black bismuth was precipitated.[20] Spectroscopically, the disappearance of the diosphenol chromophore was clearly indicated by the infrared, no bands at 1660 and 1413 cm.$^{-1}$, and by the ultraviolet absorption spectrum, the λ_{max} 267 mμ having faded away.[14] Hexahydroelaterin has been prepared by the hydrogenation of tetrahydroelaterin in acetic acid solution using platinum as catalyst. No more than one mole of hydrogen was absorbed under these conditions. During this process, the carbonyl at C-3 was reduced to the corresponding alcohol forming thereby the 1,2-diol. Thus, hexahydroelaterin did not react with the specific oxidizing reagents for 1,2-hydroxy ketones mentioned previously. Furthermore a band at 1705 cm.$^{-1}$ in the infrared spectrum of tetrahydroelaterin, which is related to the C-3 carbonyl, was not present in hexahydroelaterin.

(19) (a) J. N. T. Gilbert and D. W. Mathieson, *Tetrahedron*, **4**, 302 (1958); (b) D. Lavie and D. Willner, *J. Am. Chem. Soc.*, **82**, 1668 (1960), see Note Added in Proof.

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

In order to study the stereochemistry of the C/D rings fusion, the optical rotatory dispersion of a C-16 ketone derivative was studied. The corresponding curve was obtained by substracting the data of the monoketone (VIII) from the diketone (IX), thereby eliminating the contribution of the C-11 carbonyl in the over-all system. The resulting curve showed a negative Cotton effect with a very large amplitude $[\alpha]_{325}$ −3770°, $[\alpha]_{280}$ +4108°. Such sign and amplitude are characteristic for a 13β,14α orientation in steroids as well as in tetracyclic triterpenes[21] and, therefore indicates a lanostane type fusion in the cucurbitacins. We have proposed[6] previously such a stereochemistry between rings C and D on the basis of a study of molecular rotation differences between the C-16 ketone derivative and its corresponding alcohol.

The preparation of the diketone (IX) is shown in the following sequence of reactions. It involves the methylation of the enolic C-2 hydroxyl group in ring A of hexanorelatericin B,[11] the reduction of the double bond in the obtained X and the straightforward elimination of the C-2 and C-20 carbonyl groups through thioketalization (XI) and reduction with Raney nickel; it is noteworthy to observe the concomitant hydrogenolysis of the 2-methoxy group which occurred during the desulfurization (VIII). The monohydroxy derivative was then oxidized to the required diketone (IX).



The orientation of the side chain attached at C-17 was studied using the Cotton effect associated with the C-20 keto group which has been studied on various

(21) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958) (compound LXXV).

steroids.[22] In our series of derivatives two substances were selected for measurement: in order to eliminate the effect of the carbonyl group of ring A-nor, the rotatory dispersion curve of the monoketone (XII)[2b] was substracted from the monoketal IV eliminating thereby the effect due to the C-11 ketone. The drawn resultant showed a positive Cotton effect with a small peak $[\alpha]_{310}$ +663°. The Cotton effect in steroids with a methyl ketone β-oriented at C-17 is positive and strong ($[\alpha]_{310}$ +2400°) while, if α-oriented, the effect is opposite in sign (−1200°). Although small, the definite positive shape of the observed curve induced us to accept the β-orientation of the side chain. It should be kept in mind that in all known tetracyclic triterpenes the side chain has the same orientation as the C-13 substituent, which is also the same in the present substances. It should be noted that the triketone (III)[2b] used in our measurements was the product of the hydrogenation of the double bond Δ^{16} which was formed during the elimination of the C-16 hydroxyl group. In order to ascertain that no changes in configuration had occurred at the C-17 asymmetric center during dehydration and hydrogenation, the dispersion curve of the triketone (III) was compared with the curve of the corresponding 16-hydroxy triketone (XIII).[11] The two curves were found identical and almost superimposable, a clear and unequivocal indication that no configurational alterations had taken place at carbon 17.

The orientation of the hydroxyl at C-16 of the cucurbitacin molecule could now be determined. Although the results of our calculations have already been reported,[6] for the sake of completeness we shall repeat them briefly here. The molecular rotation of elatericin B (Ia) is $[M]_D$ −267° while the rotation of elatericin B diacetate is $[M]_D$ −492°.[15] From the two acetoxy groups, only the C-16 positive will contribute to a variation in value, the acetate at C-2 being enolic. The difference between these values is $\Delta[M]_D$ −225° which is the shift due to acetylation of the C-16 hydroxyl. Compared to similar shifts in the acetylation of C-16 hydroxyl group in steroids,[23] the sign and value of the difference ($\Delta[M]_D$ −239°) is in complete accordance with α-orientation. The reported value for β-oriented groups is $\Delta[M]_D$ +64°. A supporting evidence on the opposite orientation of the side chain and the C-16 hydroxyl group is found in the inability of this group to form a hemiketal with the C-22 carbonyl group. Such cyclizations have been reported in the literature[24] to occur readily upon heating with acid. No cyclization was observed when treated under the same conditions of reaction.

The α configuration of the C-16 hydroxyl group is also indicated by the triplet of lines in the n.m.r. spectrum[25] of elatericin A diacetate shown in Fig. 1a. This triplet can better be studied in dihydroelatericin B[15] (dihydro-Ia) (Fig. 2c). In both alternate orientations the C-16 proton is coupling its spin with the C-17,α, C-15,β, and C-15,α protons according to the two patterns drawn in Fig. 2a and 2b for C-16,β-H and

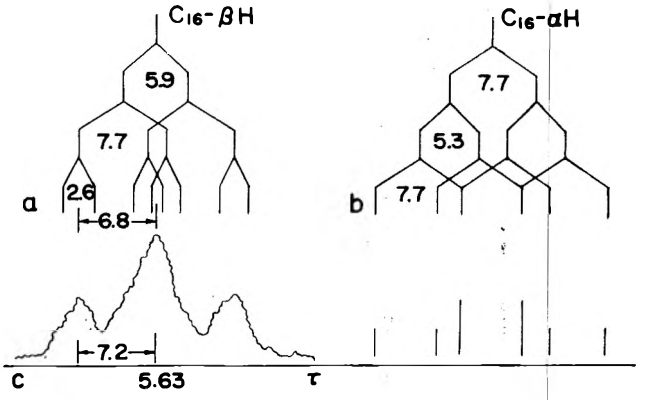


Fig. 2.—Calculated and observed n.m.r. spectra for C-16 proton in dihydroelatericin B: a, C-16, β-H epimer; b, C-16, α-H epimer; c, part of observed spectrum in chloroform-*d*.

C-16,α-H, respectively. The dihedral angles observed are: for C-16,β-H with C-17,α-H, ϕ = 137° (J = 5.9 c.p.s.); with C-15,β-H, ϕ = 10° (J = 7.7 c.p.s.); and with C-15,α-H, ϕ = 115° (J = 2.6 c.p.s.). The resulting pattern gives rise to a triplet in the ratio of 1:2:1. In the C-16,α-H alternative the respective angles and coupling constants are: ϕ = 10° (J = 7.7 c.p.s.), ϕ = 132° (J = 5.3 c.p.s.), and ϕ = 10° (J = 7.7 c.p.s.) resulting in a multiplet which probably would form a quartet in a ratio of 1:3:3:1. The observed spectrum of dihydroelatericin B in Fig. 2c, displayed a triplet of lines centered at τ = 5.63 with a peak spacing of 7.2 c.p.s. which agrees well with the pattern shown in Fig. 2a and eliminates the alternate possibility.

The angles for these calculations were measured on Dreiding models and the coupling constants are as calculated by Karplus.[26] It has already been shown that five-membered ring coupling constants agree very well with those expected from Karplus' work.[27]

The stereochemistry of the B/C rings fusion was studied using the optical rotatory dispersion curve of the monoketone XII[2b]; the Cotton effect was positive, $[\alpha]_{320}$ +3806°, $[\alpha]_{275}$ −4085°. To our knowledge, this observed large amplitude is unusual for a C-11 ketone[28] and could not be compared to previously recorded data. Of the four possible configurations at C-8 and C-9 we favor on biogenetic grounds, a β-orientation for the C-9 methyl group, in view of the occurrence of an α-oriented hydrogen at C-10. In order to decide on the configuration at C-8, the two remaining alternatives were built using models and they were observed in the light of the octant rule. With the 8β and 9β orientations, almost the entire molecule was found to fall into positive octants. This fact could very well account for the observed strong positive Cotton effect of the C-11 ketone.

It is noteworthy that in the structures recently proposed for cucurbitacin A and C, it was deduced from certain chemical reactions described there,[29] that the configuration of the B/C ring fusion is *cis*

(22) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 51.

(23) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 179.

(24) St. Kaufman and G. Rosenkranz, *J. Am. Chem. Soc.*, **70**, 3503 (1948).

(25) We thank a referee for pointing out this observation.

(26) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

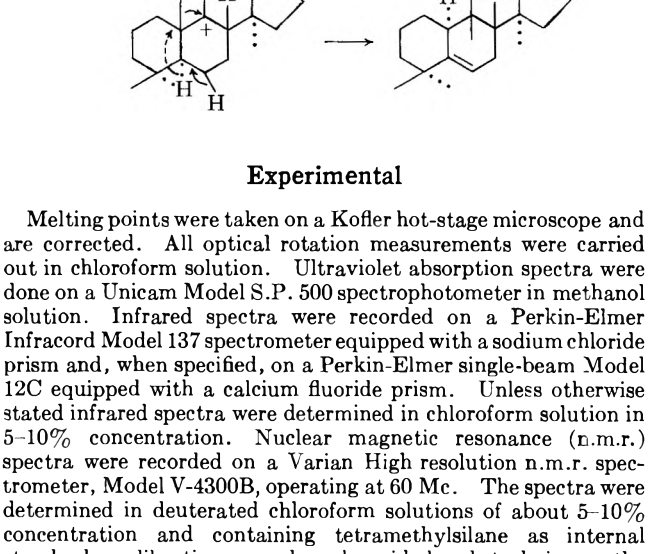
(27) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(28)(a) C. Djerassi, "Optical Rotatory Dispersion," (ref. 22, p. 44). (b) NOTE ADDED IN PROOF.—Meanwhile the optical rotatory dispersion of a steroidal C-11 ketone having rings B/C *cis* fused and the hydrogens β-oriented was reported. The recorded data agree very well with ours. See C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962), for compound XLVII.

(29) W. T. de Koch, P. R. Enslin, K. B. Norton, D. H. R. Barton, B. Sklarz, and A. A. Bothner-By, *Tetrahedron Letters*, 309 (1962).

in these compounds. No relationships between cucurbitacin A and C and the compounds dealt with in this paper have yet been determined; however, their structural similarities are striking.

In view of the stereochemistry of the cucurbitacins presented herewith, it could be assumed that these substances would originate in the plant by a secondary series of concerted stereospecific shifts from a lanostane like skeleton. Biogenetically the triterpenoids possessing a 9,10-cyclopropane ring can be regarded as intermediates between the lanostane and the cucurbitane type compounds. By β protonation at C-8 of a lanostane and formation of a "carbonium like ion" at C-9, scheme 1 would lead to a cycloartane triterpenoid, while scheme 2 to a cucurbitane skeleton. It is noteworthy that all triterpenoids possessing a 9,10-cyclopropane ring have in common a β-oriented C-8 hydrogen.



Experimental

Melting points were taken on a Kofler hot-stage microscope and are corrected. All optical rotation measurements were carried out in chloroform solution. Ultraviolet absorption spectra were done on a Unicam Model S.P. 500 spectrophotometer in methanol solution. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137 spectrometer equipped with a sodium chloride prism and, when specified, on a Perkin-Elmer single-beam Model 12C equipped with a calcium fluoride prism. Unless otherwise stated infrared spectra were determined in chloroform solution in 5–10% concentration. Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian High resolution n.m.r. spectrometer, Model V-4300B, operating at 60 Mc. The spectra were determined in deuterated chloroform solutions of about 5–10% concentration and containing tetramethylsilane as internal standard; calibration was done by side-band technique; the line positions given are τ values. Optical rotatory dispersion curves were measured on a Rudolph spectropolarimeter in dioxane solution.

16-Desoxy-A(2)-norhexanorelatericin A (III).[2b]—M.p. 179–181°; RD $[\alpha]_{589}$ +95° (*c* 1.54), $[\alpha]_{335}$ +574°, $[\alpha]_{325}$ +201°, $[\alpha]_{305}$ +2347°, $[\alpha]_{267.5}$ −538°, $[\alpha]_{250}$ +94° (*c* 0.08).

3-Monoethylene Ketal of III. (IV).—3,20-Bisethylene ketal of III[2b] (450 mg.) was dissolved in ethanol (28 ml.) and a 70% aqueous acetic acid solution (12 ml.) was added. The mixture was kept at room temperature (~25°) for the period of 8 hr., then worked up by pouring into dilute sodium bicarbonate solution, extracted with chloroform, washed with water, and dried over sodium sulfate. Evaporation of the solvent left a crude residue which was chromatographed through alumina (Alcoa F20, 40 g.). Following elution with a benzene–ether mixture 4:1 there emerged first the unchanged bisethylene ketal followed by the monoketal (102 mg.). The product crystallized from acetone–hexane, m.p. 158–161°; ν_{max}^{KBr} 1704 (overlapping of C-11 and C-20 carbonyls); RD $[\alpha]_{600}$ +103°, $[\alpha]_{589}$ +115°, $[\alpha]_{320}$ +4235°, $[\alpha]_{270}$ −5139°, $[\alpha]_{260}$ −4661° (*c* 0.13).

Anal. Calcd. for $C_{28}H_{38}O_4$: C, 74.96; H, 9.06. Found: C, 74.99; H, 9.10.

Dihydroelaterin.—Elaterin (Ib)[14] (556 mg.) in tetrahydrofuran solution (30 ml.) was added to a suspension of 5% palladium-on-carbon catalyst (100 mg.) in tetrahydrofuran and hydrogenated at atmospheric pressure. The hydrogenation was discontinued after 10 min., when the calculated amount for 1 mole of hydrogen (22.5 ml.) had been adsorbed. The catalyst was filtered and the solvent evaporated under reduced pressure. The amorphous residue was dissolved in methanol and water added to turbidity, yielding 530 mg. of crystals, m.p. 170–172°. Recrystallizations from aqueous methanol and drying at 60° under vacuum afforded long needles, m.p. 174–176°, $[\alpha]_D$ −46° (*c* 1.00); λ_{max} 266 mμ (ϵ 6970); ν_{max} 1724 and 1720 (ester), 1700, 1694 (C-22 and C-11 carbonyls), and 1664 cm.$^{-1}$ (diosphenol) (calcium fluoride prism). In ethanol, coloration was produced with ferric chloride. No formazan precipitate was formed with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{32}H_{46}O_8 \cdot H_2O$: C, 66.64; H, 8.39; one CH_3CO, 7.47. Found: C, 67.00; H, 8.44; CH_3CO, 7.83.

The substance was dried at 110° under vacuum to constant weight.

Anal. Calcd. for $C_{32}H_{46}O_8$: C, 68.79; H, 8.30; one CH_3CO, 7.70. Found: C, 68.56; H, 8.21; CH_3CO, 8.02.

This substance was found identical in all respects to **dihydroelaterin** previously[19b] obtained by the hydrogenation of elaterin in acetic acid solution with platinum as catalyst.

Tetrahydroelaterin (VIb).—Dihydroelaterin (558 mg.) was hydrogenated overnight in ethanol solution (30 ml.) over 5% palladium-on-carbon catalyst (100 mg.). One mole of hydrogen was absorbed. The catalyst was removed by filtration, and the product precipitated from its solution by adding water, 339 mg., m.p. 220–231°. Recrystallizations from aqueous methanol and drying at 60° under vacuum afforded rods, m.p. 231–233°, $[\alpha]_D$ +21° (*c* 0.96); λ_{max} 272 mμ (ϵ 857), λ_{min} 247 mμ (ϵ 510), high terminal absorption at 225 mμ (ϵ 1340); ν_{max} 1724 (ester), 1705 and 1702 (C-3 and C-22 carbonyls) and 1696 cm.$^{-1}$ (C-11 carbonyl) (calcium fluoride prism), and 1100 cm.$^{-1}$ (for C-2 axial hydroxyl). In ethanol, no coloration was produced with ferric chloride. A dark red crystalline precipitate of formazan was obtained with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{32}H_{48}O_8$: C, 68.54; H, 8.63; one CH_3CO, 7.68. Found: C, 68.57; H, 8.54; CH_3CO, 7.35.

The same compound was obtained in lower yield if elaterin (556 mg.) in acetic acid solution (30 ml.) was added to platinum catalyst (100 mg.) in acetic acid (5 ml.). Hydrogenation was discontinued (17 min.) when the calculated amount for 2 moles of hydrogen (45 ml.) had been absorbed.

Hexahydroelaterin.—Tetrahydroelaterin (VIb) (560 mg.) in acetic acid solution (30 ml.) was added to platinum catalyst (100 mg.) in acetic acid (5 ml.) and hydrogenated at atmospheric pressure overnight. One mole (22.5 ml.) of hydrogen was absorbed. The catalyst was filtered and the solvent evaporated under reduced pressure. The amorphous residue was dissolved in benzene and purified by chromatography on acid-washed alumina (Merck). Small quantities of starting material were eluted with benzene–ether 1:1. The main fraction (308 mg.) was obtained with ether–methanol 3:1 as an amorphous solid which crystallized upon addition of ether, m.p. 212–215°. Recrystallization from ether and drying at 110° in vacuum afforded hexagonal plates, m.p. 221–223°, $[\alpha]_D$ +54° (*c* 0.96); λ_{max} 271 mμ (ϵ 393), λ_{min} 241 mμ (ϵ 194), high terminal absorption at 218 mμ (ϵ 850); ν_{max} 1724 (ester), 1702 and 1696 cm.$^{-1}$ (C-22 and C-11 carbonyls) (calcium fluoride prism). In ethanol, no coloration was produced with ferric chloride. No formazan precipitate was obtained with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{32}H_{50}O_8$: C, 68.30; H, 8.96; one CH_3CO, 7.66. Found: C, 67.87; H, 8.82; CH_3CO, 6.95.

Tetrahydroelatericin B (VIa).—Elatericin B (Ia)[15] (10.24 g.) in ethanol solution (250 ml.) was hydrogenated over 10% palladium-on-carbon catalyst (1 g.) at atmospheric pressure until 1.8 moles were absorbed. The filtered solution was evaporated and the residue dissolved in chloroform. The solution was treated with cold 4% aqueous sodium hydroxide (to eliminate unreacted material), washed with water, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure yielded crude tetrahydroelatericin B (VIa) (8.7 g.) that gave negative ferric chloride and positive triphenyltetrazolium chloride tests. The product was crystallized twice from ether–methanol, prismatic needles, m.p. 174–176°, $[\alpha]_D$ +59° (*c* 0.88); λ_{max} 278 mμ (ϵ 180), λ_{min} 256 mμ (ϵ 130); ν_{max} 1705 (broad band) and 1694 (C-11 carbonyl) (calcium fluoride prism), and 1100 cm.$^{-1}$ (for C-2 axial hy-

droxyl). RD $[\alpha]_{589}$ +59°, $[\alpha]_{450}$ +70°, $[\alpha]_{350}$ +440° (*c* 0.04); $[\alpha]_{325}$ +1550°, $[\alpha]_{312}$ +800°, $[\alpha]_{308}$ +910°, $[\alpha]_{305}$ −580° (*c* 0.02).

Dihydroelatericin B.—In order to prepare a purified sample of dihydroelatericin B, the crude hydrogenation product of elatericin B[15] (one mole of hydrogen) was extracted in 4% aqueous sodium hydroxide solution, which was then acidified and reextracted in chloroform. The residue crystallized from a solvent mixture of ether–benzene–hexane, m.p. 158–160° dec. (sinters ~135°); $[\alpha]_D$ −44° (*c* 0.91).

Acetylation of Tetrahydroelatericin B.—Tetrahydroelatericin B (VIa) (8.80 g.) was acetylated in a mixture of acetic anhydride (50 ml.) and dry pyridine (50 ml.) overnight at room temperature. The solution was decomposed with ice–water. The precipitate of tetrahydroelatericin B diacetate (9.64 g.) was filtered and washed with water. The amorphous solid was dried in vacuum at 60°, $[\alpha]_D$ −24° (*c* 1.07); λ_{infl} at 270 mμ (ε 250); ν_{max} 1724 (esters) and 1700 cm.$^{-1}$ (overlapping of C-11 and C-22 carbonyls).

Anal. Calcd. for $C_{34}H_{52}O_9$: C, 67.75; H, 8.36; two CH_3CO, 14.28. Found: C, 67.21; H, 8.38; CH_3CO, 14.92.

Acetylation of Dihydroelatericin A.—Dihydroelatericin A (Va)[10] (100 mg.) was acetylated in a mixture of acetic anhydride (1 ml.) and pyridine (1 ml.) overnight at room temperature. The solution was decomposed with ice–water. The amorphous solid was dried in vacuum at 60°, $[\alpha]_D$ −11° (*c* 1.16); λ_{max} 284 mμ (ε 240), λ_{min} 254 mμ (ε 170); ν_{max} 1724, 1700, 1240, and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{52}O_9$: C, 67.75; H, 8.36; two CH_3CO, 14.28. Found: C, 67.15; H, 8.53; CH_3CO, 14.78.

Dihydroelatericin A (Va).[10]—RD $[\alpha]_{589}$ +83° (*c* 1.27); $[\alpha]_{400}$ +300°, $[\alpha]_{350}$ +732° (*c* 0.045); $[\alpha]_{325}$ +2200°, $[\alpha]_{302}$ −1870°, $[\alpha]_{290}$ −3130° (*c* 0.011).

Ultraviolet Absorption Spectra.—In order to indicate the effect of acetylation on the ultraviolet absorption, the following data are presented: dihydroelatericin A (Va), λ_{infl} 273 mμ (ε 300); dihydroelatericin A diacetate, λ_{max} 284 mμ (ε 240), λ_{min} 254 mμ (ε 170); tetrahydroelatericin B (VIa), λ_{max} 278 mμ (ε 180), λ_{min} 256 mμ (ε 130); and tetrahydroelatericin B diacetate, λ_{infl} 270 mμ (ε 250).

Dihydrohexanorelaterin-2-methyl Ether-3,20-Bisethylenedithioketal (XI).—Hexanorelaterin-2-methyl ether (X)[19b] (680 mg.) was hydrogenated in ethanol solution (50 ml.) over 10% palladium-on-carbon catalyst. The filtered solution was evaporated *in vacuo* to dryness to give the **dihydro X** derivative which was crystallized from ether, m.p. 166–168°, $[\alpha]_D$ +165° (*c* 1.21); ν_{max} 1728 and 1705 cm.$^{-1}$.

To a mixture of dihydro X (400 mg.) and 1,2-ethanedithiol (0.5 ml.) in an ice bath, boron trifluoride etherate (0.2 ml.) was added as catalyst. The solution was stirred for 5 min. and then left at room temperature for 5 hr. Chloroform was added and any unchanged dithiol was removed by shaking with a 10% sodium hydroxide aqueous solution. Upon evaporation of the solvent the residue crystallized, it was collected (450 mg.) and washed with ether, m.p. 215–225°; ν_{max} 1698 cm.$^{-1}$.

Desulfurization of XI to VIII.—To the substance XI (440 mg.) in dioxane solution (100 ml.), Raney nickel (prepared from 25 g. of alloy) in dioxane suspension was added. The mixture was stirred and maintained at reflux temperature overnight. The Raney nickel was removed and the filtrate evaporated *in vacuo* leaving an oily residue. It was crystallized several times from ether, m.p. 161–170°, and then sublimed at 140° (0.5 mm.), ν_{max} 1698 cm.$^{-1}$. RD $[\alpha]_{589}$ +182° (*c* 1.69); $[\alpha]_{322.5}$ +4043°, $[\alpha]_{280}$ −3436°, $[\alpha]_{270}$ −3120° (*c* 0.083).

Oxidation of VIII to IX.—To a stirred ice-cooled solution of VIII (150 mg.) in purified acetone (50 ml.), 0.3 ml. of a chromium trioxide solution (68 g. of chromium trioxide and 57 ml. of concentrated sulfuric acid diluted to 250 ml. with water) was added dropwise during 30 min. The excess oxidant was destroyed with methanol, water was added, and the product extracted with chloroform. The solution was washed and dried. Evaporation of the solvent left a residue which crystallized from ether, m.p. 184–187°; ν_{max}^{KBr} 1750 and 1698 cm.$^{-1}$. RD $[\alpha]_{589}$ +55° (*c* 0.9); $[\alpha]_{360}$ +212°, $[\alpha]_{340}$ −99°, $[\alpha]_{320}$ +1147°, $[\alpha]_{315}$ +500°, $[\alpha]_{307.5}$ +1448°, $[\alpha]_{280}$ +672° (*c* 0.116).

Anal. Calcd. for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.50; H, 9.93.

Monoketone XII.[2b]—RD $[\alpha]_{589}$ +127° (*c* 0.94); $[\alpha]_{358}$ +1000°, $[\alpha]_{320}$ +3806°, $[\alpha]_{275}$ −4085°, $[\alpha]_{260}$ −3484° (*c* 0.14).

A(2)-Norhexanorelatericin A (XIII).[11]—RD $[\alpha]_{589}$ +66° (*c* 1.65); $[\alpha]_{335}$ +461°, $[\alpha]_{322.5}$ +303°, $[\alpha]_{305}$ +2091°, $[\alpha]_{270}$ −856°, $[\alpha]_{250}$ −371° (*c* 0.13).

Acknowledgment.—We thank Mrs. R. Tugenhaft for technical assistance; Mlle. H. Hermann, Université de Strasbourg, for taking the optical rotatory dispersion curves; and Professor G. Ourisson for stimulating and helpful discussions pertaining to their interpretation.

Neighboring Group Reactions. VIII. Reactions of 3-(ω-Bromoalkyl)-3-phenyl-2-benzofuranones with Ammonia and Primary Amines

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Reactions of a series of ω-bromoalkylbenzofuranones I (n = 0–2) with ammonia and primary amines are described. The first member of the series (I, n = 0) reacts with ammonia and cyclohexylamine to give the α-amino amide V. With ammonia the two other homologs (I, n = 1,2) form only the rearranged amide VI (n = 1,2). Primary amines, however, yield appreciable quantities of a second product in addition to the rearranged amide VI (n = 1,2). From the bromomethyl homolog (n = 1), β-aminopropionamides VII are obtained and from the bromoethyl derivative (n = 2) five-membered ring imidates VIII are secured. Relative yields of the two products are found to depend on the amine used and on the solvent system. Both amino amides V and VII are weak bases ($pK_a \sim 4$) and acylate preferentially on the phenolic oxygen atom. Evidence is presented in support of a mechanism for the formation of VII which involves the intermediacy of the four-membered cyclic imidate A.

A previous paper[1] of this series described the reactions of 3-(ω-haloalkyl)-3-phenyl-2-benzofuranones (I) with secondary amines. Depending on the length of the haloalkyl side chain, the amine used, the temperature, and solvent, any one or several of three products was formed. With morpholine, for example, the bromomethyl homolog I (n = 1) under all conditions, gave only the rearranged amide II. The three extreme members of the series (n = 0,3,4), formed only the product III of direct halogen displacement. In excess morpholine at room temperature, the bromoethyl homolog I (n = 2) gave exclusively the trapped tetrahedral intermediate IV; but at raised temperatures (95–100°), or in dimethylformamide or dimethyl sulfoxide solution at room temperature, only the displacement product III (n = 2) was obtained. With other secondary amines more basic than morpholine, the bromoethyl derivative I (n = 2) gave varying amounts of the re-

(1) H. E. Zaugg, F. E. Chadde, and R. J. Michaels, *J. Am. Chem. Soc.*, **84**, 4567(1962).

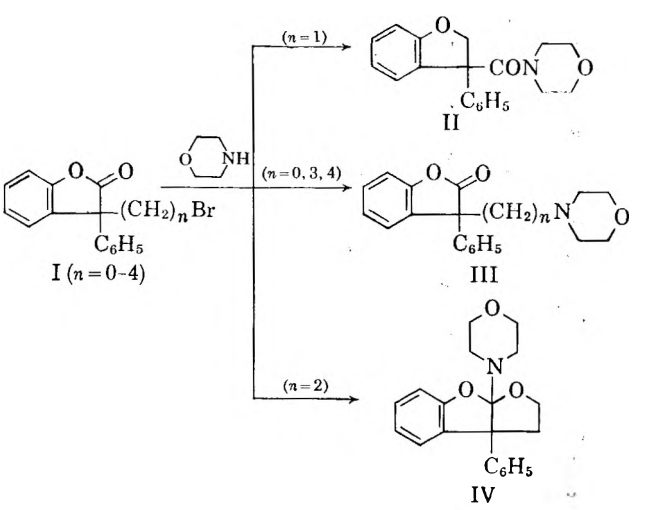
TABLE I

REACTION[a] OF 3-BROMOMETHYL-3-PHENYL-2-BENZOFURANONE WITH PRIMARY AMINES

I (n = 1) + RNH_2 ⟶ VII + VI (n = 1)

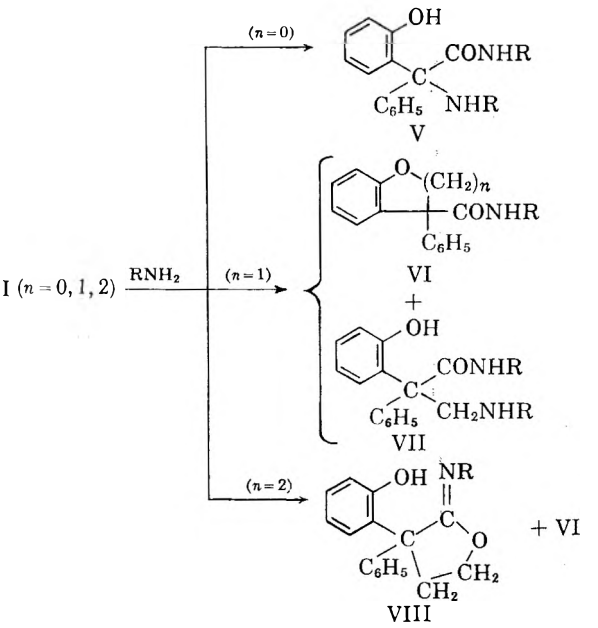
R	Yield of VII, %	M.p., °C.	$\lambda_{max}^{CHCl_3}$ C=O, μ	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield of VI, %	M.p., °C.	$\lambda_{max}^{CHCl_3}$ C=O, μ	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Cyclopropyl	46	188–190	6.06[b]	$C_{20}H_{24}N_2O_2$	74.97	75.25	7.20	7.27	8.33	8.44	10	133–134	5.96	$C_{18}H_{17}NO_2$	77.40	77.67	6.14	6.48	5.02	5.10
n-Propyl	10	143–144	5.97 6.08	$C_{21}H_{28}N_2O_2$	74.07	74.15	8.29	8.25	8.23	8.07	46	111–112	5.98	$C_{18}H_{19}NO_2$	76.82	76.81	6.80	6.69	4.98	5.09
Cyclobutyl	26	163–165	5.98	$C_{22}H_{28}N_2O_2$	75.79	76.08	7.74	8.06	7.69	7.59	27	153–154	6.00	$C_{19}H_{19}NO_2$	77.79	77.67	6.53	6.72	4.79	4.82
n-Butyl	7	117–119	5.96 6.07	$C_{23}H_{30}N_2O_2$	74.96	74.79	8.76	8.57	7.60	7.79	45	109–110	5.96[c]	$C_{19}H_{21}NO_2$	77.25	77.27	7.17	7.18	4.74	4.73
Cyclopentyl	18	146–147	5.99	$C_{24}H_{30}N_2O_2$	76.49	76.26	8.22	8.28	7.14	7.25	25	170–171	6.01	$C_{20}H_{21}NO_2$	78.14	78.07	6.89	6.70	4.56	4.62
Cyclohexyl	13	145–147[d] 178–179[e]	5.98	$C_{25}H_{32}N_2O_2$[f]	77.10	77.12	8.63	8.55	6.66	6.89	56	189–190	5.99	$C_{21}H_{23}NO_2$	78.47	78.73	7.22	7.06	4.36	4.40
Cycloheptyl	6	132–133[g]		$C_{31}H_{44}N_2C_4$[g]	66.88	66.41	7.97	7.75	5.03	5.05	30	151–152	6.01	$C_{22}H_{25}NO_2$	78.78	78.50	7.51	7.53	4.18	4.21
Benzyl	25	164–165	6.08	$C_{29}H_{28}N_2O_2$	79.79	79.69	6.47	6.46	6.42	6.21	[h]									

[a] According to procedure 1. [b] In Nujol mull. [c] In carbon tetrachloride. [d] Metastable dimorph. [e] Stable dimorph. See Table IVD for the n.m.r. spectrum. [f] Hydrochloride, m.p. 215–216°, pK_a (water—extrapolated) 4.2: *Anal.* Calcd. for $C_{25}H_{33}ClN_2O_2$: C, 70.96; H, 8.16; N, 6.13. Found: C, 70.68; H, 8.19; N, 6.09. [g] Oxalic acid salt monohydrate. *Anal.* Calcd. O, 20.12. Found: O, 20.27. [h] No amide could be isolated in pure form from the neutral fraction.



arranged amide (corresponding to II), at the expense of the trapped tetrahedral intermediate (*e.g.*, IV).

The present paper reports the extension of these investigations to the reactions with ammonia and primary amines of the first three members of this homologous series. Similarities to and differences from the previous work were encountered. Results may be summarized as shown.



The reaction of I (n = 0) with aqueous ammonia gave[2] the α-amino amide V (R = H). However, with either liquid ammonia or ammonia in acetonitrile, the bromomethyl compound I (n = 1) produced only the rearranged amide VI (n = 1, R = H). From the bromoethyl derivative I (n = 2) the corresponding amide VI (n = 2, R = H) was the sole product with either aqueous or anhydrous ammonia and the main product with ammonia in acetonitrile.

With cyclohexylamine, the α-amino amide V (R = cyclohexyl) was again the only product obtained (85% yield) from I (n = 0). Unexpectedly, the bromomethyl homolog I (n = 1), with primary amines (unlike secondary amines[1] and ammonia), did not lead exclusively to the rearranged amides VI (n = 1). In addition, appreciable amounts of the β-amino amides VII

(2) G. Cramer, *Ber.*, **31**, 2813 (1898). We are indebted to N. F. Ryan for repeating this reaction.

TABLE II

EFFECT OF SOLVENT ON THE REACTION[a] OF 3-BROMOMETHYL-3-PHENYL-2-BENZOFURANONE WITH CYCLOHEXYLAMINE

$$I(n = 1) + C_6H_{11}NH_2 \longrightarrow VII\ (R = \text{cyclohexyl}) + VI\ (n = 1, R = \text{cyclohexyl})$$

Solvent	Yield of VII, %	Yield[b] of VI, %
Cyclohexylamine	18	42
Cyclohexane	33	42 (65)
Benzene	13	56
Ethyl ether	35	25 (59)
Tetrahydrofuran	30	51 (67)
1,2-Dimethoxyethane	21	58 (72)
Acetonitrile	13	67
Dimethylformamide	0	68
Dimethyl sulfoxide	0	54

[a] According to procedure 1. [b] Except for those in parentheses, numbers represent yields of isolated product. Parenthesized values are corrected yields based on infrared examination of the neutral residues (using the intensity of the 5.99-μ amide peak to estimate the amount of VI). Slight absorption at 5.55 μ in the neutral residues corresponded to the presence of from 2 to 5% of unchanged bromide I ($n = 1$).

were formed under mildly exothermic conditions. Relative yields of the two products varied with the amine and solvent used. Results are summarized in Table I (variation of amine) and Table II (variation of solvent).

Two products were obtained likewise from the bromoethyl derivative I ($n = 2$). In addition to the usual rearranged amide VI ($n = 2$), the cyclic imidate VIII was formed. Again, relative yields of the two products depended on the amine used (see Table III). It is interesting to note that of all the primary amines used in the reactions with both bromo homologs ($n = 1,2$), cyclopropylamine, which is the weakest base[3] of any of them, gave the lowest yields of rearranged amides VI ($n = 1,2$) and highest yields of VII and VIII. A similar phenomenon was encountered previously[1] in the reactions of I ($n = 2$) with secondary amines. Morpholine, the weakest base of the series, was the only amine that produced the trapped tetrahedral intermediate IV as the sole product. From the other amines, varying amounts of rearranged amides could be isolated. The anomalous behavior of 1,1-dimethylhydrazine toward I ($n = 2$) in which a 90% yield of cyclic imidate VIII was formed (Table III) may also be due to its relatively low (and optimal[1]) basicity ($pK_a \sim 7$).

The structure VII assigned to the products obtained from the bromomethyl derivative is based on microanalytical results (Table I), infrared spectra, n.m.r. spectra of the cyclohexyl derivative (Table IV D), and the surprisingly low pK_a's (4.0–4.2) of several hydrochlorides of the series, an abnormality shared by the hydrochloride of the α-amino amide V (R = cyclohexyl). In addition, lithium aluminum hydride reduction of VII (R = $n - C_3H_7$) gave a diamine IX capable of forming a dihydrochloride. Interestingly, but not surprisingly,[4] the corresponding cyclopropyl amino amide VII (R = cyclopropyl) was converted to the identical

(3) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5030 (1951).

(4) C. Kaiser, A. Burger, L. Zirngibl, C. S. Davis, and C. L. Zirkle, *J. Org. Chem.*, **27**, 768 (1962), have found that a number of cyclopropylamines possessing a replaceable hydrogen on the nitrogen atom undergo ring cleavage with lithium aluminum hydride. We have observed similar behavior in several other cases. Also, in agreement with these workers, we have found that N,N-disubstituted cyclopropylamines are resistant to lithium aluminum hydride cleavage.

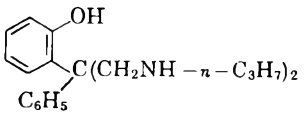
TABLE III

REACTION[a] OF 3-(β-BROMOETHYL)-3-PHENYL-2-BENZOFURANONE WITH PRIMARY AMINES

$$I(n = 2) + RNH_2 \longrightarrow VIII + VI\ (n = 2)$$

R	Yield of VIII, %	M.p., °C.	$\lambda_{max}^{CHCl_3}$ OH, μ[b]	$\lambda_{max}^{CHCl_3}$ C=N, μ	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield of VI, %	M.p., °C.	$\lambda_{max}^{CHCl_3}$ C=O, μ
Cyclopropyl	52	130–131	3.8	5.88[c]	$C_{19}H_{19}NO_2$[d]	77.78	77.85	6.53	6.77	4.78	4.80	37	Oil[e]	5.97[f]
Cyclobutyl	47	99–101	4.0	5.91	$C_{20}H_{21}NO_2$	78.14	78.15	6.89	7.16	4.56	4.42	42	140–141[g]	6.02
n-Butyl[h]	16	62–64	3.9[i]	5.87[i]	$C_{20}H_{23}NO_2$	77.64	77.88	7.49	7.26	4.53	4.37	60	Oil[e]	6.00
Cyclohexyl	20	107–108	3.9[i]	5.88[i]	$C_{23}H_{25}NO_2$[j]	78.78	78.98	7.52	7.68	4.18	4.26	66	85–87[k]	6.02
Benzyl[h]	15	112–113	3.9[i]	5.90[i]	$C_{23}H_{21}NO_2$	80.44	80.77	6.16	6.15	4.08	4.03	70	87–88[l]	5.96[i]
d-$C_6H_5CH_2CH(CH_3)$-[m]	9	177–178	3.9	5.89	$C_{25}H_{27}NO_2$	80.82	80.89	6.78	7.03	3.78	3.76	"		
$(CH_3)_2N$[n]	90	165–166	3.7	5.97	$C_{18}H_{20}N_2O_2$[p]	72.93	72.86	6.80	6.89	9.45	9.39	<3[o]		

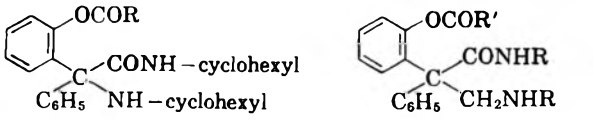
[a] According to procedure 2, unless otherwise noted. [b] None of the cyclic imidates VIII showed normal hydroxyl absorption either in the near (1.45-μ) or middle (2.7–2.9-μ) infrared region. However, they all absorbed broadly (and weakly) in the 3.5–5.0-μ region. The listed wave lengths give the approximate centers of these broad bands. [c] The presence of cyclopropyl was checked by its absorption in the near infrared: $\lambda_{max}^{CHCl_3}$ 1.63 μ. [d] See Table IVA for the n.m.r. spectrum. [e] The amide was not purified. The yield represents the entire neutral fraction. [f] Undiluted with solvent. [g] *Anal.* Calcd. for $C_{25}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.26; H, 6.91; N, 4.46. [h] By procedure 3. [i] In carbon tetrachloride solution. [j] Hydrochloride, m.p. 167–168°, pK_a 9.15. *Anal.* Calcd. for $C_{24}H_{26}ClNO_2$: C, 71.05; H, 7.05; N, 3.77. Found: C, 71.19; H, 6.99; N, 3.86. $\lambda_{max}^{CHCl_3}$ 5.94 μ (C=N). [k] *Anal.* Calcd. for $C_{22}H_{25}NO_2$: C, 78.78; H, 7.52; N, 4.18. Found: C, 78.40; H, 7.78; N, 4.09. [l] *Anal.* Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.23; H, 6.39; N, 3.95. [m] *d*-Amphetamine was the base used. [n] Only 44% of the theoretical amount of *d*-amphetamine hydrobromide was formed after 19 days at room temperature. The corresponding amide could not be separated from unchanged bromide I. [o] Unsymmetrical dimethylhydrazine was the base using procedure 3. [p] See Table IVB for the n.m.r. spectrum.



IX

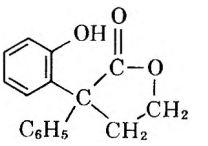
di-*normal* propylamine IX on similar treatment with lithium aluminum hydride.

Of some interest is the behavior of the α- and β-amino amides V and VII towards acylating agents. Compound V (R = cyclohexyl), with acetyl and propionyl chlorides in the presence of excess triethylamine, gives the O-acyl derivatives Xa and Xb, respectively, and from the requisite β-amino amides VII (R = cyclopropyl and cyclohexyl) the analogous products XIa–c were obtained (see Table IVC for the n.m.r. spectrum of XIb). The abnormally low basicity of these amines probably contributes to this preferential oxygen acylation. However, an attempt to effect, O,N-diacetylation using excess reagent under more drastic conditions failed. This suggests that a steric factor may also operate to prevent N-acylation in these compounds.



Xa. R = CH_3 XIa. R = cyclopropyl, R′ = OC_2H_5
Xb. R = C_2H_5 XIb. R = cyclohexyl, R′ = CH_3
XIc. R = cyclohexyl, R′ = C_2H_5

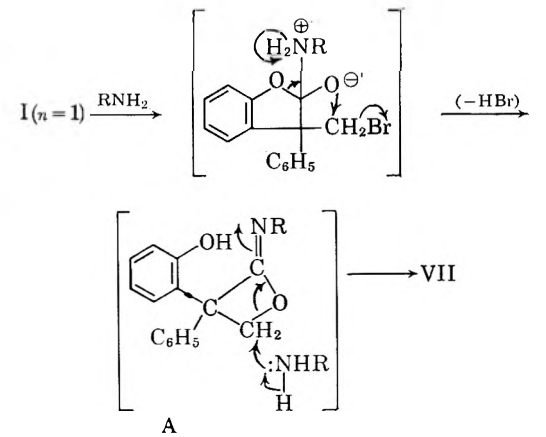
The structure VIII assigned to the basic products derived from the bromoethyl derivative is also based on microanalytical results (Table III), infrared spectra,[5] the n.m.r. spectrum of the cyclopropyl and 1,1-dimethylhydrazine derivatives of VIII (Table IV),[7] and on the products obtained from hydrolysis and aminolysis. Acid hydrolysis of VIII (R = benzyl) gave the lactone XII[9] (81% yield) and refluxing VIII (R = cyclohexyl) in morpholine containing morpholine hydrobromide led to the morpholinoethylbenzofuranone III (n = 2) in good yield (81%). Omission of the morpholine salt slowed but did not prevent aminolysis.



XII

Discussion

The unexpected displacement of a neopentyl-type bromine atom by primary amines [*i.e.*, I (n = 1) → VII] under mildly exothermic conditions is strong indication that, as is clearly the case in the formation of VI (n = 1), an intramolecular mechanism is involved.[10,12] The observation that the seemingly "direct" displacement of halogen in the production of VII is invariably accompanied by aminolysis of the lactone ring of I suggests that the intermediate involved is the four-membered cyclic imidate A analogous to the five-membered imidate VIII actually obtained from the higher homolog I (n = 2).[13] The mechanism can be represented as shown.



A

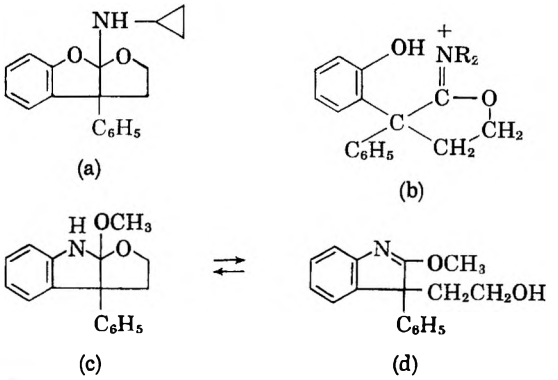
The process leading to A (and VIII) is undoubtedly the same as that by which the tetrahedral intermediates (*e.g.*, IV) are formed from I (n = 2) and secondary amines. This has been discussed previously[1] and will not be repeated. Considerable driving force leading

(5) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960), have reported $\lambda_{max}^{CHCl_3}$ 5.99 μ for the >C=NH group of a five-membered cyclic imidate. The range 5.87–5.91 μ observed (Table III) for compounds VIII is, therefore, consistent with an *N-alkylated* five-membered cyclic imidate structure. Substitution on nitrogen by the less electropositive $(CH_3)_2N$– group, as expected, gives a λ_{max} 5.97 μ, closer to that of the unsubstituted model.

The abnormal hydroxyl absorption (3.7–4.0 μ) exhibited by these compounds (Table III, footnote *b*) is also consistent with the presence of strong intramolecular hydrogen bonding with the basic imino nitrogen atom.[6] (This displaced hydroxyl absorption is also characteristic of most of the β-amino amides VII, but to a less obvious degree.)

(6) Compare H. H. Freedman, *J. Am. Chem. Soc.*, **83**, 2900 (1961).

(7) The n.m.r. spectrum of VIII (R = cyclopropyl) (see Table IVA) is best interpreted on the basis that, in carbon tetrachloride solution, structure VIII is in equilibrium with 10–15% of the tetrahedral intermediate (a). The clear preference shown for the imidate *vs.* the tetrahedral structure is consistent with the previous observation[8] that in the equilibrium c ⇄ d, the imidate tautomer (d) is favored by a factor of 3. Furthermore, protonation of tetrahedral intermediates of type IV has been found[1] to occur on oxygen rather than nitrogen to give quaternary imidate cations of type b.



(a) (b) (c) (d)

(8) H. E. Zaugg and R. W. DeNet, *J. Am. Chem. Soc.*, **84**, 4574 (1962).

(9) H. E. Zaugg, R. W. DeNet, R. J. Michaels, W. H. Washburn, and F. E. Chadde, *J. Org. Chem.*, **26**, 4753 (1961).

(10) The facile reactivity of neopentyl(or neophyl)-type halides toward *intramolecular* displacement is well known.[11]

(11) (a) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley, and Son, Inc., New York, N. Y., 1956, p. 464; (b) J. L. Greene, Jr., and H. J. Hagemeyer, Jr., *J. Am. Chem. Soc.*, **77**, 3016 (1955); (c) H. E. Zaugg, *ibid.*, **72**, 2998 (1950).

(12) The effect of dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) on the reaction of I (n = 1) with cyclohexylamine (Table II) further argues against a direct displacement mechanism. In these solvents, formation of the amino amide is completely suppressed in favor of the rearranged amide VI. Yet, in the reaction of morpholine with the bromoethyl homolog I (n = 2) where intermolecular displacement of bromide is possible, DMF and DMSO produce just the opposite effect.[1] Both *intramolecular* displacements [*i.e.*, I (n = 2) → IV + rearranged amide] are entirely suppressed in favor of the *intermolecular* displacement reaction [I (n = 2) → III (n = 2)].

(13) It must be stated that in contrast to secondary amines which are inert, primary amines (at 100°) readily aminolyze 3-phenyl-2-benzofuranones, containing an additional nonfunctional 3-substituent, to give the corresponding hydroxy amides. These reactions, however, are far from being even mildly exothermic (R. W. DeNet—unpublished).

to further reaction of A with amine should stem from two sources: strain energy of the four-membered ring[14] and acid catalysis by the phenolic hydroxyl. The latter effect is indeed demonstrable in the five-membered imidate series. Aside from infrared evidence[5,6] suggesting that, in VIII, the hydroxyl proton is strongly bonded to nitrogen, the observed reactivity of VIII toward morpholine to give III (n = 2) is firmly indicative of such catalysis. Although reaction is faster (80% yield *vs.* 40% in 22 hr. at 150°) in the presence of morpholine hydrobromide, it *does* occur even in its absence. By contrast, the reaction of the tetrahedral intermediate IV with morpholine requires the presence of amine salt for the same conversion.[1] The reactive species in this case is, in fact, the protonated form of IV, the imidate salt (b).[7]

The foregoing mechanism does not explain why ammonia behaves toward the bromomethyl compound I (n = 1) more like a secondary than a primary amine. The rearranged amide VI (R = H, n = 1) is the sole product formed under all conditions tried. But a clearly similar and equally puzzling preference for production of the amide VI (n = 2) is also exhibited toward the bromoethyl homolog I (n = 2). It would seem that we are dealing here with another example to add to the many already observed of the apparently quixotic behavior of ammonia and amines toward lactones[1,15] and esters,[16] a behavior probably stemming from the subtleties inherent in the nature and timing of proton transfer processes.[17]

Experimental

Reaction of 3-Bromomethyl-3-phenyl-2-benzofuranone with Cyclopropylamine and Other Primary Amines. Procedure 1.—To a stirred solution of 3-bromomethyl-3-phenyl-2-benzofuranone[18] (90.9 g., 0.3 mole) in dry benzene (450 ml.) was added over a period of 10 min., a solution of cyclopropylamine (51.3 g., 0.9 mole[19]) in dry benzene (50 ml.). An ice bath was used to maintain the reaction temperature below 35°. After standing at room temperature for 2 days, precipitated solid (99.4 g.) was removed by filtration and stirred vigorously with water (300 ml.) for 10 min., once again collected at the filter, and dried. The crude product (60.5 g., m.p. 173–176°); the difference in weight, 38.9 g., between this and the original 99.4 g., represented an 89% yield of the water-soluble cyclopropylamine hydrobromide), was recrystallized from dry ethanol to give 43.3 g. (43%) of **N-cyclopropyl-β-cyclopropylamino-α-(o-hydroxyphenyl)-α-phenylpropionamide (VII. R = cyclopropyl)**, m.p. 188–190°. (For microanalytical results, see Table I.)

The original benzene filtrate was extracted with two portions (100 ml.) of 10% hydrochloric acid which were combined and made alkaline by the careful addition of excess 40% sodium hydroxide solution. Filtration and drying of the resulting precipitate gave an additional quantity (3.7 g., 3%) of VII (R = cyclopropyl), m.p. 186–188°.

The neutral fraction in benzene solution was concentrated to dryness under reduced pressure. The resulting oil (30.7 g.), on trituration with isopropyl alcohol, partially solidified to give a solid substance (20 g., m.p. 104–109°). Two recrystallizations from ethanol produced 8.4 g. (10%) of **N-cyclopropyl-2,3-dihydro-3-phenylbenzofuran-3-carboxamide (VI. n = 1, R = cyclopropyl)**, m.p. 133–134°. (For microanalytical results, see Table I.)

By substituting the appropriate primary amine for cyclopropylamine in procedure 1 (in some cases with minor variations) the corresponding products of type VII and type VI (n = 1) were obtained. These are listed in Table I.

The effect of change in solvent on the outcome of procedure 1, as applied to cyclohexylamine, is summarized by the data listed in Table II.

N,N'-Di-*n*-propyl-2-(*o*-hydroxyphenyl)-2-phenyl-1,3-propanediamine (IX).—To a stirred suspension of lithium aluminum hydride (14.8 g., 0.39 mole) in dry 1,2-dimethoxyethane (500 ml.) solid VII (R = cyclopropyl) (43.7 g., 0.13 mole) was added portionwise over a 30-min. period. The mixture was then stirred and refluxed for 42 hr. Excess reducing agent was decomposed by successive addition of water (50 ml.) and 50% sodium hydroxide solution (50 ml.) followed by a period (1 hr.) of reflux. The organic layer was then decanted from the precipitate and concentrated to dryness under reduced pressure. The residual solid (41.9 g., m.p. 88–95°) was recrystallized twice from 95% ethanol to give 27.9 g. (67%) of IX, m.p. 102–103°, $\lambda_{max}^{CHCl_3}$ 1.54 μ (N–H), no absorption at 1.63 μ typical of a cyclopropyl CH_2 group.

Anal. Calcd. for $C_{21}H_{30}N_2O$: C, 77.25; H, 9.26; N, 8.58; O, 4.91. Found: C, 77.27; H, 9.21; N, 8.71; O, 5.00.

IX dihydrochloride had m.p. 252–254° (from ethanol).

Anal. Calcd. for $C_{21}H_{32}Cl_2N_2O$: C, 62.99; H, 8.07; N, 6.84. Found: C, 62.75; H, 7.95; N, 7.25.

Reduction of VII (R = *n*-propyl) according to the foregoing procedure likewise gave IX (92%) identified by melting point, mixture melting point, infrared spectrum, and by conversion to the dihydrochloride, m.p. 252–254°.

Reaction of the Bromides I (n = 1,2) with Ammonia.—To anhydrous liquid ammonia (2.5 l.) was added portionwise with stirring over a period of 0.5 hr., 242.4 g. (0.8 mole) of solid 3-bromomethyl-3-phenyl-2-benzofuranone. The resulting green solution was stirred for 7 hr. and allowed to stand overnight at room temperature. The residue remaining after evaporation of the ammonia was partitioned between water and chloroform and separated. Removal of the chloroform by distillation gave a solid residue which was recrystallized from 95% ethanol to give 152 g. (79%) of 2,3-dihydro-3-phenylbenzofuran-3-carboxamide (VI, n = 1, R = H), m.p. 154–156°, identical with the material prepared from the corresponding acid chloride.[18] Similar treatment of the bromomethyl compound with ammonia in acetonitrile solution resulted in a quantitative conversion to rearranged amide VI (n = 1, R = H).

When 3-(β-bromoethyl)-3-phenyl-2-benzofuranone (I. n = 2) was subjected to the foregoing conditions, there was obtained a 93% yield of 4-phenyl-4-chromancarboxamide (VI. n = 2, R = H), m.p. 181–182°, identical (mixture melting point and infrared spectrum) with an authentic[18] sample.

When powdered bromoethyl derivative I (n = 2) was stirred with concentrated ammonium hydroxide for 21 hr. at room temperature, a 60% conversion to the corresponding amide VI took place. The remainder of the product appeared to be unchanged bromide. With ammonia in acetonitrile solution, however, the reaction deviated from a unidirectional course. From 6.3 g. (0.02 mole) of the bromoethyl derivative, in addition to a predominant neutral fraction (5.0 g.) consisting mainly of amide VI, there was obtained 1.93 g. of a basic oil. The structure of a pure compound obtained from it will be the subject of a future note.

Reaction of 3-(β-Bromoethyl)-3-phenyl-2-benzofuranone with Primary Amines. Procedure 2.—This procedure is exemplified by the reaction with cyclopropylamine. A solution of the bromide I (n = 2) (15.9 g., 0.05 mole) and cyclopropylamine (6.3 g., 0.1 mole) in dry benzene (100 ml.) was allowed to stand at room temperature for 6 days. The cyclopropylamine hydrobromide (6.6 g., 91%), m.p. 152–155°, was removed by filtration and washed with ether. The combined filtrate and ether washings were concentrated to dryness under reduced pressure; the residue was taken up in ether and extracted with two portions (50 ml.) of 10% sulfuric acid. From the neutral ether layer was obtained, in the usual way (procedure 1), the amide VI (n = 2, R = cyclopropyl) and from the acid extract (in the usual way), the cyclic imidate VIII (R = cyclopropyl). See Table III for further details.

(14) Facile displacements by amines at the β-carbon atom of β-laetones are well known.[15]

(15) (a) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. T. Fiedorek, *J. Am. Chem. Soc.*, **73**, 3168 (1951); (b) H. E. Zaugg in "Organic Reactions," Vol. VIII, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1954, p. 305.

(16) M. M. Joullié and A. R. Day, *J. Am. Chem. Soc.*, **76**, 2990 (1954).

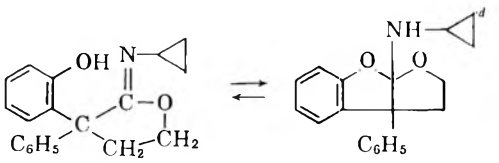
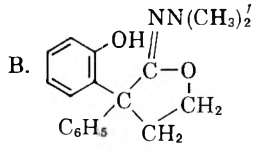
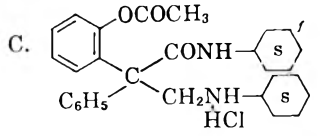
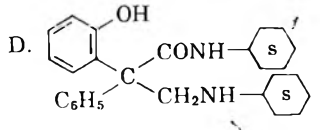
(17) M. L. Bender, *Chem. Rev.*, **60**, 91 (1960), and references cited therein.

(18) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *J. Org. Chem.*, **26**, 4821 (1961).

(19) One-third (0.3 mole) of the cyclopropylamine could be replaced by an equivalent quantity of triethylamine without affecting the course of the reaction.

TABLE IV

N.M.R. SPECTRA[a]

Chemical shift,[b] c.p.s.	Assignment	Relative area[c]	
A. 			
7–25	>NH	0.81[e]	
37–55	Cyclopropyl—CH_2CH_2—	3.65	5.13
125–160	Cyclopropyl—CH	1.48	
165–210	C—CH_2—C	2.02	
230–275	O—CH_2—C	2.04	
390–450	Aromatic H	9.00[c]	
653.2	OH	0.86	
B. 			
162.5	$N(CH_3)_2$	6.15	10.0
140–207	C—CH_2CH_2—O	3.85	
400–450	Aromatic H	9.00[c]	
618	OH	0.96	
C. 			
28–133	Cyclohexyl CH_2	20.00	27.5[g]
139	—$COCH_3$	3.32	
147–239	Cyclohexyl CH	2.23	
261	—N—CH_2—C	1.96	
370–398[h]	NH	0.98[e]	
398–504	Aromatic H	9.00[c]	
542–579[h]	NH	0.85[e]	
618–662[h]	NH	0.85[e]	
D. 			
40–120	Cyclohexyl CH_2	19.00	21.6[i]
120–150	Cyclohexyl CH	1.35	
185–250	Cyclohexyl CH	1.20	
214 (4)	N—CH_2—C	1.85	
328–355[h]	OH	0.90	
400–460[j]	Aromatic H	9.00[c]	

[a] 60-Mc. [b] Tetramethylsilane as internal standard. Numbers denote range of frequencies of complex absorption except where digits in parentheses indicate the number of peaks in a symmetrical multiplet centered at the indicated frequency. A single frequency notation with no parenthetical digit following it represents a singlet. [c] Assuming 9 aromatic protons. [d] In CCl_4 solution. [e] Due to the quadrupole moment of nitrogen this area cannot be compared with the other areas. [f] In $CDCl_3$ solution. [g] Total required, 27.0. [h] Band disappears when D_2O is added. [i] Total required, 22.0. [j] No bands corresponding to the two NH protons could be identified. However, absorption at 1.49 μ in the near infrared provided firm evidence for the presence of the amide NH group; and, since both the near infrared and n.m.r. spectra of the corresponding acetyl derivative XIb indicate the presence of both NH groups, they must also both be present in the precursor of XIb.

Procedure 3 differed from procedure 2 only in the omission of benzene as solvent. Instead, excess of the liquid amine (10 to 15 ml. per 0.01 mole of bromide) was used. The reaction mixture was then worked up by removing the amine under reduced pressure in a rotating evaporator, partitioning the residue between ether and water, separating, and treating the ether layer as in procedure 2.

Under the conditions of procedure 2, no reaction occurred with aniline. After 11 days, 90% of the bromide I (n = 2) was recovered unchanged.

N-Cyclohexyl-α-cyclohexylamino-α-(*o*-hydroxyphenyl)-α-phenylacetamide Hydrochloride (V. R = Cyclohexyl).—A solution of 10 g. (0.0346 mole) of 3-bromo-3-phenyl-2-benzofuranone[2] and 10 g. (0.1038 mole) of cyclohexylamine in benzene (150 ml.) was kept overnight at room temperature. The precipitated cyclohexylamine hydrobromide (6.2 g., m.p. 196–198°) was removed by filtration and washed with ether. The combined filtrate and washings were concentrated to dryness *in vacuo* and the residual oil (14.1 g.) was taken up in dry ether, decolorized with charcoal and treated with excess ethereal hydrogen chloride. Filtration and drying gave 13.0 g. (85%) of the hydrochloride of V (R = cyclohexyl), m.p. 160–161°. Recrystallization from an ethanol–ether mixture did not change the m.p., $\lambda_{max}^{CHCl_3}$ (μ) 1.49, 2.95, 5.94, pK_a (water) 4.1 (by titration with methanolic potassium hydroxide in different aqueous methanol solutions and extrapolating to 100% water).

Anal. Calcd. for $C_{26}H_{35}ClN_2O_2$: C, 70.49; H, 7.96; N, 6.32. Found: C, 70.44; H, 7.80; N, 6.48.

Aminolysis of VIII (R = Cyclohexyl) with Morpholine.—A mixture of 3.4 g. (0.01 mole) of the imidate VIII (R = cyclohexyl), 1.7 g. (0.01 mole) of morpholine hydrobromide, and 20 ml. of morpholine was refluxed for 22 hr. in an oil bath held at 150°. The solution was concentrated to dryness under reduced pressure and the residue was taken up in ether. After washing with water to neutrality, the ether solution was extracted with dilute (10%) hydrochloric acid. The cold acid extract was then treated with excess 40% sodium hydroxide solution and the precipitated base was taken up in ether and dried. Isolation by filtration and distillation of the ether gave a crude base (3.1 g., 97%), m.p. 85–90°. Recrystallization from isopropyl alcohol gave pure 3-(β-morpholinoethyl)-3-phenyl-2-benzofuranone (III. n = 2) (81%), m.p. 94–95°, identical (mixture melting point and infrared spectrum) with an authentic sample.[1]

When the foregoing procedure was repeated, but with the omission of morpholine hydrobromide, infrared examination of the crude reaction product (after 22 hr.) indicated that only 40% of the imidate had been converted to the benzofuranone III (n = 2). The remainder was unchanged.

When the β-amino amide VII (R = cyclohexyl) was submitted to the foregoing conditions (including morpholine hydrobromide) only starting material (> 70%) was recovered. No benzofuranone product (λ_{max} 5.55 μ) could be detected by infrared examination of the residues.

Hydrolysis of VIII (R = Benzyl).—The cyclic imidate VIII (R = benzyl) (0.50 g., 0.00146 mole) was refluxed for 2 hr. with 25 ml. of 10% hydrochloric acid. After cooling, solid product was removed by filtration and recrystallized from benzene to give 0.30 g. (81%) of 2-(*o*-hydroxyphenyl)-2-phenyl-4-hydroxybutyric acid γ-lactone (XII), m.p. 159–160°, identical with an authentic sample.[9] From the acid filtrate was obtained 0.10 g. (50% yield) of benzylamine hydrochloride, m.p. 259–261°.

N-Cyclohexyl-β-cyclohexylamino-α-(*o*-acetoxyphenyl)-α-phenylpropionamide Hydrochloride (XIb).—To a solution of 8.4 g. (0.02 mole) of the amino amide VII (R = cyclohexyl) in 100 ml. of 1,2-dimethoxyethane containing 4.0 g. (0.04 mole) of triethylamine was added dropwise with stirring over a period of 5 min. 1.6 g. (0.02 mole) of acetyl chloride dissolved in 10 ml. of 1,2-dimethoxyethane. The mixture was stirred at room temperature for 6 hr., refluxed and stirred for 1 hr. and then allowed to stand overnight at room temperature. The precipitated triethylamine hydrochloride (3.3 g., m.p. 259–260°) was removed by filtration and the filtrate was concentrated *in vacuo* on the steam bath. The residual oil [$\lambda_{max}^{CCl_4}$ (μ) 1.49 (amide NH), 1.53 (amine NH); $\lambda_{max}^{CHCl_3}$ (μ) 5.65 (ester >C=O), 6.01 (amide > C=O)] was taken up in dry ether and treated with excess ethereal hydrogen chloride. No precipitate resulted so the solution was concentrated to dryness and the residual solid was recrystallized from acetone to give 8.0 g. (80%) of XIb, m.p. 209–210°. One more recrystallization for analysis gave 6.6 g., m.p. 212–213°, $\lambda_{max}^{CHCl_3}$ (μ) 5.66 (ester >C=O), 5.96 (amide >C=O), pK_a (water—extrapolated) 4.0, for the n.m.r. spectrum see Table IVC.

Anal. Calcd. for $C_{29}H_{39}ClN_2O_3$: C, 69.79; H, 7.88; N, 5.61. Found: C, 69.81; H, 7.96; N, 5.58.

An attempt to prepare the O,N-diacetyl derivative by refluxing the amino amide VII (R = cyclohexyl) with excess acetyl chloride for 48 hr. failed. Only the mono-O-acetyl derivative could be obtained *even in the presence of excess triethylamine.*

Substituting propionyl chloride for the acetyl chloride in the foregoing procedure gave the similarly ether soluble **N-cyclohexyl-β-cyclohexylamino-α-(o-propionoxyphenyl)-α-phenylpropionamide hydrochloride (XIc)** in 53% yield, m.p. 190–191°, $\lambda_{max}^{CHCl_3}$ 5.69 μ (ester >C=O), 5.98 μ (amide >C=O).

Anal. Calcd. for $C_{30}H_{41}ClN_2O_3$: C, 70.22; H, 8.06; N, 5.46. Found: C, 70.18; H, 8.06; N, 5.67.

Substituting the amino amide VII (R = cyclopropyl) for the cyclohexyl analog and ethyl chloroformate for the acetyl chloride in the foregoing procedure gave **N-cyclopropyl-β-cyclopropylamino-α-(o-ethoxycarbonyloxy)-α-phenylpropionamide hydrochloride (XIa)**, m.p. 177–178°, $\lambda_{max}^{CHCl_3}$ 1.49 μ (NH), 1.63 μ (cyclopropyl), 5.69 μ (ester >C=O), 5.89 μ (amide >C=O).

Anal. Calcd. for $C_{24}H_{29}ClN_2O_4$: C, 64.77; H, 6.57; N, 6.30; O, 14.38. Found: C, 64.62; H, 6.39; N, 6.29; O, 14.57.

Treatment of the amino acetamide V (R = cyclohexyl) with acetyl chloride according to the above procedure and isolation of the product as the base gave, in 45% yield, **N-cyclohexyl-α-cyclohexylamino-α-(o-acetoxyphenyl)-α-phenylacetamide (Xa)**, m.p. 143–144°, $\lambda_{max}^{CHCl_3}$ (μ) 3.02 (NH), 5.67 (ester >C=O), 6.01 (amide >C=O).

Anal. Calcd. for $C_{28}H_{36}N_2O_3$: C, 74.97; H, 8.09; N, 6.24. Found: C, 75.07; H, 8.14; N, 6.31.

Likewise, from propionyl chloride and V (R = cyclohexyl) was obtained in 40% yield, **N-cyclohexyl-α-cyclohexylamino-α-(o-propionoxyphenyl)-α-phenylacetamide (Xb)**, m.p. 118–119°, $\lambda_{max}^{CHCl_3}$ (μ) 3.01 (NH), 5.68 (ester >C=O), 6.01 (amide >C=O).

Anal. Calcd. for $C_{29}H_{38}N_2O_3$: C, 75.29; H, 8.28; N, 6.05. Found: C, 75.74; H, 8.39; N, 5.77.

Acknowledgment—We wish to thank Mr. Dave Wimer for the potentiometric titrations; Mr. W. H. Washburn for the infrared spectra; Mr. E. F. Shelberg and associates for the microanalyses; Mr. G. M. Bradford and Mr. N. F. Ryan for technical assistance; and Mr. T. F. Page, Jr., Battelle Memorial Institute, and Dr. R. W. Mattoon for the n.m.r. spectra.

Neighboring Group Reactions. IX. Some Cyclic Imidates and Related Lactones with Functional Substituents

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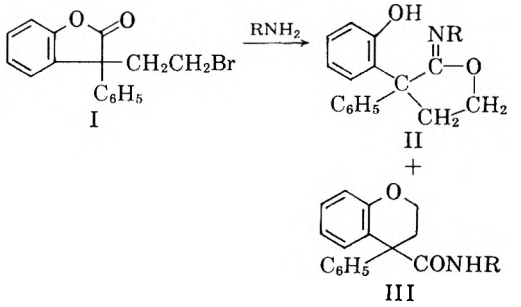
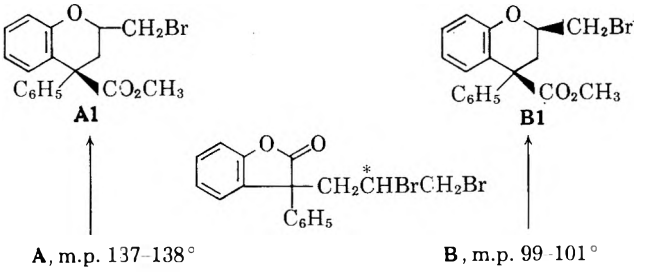
Cyclopropylamine effects preferential and stereospecific intramolecular displacement of the 2′-bromine atom from the two diastereoisomers **A** and **B** of 3-(2′,3′-dibromopropyl)-3-phenyl-2-benzofuranone. Fair yields (60–70%) of the geometrically isomeric cyclic imidates **A2** and **B2** result. The multiplicity and variable proximity of functional groups in these compounds, as well as in the isomeric lactones (**A4** and **B4**) derived from them, lead to a variety of intramolecular reactions. These are summarized in the accompanying flow chart.

The purpose of the present work was the development of a synthetic sequence derived from the combination of results reported in two previous papers of this series. The accompaning paper[1] described the reaction of 3-(β-bromoethyl)-3-phenyl-2-benzofuranone (I) with primary amines. Products consisted of varying amounts of cyclic imidates II and rearranged amides III. Another report[2] described the reactions of the two diastereoisomeric dibromopropylbenzofuranones **A** and **B** with sodium methoxide. In each case preferential and stereospecific displacement of the secondary bromine atom occurred with rearrangement to give the geometrically isomeric bromo esters **A1** and **B1**,[3] respectively, in good yields (89–96%). Similar selective behavior of **A** and **B** toward primary amines, analogous to that of I to produce II, would be expected to yield products possessing an unusual combination of functional groups in a single molecule. Cyclopropylamine was chosen to verify this expectation because it, of all the primary amines used[1] in reactions with I, produced the best yields of II at the expense of III. Reactions of **A** and **B** with cyclopropylamine and subsequent transformations of the resulting products are outlined in the attendant chart.





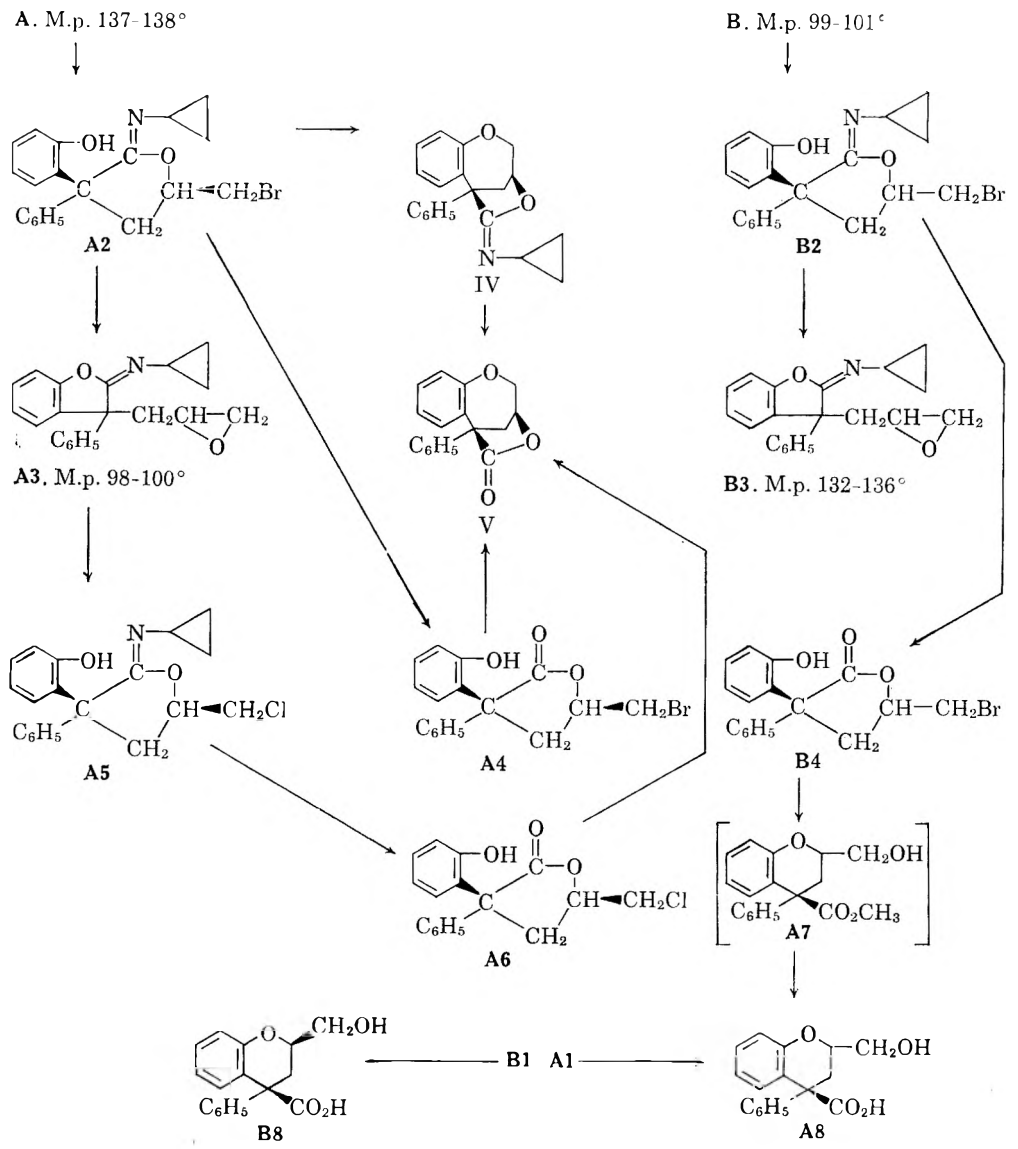
Treatment of the isomeric dibromides **A** and **B** with cyclopropylamine at room temperature gave the expected cyclic imidates **A2** and **B2**, respectively, in 73% and 58% yields.[4] These products each contain two electrophilic carbon atoms (>C=N— and —CH_2Br)

(1) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *J. Org. Chem.*, **28**, 1795 (1963).

(2) H. E. Zaugg, R. W. DeNet, and E. T. Kimura, *J. Med. Pharm. Chem.*, **5**, 430 (1962).

(3) The notational convention used in this paper is designed to facilitate recognition of the steric relationships among isomers. For example, all products derived from **A**, m.p. 137–138°, by only one inversion at the carbon atom marked with an asterisk, are members of the **A** family. The **B** family derives similarly from **B**, m.p. 99–101°. It follows that two inversions at this asymmetric center effect family interconversion. Two compounds with the same number (*e.g.*, **A1**, **B1**) constitute diastereoisomeric pairs.

(4) The infrared spectra of these bases were typical of this structure (*i.e.*, II[1]), namely broad and weak absorption centered at 3.9 μ (bonded OH) and strong absorption at 5.87–5.88 μ (C=N). The neutral fractions of these reactions were not examined for the presence of rearranged amide [*i.e.*, the 2-bromomethyl derivative of III (R = cyclopropyl)].



and a potentially available nucleophilic center (ArOH → ArO$^{\ominus}$). However, only in the *cis*-bromophenol **A2**[5] does the phenoxide ion (generated by treatment with base) have the option of reacting with either or both of these electrophilic centers. Thus, treatment of **A2** with an equivalent of sodium methoxide in 1,2-dimethoxyethane gave an 86% yield of the bridged bicyclic imidate IV,[6] the product of direct bromide ion displacement by the phenoxide oxygen atom. In methanol solution, however, the yield of IV was reduced to 46% and a 33% yield of the epoxyimidate **A3** was secured.[7] From the *trans*-bromophenol **B2**, on the other hand, the isomeric epoxyimidate **B3** was the only isolable product (58% yield).[8]

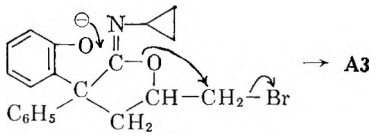
The structure assigned to **A3** (and **B3**) was supported by its reaction with ethereal hydrogen chloride. It gave in 69% yield the hydrochloride of **A5** which is the chloro analog of **A2**.[10] Acid hydrolysis of **A5** gave the phenolic γ-lactone **A6** (91% yield) which with sodium methoxide cyclized (65% yield) to the bridged γ-lactone V,[6] identical with the lactone obtained (97% yield) from acid hydrolysis of the bridged bicyclic imidate IV.

Acid hydrolysis of the two cyclic imidates **A2** and **B2** gave the corresponding lactones **A4** and **B4**, respectively, in 49% and 85% yields. These two isomers

(5) Since the geometry of **A1** was known,[2] the reasonable assumption that formation of **A1** and **A2** both occur with complete inversion allowed the prediction that the cyclic imidate obtained from A would indeed have the structure (*i.e.*, **A2**) in which the bromomethyl and phenolic groups would both be on the same side of the plane defined by the heterocycle.

(6) The assignment of structure is documented in Experimental.

(7) Formation of **A3** can be envisaged as a concerted intramolecular process induced by initial attack of phenoxide ion at the imino carbon atom of **A2**.



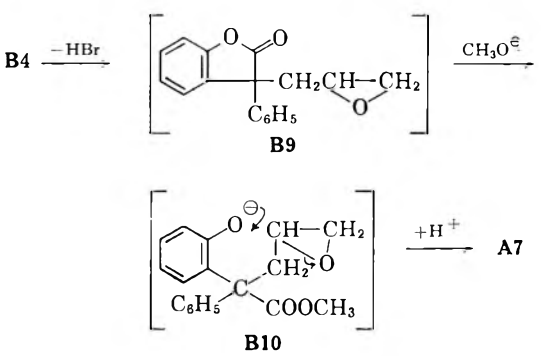
(8) The presence of the epoxide ring in **A3** and **B3** could not be demonstrated unequivocally by the near infrared correlation at 1.63 μ because of the cyclopropyl ring in the same molecule (the 1.63-μ band is characteristic of a —CH$_2$— group in a three-membered ring).[9] However, the intensity of this absorption in both **A3** and **B3** was distinctly greater than that in IV, suggesting the presence in them of more than one three-membered ring.

The observed >C=N— absorption at 5.80 μ in both **A3** and **B3** is consistent with its occurrence at 5.87–5.88 μ in **A2** and **B2**. By analogy, lactone carbonyl absorption in benzofuranones (*e.g.*, I) occurs at 5.55 μ compared to 5.65 μ characteristic of saturated five-membered lactones.

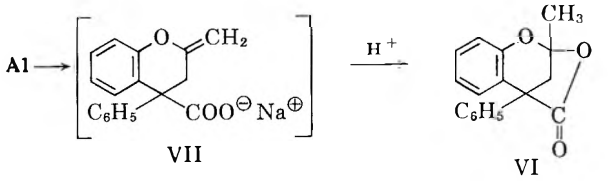
(9) W. H. Washburn and M. J. Mahoney, *J. Am. Chem. Soc.*, **80**, 504 (1958).

(10) The infrared spectra of **A2** and **A5** were nearly superimposable. This reaction with hydrogen chloride can be regarded as a concerted intramolecular process just the reverse of the one pictured[7] (**A3** from **A2**).

and the chloro analog **A6** all showed hydroxyl and carbonyl absorption in the infrared singularly characteristic[11] of this hydroxy lactone system. The *cis* isomer **A4**, like **A6**, led, as expected, to the bridged lactone V (65% yield). However, the *trans* isomer **B4**, with sodium methoxide, produced a hydroxy ester, **A7**, which could not be isolated in pure form but was saponified to the corresponding hydroxy acid **A8**, identical with a sample prepared from the bromo ester **A1** and different from the isomeric hydroxy acid **B8** derived from **B1**. Since it is highly unlikely that any, let alone total, inversion occurred in both processes **A1** → **A8** and **B1** → **B8**, this means that in going from **B4** to **A7** an inversion has occurred.[3] A reasonable mechanism to account for this involves the intermediacy of an epoxy lactone **B9** formed in the same way[7] as the epoxy imidates **A3** and **B3**. Attack of methoxide ion at the carbonyl group of **B9** followed by intramolecular reaction of the expelled phenoxide ion at the asymmetric epoxide carbon atom (accompanied by inversion, *i.e.*, **B10**) would produce the hydroxy ester, **A7**, of observed configuration.



Worthy of incidental note is the formation of the bridged lactone VI[6] as a by-product (31% yield) in the saponification of the bromo ester **A1**. Very likely it is produced as a result of combined dehydrobromination and hydrolysis to the salt of the unsaturated acid VII which, after acidification, cyclizes spontaneously to VI. Although the lactone VI could be formed from **B1** as well as from **A1**, none of it was isolated from this source. This suggests that bromide replacement in **B1** is anchimerically assisted by its ability to form the bridged δ-lactone[2] once the carboxylate ion is generated from the ester. Thus it competes more effectively than **A1** with the elimination reactions.



Experimental

***cis*-5-Bromomethyl-N-cyclopropyl-3-(*o*-hydroxyphenyl)-3-phenyl-2-tetrahydrofuranoneimine (A2).**—To a solution of 410 g. (1.0 mole) of 3-(2′,3′-dibromopropyl)-3-phenyl-2-benzofuranone (**A**), m.p. 137–138°,[2] in 2 l. of dry benzene was added, in a steady stream with stirring at 30°, 125 g. (2.2 moles) of cyclopropylamine. No heat of reaction was detectable. After stirring for 2 hr., the mixture was allowed to stand at room temperature for 1 week.

The precipitated cyclopropylamine hydrobromide (116 g., 84%, m.p. 149–153°) was removed by filtration and washed with benzene. The combined filtrate and washings were concentrated to dryness under reduced pressure. The oily residue was taken up in 500 ml. of chloroform and treated with 20% aqueous hydrochloric acid until no more salt precipitated. This salt was collected at the filter and washed with more chloroform. The combined filtrate and washings were separated from the aqueous layer and concentrated to dryness on the steam bath in order to recover unchanged dibromide A (49 g., 12%, m.p. 135–137°).

The crude hydrochloride was suspended in chloroform and treated with excess 20% aqueous sodium hydroxide. Separation and concentration of the chloroform solution to dryness gave a viscous oil which solidified. Two recrystallizations from 350–400 ml. of absolute ethanol gave **A2** (249 g., 64% conversion, 73% yield) of sufficient purity (m.p. 110–115°) for further use. A sample was recrystallized several more times to a constant m.p. 116–117°; $\lambda_{max}^{CHCl_3}$ (μ) 3.9 (broad and weak), 5.87 (s).

Anal. Calcd. for $C_{20}H_{20}BrNO_2$: C, 62.17; H, 5.22; N, 3.63. Found: C, 62.11; H, 5.47; N, 3.52.

A2 hydrochloride has m.p. 201–203° (from ethanol); λ_{max}^{Nujol} (μ) 5.97 (s).

Anal. Calcd. for $C_{20}H_{21}BrClNO_2$: C, 56.81; H, 5.00; N, 3.31. Found: C, 56.50; H, 5.00; N, 3.27.

A2 hydrobromide has m.p. 223–224° (from ethanol).

Anal. Calcd. for $C_{20}H_{21}Br_2NO_2$: C, 51.41; H, 4.53; N, 3.00. Found: C, 51.98; H, 4.66; N, 3.03.

***trans*-5-Bromomethyl-N-cyclopropyl-3-(*o*-hydroxyphenyl)-3-phenyl-2-tetrahydrofuranoneimine (B2).**—Application of the foregoing procedure to the diasterioisomeric dibromopropylbenzofuranone (B), m.p. 99–101°, gave a 58% yield of the *trans*-imidate **B2**, m.p. 146–147° (from ethanol); $\lambda_{max}^{CHCl_3}$ (μ) 3.9 (broad and weak), 5.88 (s).

Anal. Calcd. for $C_{20}H_{20}BrNO_2$: C, 62.17; H, 5.22; N, 3.63. Found: C, 62.29; H, 5.23; N, 3.43.

N-Cyclopropyl-3-(2′,3′-epoxypropyl)-3-phenyl-2-benzofuranoneimine (M.p. 132–136°) (B3).—A solution of 3.5 g. (0.009 mole) of the cyclic imidate **B2** in 50 ml. of dry 1,2-dimethoxyethane was refluxed and stirred for 16 hr. with 0.5 g. (0.009 mole) of sodium methoxide. The mixture was then concentrated to dryness under reduced pressure, treated with 50 ml. of water, and extracted with chloroform. From the chloroform layer, after separation and concentration to dryness, was obtained a semisolid product (2.7 g.) which was recrystallized three times from 95% ethanol to give the epoxide **B3** (1.6 g., 58%), m.p. 132–136°; $\lambda_{max}^{CS_2}$ 1.63 μ, no NH or OH absorption; $\lambda_{max}^{CHCl_3}$ (μ) 5.80 (s). The infrared spectrum in the 3–8-μ region was qualitatively identical to that of the isomer **A3**.

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.65; H, 6.28; N, 4.59. Found: C, 78.40; H, 5.97; N, 4.39.

4,5-Benzo-7-cyclopropylimino-3,8-dioxa-6-phenylbicyclo[4.2.1]nonane (IV).—Extension of the foregoing procedure to the isomeric cyclic imidate **A2**, m.p. 116–117° (105.2 g., 0.272 mole), using 15.1 g. (0.28 mole) of sodium methoxide in 325 ml. of 1,2-dimethoxyethane gave 71.9 g. (86%) of IV, m.p. 186–188°. Recrystallization of a sample from dry ethanol to constant melting point gave pure IV, m.p. 190–191°; $\lambda_{max}^{CHCl_3}$ (μ) 1.63 (cyclopropyl-CH_2), 5.90 (s), no NH or OH absorption; 60-Mc. chemical shifts (c.p.s.) from tetramethylsilane in deuteriochloroform solution with relative areas in parentheses, assuming 9 aromatic protons: 25–50 (4), 123–181 (2), 181–225 (1), 225–283 (2), 283–302 (1), 388–480 (9, assumed) (total area corresponds to 19 protons).

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.65; H, 6.28; N, 4.59; O, 10.48. Found: C, 78.61; H, 6.06; N, 4.51; O, 10.58.

N-Cyclopropyl-3-(2′,3′-epoxypropyl)-3-phenyl-2-benzofuranoneimine (M.p. 98–100°) (A3).—A solution of 20.8 g. (0.054 mole) of cyclic imidate **A2** in 75 ml. of dry methanol was stirred for 4 days at room temperature with an equivalent quantity of sodium methoxide. Filtration of the reaction mixture gave directly, 7.6 g. (46%) of the bridged imidate IV, m.p. 189–190°. The filtrate was concentrated to dryness under reduced pressure and the residue was taken up in a mixture of ether (150 ml.) and water. The ether layer was separated, washed with two portions (30 ml.) of cold 10% hydrochloric acid, dried (anhydrous magnesium sulfate, and concentrated to dryness. The residual oil (5.5 g., 33%) solidified, m.p. 95–100°, and a sample was recrystallized twice from 95% ethanol to give the epoxide **A3**, m.p. 98–100°; $\lambda_{max}^{CS_2}$ 1.63 μ, no NH or OH absorption; $\lambda_{max}^{CHCl_3}$ (μ) 5.80 (s).

(11) H. E. Zaugg, R. W. DeNet, R. J. Michaels, W. H. Washburn, and F. E. Chadde, *J. Org. Chem.*, **26**, 4753 (1961).

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.65; H, 6.28; N, 4.59. Found: C, 78.47; H, 6.28; N, 4.38.

trans-**5-Bromo-4-hydroxy-2-(*o*-hydroxyphenyl)-2-phenylvaleric Acid γ-Lactone (B4)**—A mixture of 5.9 g. (0.015 mole) of the *trans*-cyclic imidate **B2**, 40 ml. of 12% aqueous hydrobromic acid, and 10 ml. of glacial acetic acid was heated on the steam bath for 5 hr. The mixture was concentrated to dryness under reduced pressure, the residue was taken up in benzene, washed with three portions of water, and concentrated once more to dryness. The residue (4.5 g., 85%, m.p. 110–115°) was recrystallized three times from a benzene–hexane mixture to give 2.1 g. of the γ-lactone **B4**, m.p. 120° to a turbid melt clearing at 133°; $\lambda_{max}^{CHCl_3}$ (μ) 2.8 (w), 3.0 (w), 5.65 (m) (sh), 5.74 (s), 6.21 (w), 6.33 (w), 6.74 (m). (This combination of bands is nearly identical to that found[11] for the corresponding lactone, lacking only the bromomethyl group of **B4**.)

Anal. Calcd. for $C_{17}H_{15}BrO_3$: C, 58.81; H, 4.36; O, 13.82. Found: C, 58.97; H, 4.46; O, 13.94.

cis-**5-Bromo-4-hydroxy-2-(*o*-hydroxyphenyl)-2-phenylvaleric Acid γ-Lactone (A4)**.—Treatment of 8.5 g. (0.22 mole) of the *cis*-cyclic imidate **A2** according to the foregoing procedure, gave 2.7 g. (26%) of unchanged **A2** isolated as the hydrobromide, m.p. 222–223°, and 3.7 g. (49%) of **A4**, m.p. 201–203° (from ethanol; insoluble in chloroform); λ_{max}^{Nujol} (μ) 2.98 (m), 5.72 (s). (The weak absorption at 2.8 μ and the shoulder at 5.65 μ which appear in chloroform solution are absent in the solid spectra of these lactones. This is consistent with the view that, in the solid phase, these substances exist entirely in the >C=O· · · HO— bonded form).[11]

Anal. Calcd. for $C_{17}H_{15}BrO_3$: C, 58.81; H, 4.36; O, 13.82. Found: C, 59.09; H, 4.53; O, 14.21.

cis-**5-Chloromethyl-N-cyclopropyl-3-(*o*-hydroxyphenyl)-3-phenyl-2-tetrahydrofuranoneimine (A5)**.—A solution of 2.7 g. (0.0088 mole) of the epoxide **A3**, m.p. 98–100°, in dry ether was treated with excess ethereal hydrogen chloride. The precipitated salt was collected at the filter and recrystallized twice from a dry ethanol–ether mixture to give 2.3 g. (69%) of **A5** hydrochloride, m.p. 199–200°; λ_{max}^{Nujol} (μ) 6.00 (s).

Anal. Calcd. for $C_{20}H_{21}Cl_2NO_2$: C, 63.49; H, 5.30; N, 3.71; Cl (total), 18.74; Cl (ionic), 9.37. Found: C, 63.51; H, 5.54; N, 3.78; Cl (total), 18.64; Cl (ionic), 9.16.

Treatment of an aqueous solution of the hydrochloride (0.8 g.) with sodium bicarbonate precipitated the corresponding base which was recrystallized from 95% ethanol to give pure **A5** (0.5 g., 70%), m.p. 105–106°; $\lambda_{max}^{CHCl_3}$ (μ) 3.9 (broad and weak), 5.87 (s). Except for slight differences in the 9–10-μ region its infrared spectrum (chloroform) was qualitatively identical to that of the corresponding bromo analog **A2**.

Anal. Calcd. for $C_{20}H_{20}ClNO_2$: C, 70.27; H, 5.89; N, 4.10; Cl, 10.38. Found: C, 70.14; H, 6.13; N, 4.21; Cl, 10.32.

cis-**5-Chloro-4-hydroxy-2-(*o*-hydroxyphenyl)-2-phenylvaleric Acid γ-Lactone (A6)**.—A solution of 1.5 g. (0.004 mole) of **A5** hydrochloride, m.p. 199–200°, in 15 ml. of 10% hydrochloric acid and 3 ml. of glacial acetic acid was heated on the steam bath for 5 hr. Cooling, collecting the product at the filter, and washing with water gave a crude product (1.1 g., 91%, m.p. 195–198°). Two recrystallizations from 95% ethanol gave pure **A6** (0.9 g.), m.p. 197–198° (m.m.p. with **A5** hydrochloride, 170–185°); $\lambda_{max}^{CHCl_3}$ (μ) 2.8 (w), 3.0–3.1 (w), 5.64 (m) (sh), 5.73 (s); λ_{max}^{Nujol} (μ) 2.99 (m), 5.71 (s). [This combination of bands and the effect on them of phase change (chloroform → Nujol) is, as indicated above under **A4** and **B4**, typical of the hydroxy lactone system common to all three compounds.][11]

Anal. Calcd. for $C_{17}H_{15}ClO_3$: C, 67.43; H, 4.99; Cl, 11.67; O, 15.85. Found: C, 67.33; H, 4.96; Cl, 11.43; O, 16.13.

3-Hydroxy-5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylic Acid γ-Lactone (V). A. From the Bridged Imidate IV.—A mixture of 30 g. (0.098 mole) of IV, 300 ml. of 10% hydrochloric acid, and 50 ml. of glacial acetic acid was stirred and refluxed for 16 hr. and then worked up as in the foregoing procedure. There was obtained 25.3 g. (97%) of crude lactone, m.p. 168–172°. Recrystallization of a sample from 95% ethanol gave pure V, m.p. 171–172°; $\lambda_{max}^{CHCl_3}$ (μ) 5.63 (s); $\lambda_{max}^{C_2H_5OH}$ (mμ) 265 (ε 760), 273 (ε 680); for the n.m.r. spectrum see Table I.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30; O, 18.03. Found: C, 76.67; H, 5.50; O, 17.83.

B. From the Bromo Lactone A4.—Treatment of 1.8 g. (0.0052 mole) of **A4** with an equivalent of sodium methoxide in 1,2-dimethoxyethane, exactly as described for the preparation of compound **B3**, gave 0.90 g. (65%) of the bridged lactone V, m.p. 169–170°, identical (infrared spectrum and mixture melting point) with the material prepared from the bridged imidate IV.

C. From the Chloro Lactone A6.—Likewise, 0.54 g. (0.00178 mole) of **A6**, treated with sodium methoxide in 1,2-dimethoxyethane in the usual way, gave 0.31 g. (65%) of the bridged lactone V, identical with the material obtained from IV.

Proton Magnetic Resonance Spectrum of the Bridged Lactone V.—The complex spectrum, peak assignments, and relative integrated areas (assuming 9 aromatic hydrogens) are summarized in Table I. It is apparent that the spectrum is consistent with the assigned structure.

TABLE I

Multiplet centers, τ	Assignment, *cf.* V	Relative area
2.25, 2.62, 2.94, 3.54	Aromatic H's	9 (assumed)
5.07	—CH—O—C=O	1
5.54, 5.94	—O—CH_2—C—O—C=O	2
7.05, 7.12	—C—CH_2—C—O—C=O	2

trans-**2-Hydroxymethyl-4-phenyl-4-chromancarboxylic Acid (A8)**.—Treatment of 3.5 g. (0.01 mole) of the *trans*-bromo lactone **B4** with an equivalent of sodium methoxide in 1,2-dimethoxyethane as described for the preparation of **B3** gave 1.4 g. of a glassy substance which could not be crystallized but whose infrared spectrum indicated that it was a hydroxy ester: $\lambda_{max}^{CHCl_3}$ (μ) 2.83 (OH), 5.80 (ester >C=O). This glass was refluxed in 15 ml. of 10% aqueous potassium hydroxide for 36 hr., cooled, extracted with ether to remove a little insoluble material, and acidified with concentrated hydrochloric acid. Isolation in the usual way gave the crude hydroxy acid (1.1 g., m.p. 170–175°), which was crystallized three times from a 2-butanone–pentane mixture to give pure **A8** (0.4 g.), m.p. 189–190°; λ_{max}^{Nujol} (μ), 2.99 (w) 5.88 (s).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67; O, 22.51. Found: C, 72.01; H, 5.75; O, 22.39.

2-Hydroxy-2-methyl-4-phenyl-4-chromancarboxylic Acid γ-Lactone (VI) and A8 from the *trans*-Bromo Ester A1.—A suspension of 2.2 g. (0.006 mole) of methyl *trans*-2-bromomethyl-4-phenyl-4-chromancarboxylate (**A1**)[2] in 18 ml. of 10% aqueous potassium hydroxide was refluxed for 48 hr. The reaction mixture was worked up as in the foregoing procedure to obtain 1.7 g. of a glass which crystallized on trituration with aqueous methanol. Recrystallization from aqueous ethanol gave 0.5 g. (31%) of pure VI, m.p. 132–133°; $\lambda_{max}^{CHCl_3}$ (μ), 5.60 (s), no hydroxyl or carboxyl absorption; for the n.m.r. spectrum see Table II.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30; O, 18.03. Found: C, 76.40; H, 5.50; O, 17.75.

From the filtrate was obtained 0.5 g. (28%) of crude hydroxy acid **A8**, m.p. 180–184°. Two recrystallizations from a 2-butanone–pentane mixture gave 0.3 g. of pure **A8**, m.p. 189–190°, shown by elemental analysis, mixture melting point, and infrared spectrum to be identical with the sample prepared from the bromo lactone **B4**.

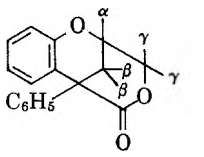
Proton Magnetic Resonance Spectrum of the Bridged Lactone VI.—Table II summarizes the data assuming that 9 aromatic hydrogens are present in the molecule.

TABLE II

Single peaks, τ	Assignment, *cf.* VI	Relative area
2.3–3.0	Aromatic H's	9 (assumed)
7.32	—C—CH_2—C—	2
8.08	CH_3	3

The occurrence of methyl absorption as a single peak is in accord with the assigned structure. However, the absence of

mutual spin–spin splitting by the methylene hydrogens is unexpected. Nevertheless, it is in line with the surprisingly simple spectrum of the following isomeric lactone.[2]



In this case, both β-CH_2 and γ-CH_2 absorptions occur as two doublets (J = 2.8 c.p.s.) centered at 7.63 and 5.37 τ, respectively, and the α-CH appears as a quintet (J = 2.8 c.p.s.) centered at 5.25 τ. This shows that neither the β-CH_2 nor the γ-CH_2 protons undergo appreciable mutual spin–spin splitting in this molecule.

cis-2-Hydroxymethyl-4-phenyl-4-chromancarboxylic Acid (B8). —A suspension of 1.8 g. (0.005 mole) of methyl *cis*-2-bromomethyl-4-phenyl-4-chromancarboxylate (B1)[2] in 15 ml. of 10% aqueous potassium hydroxide was refluxed for 64 hr. Isolation in the usual manner gave 1.2 g. (89%, m.p. 173–176°) of crude product which was recrystallized twice from aqueous ethanol to give pure *cis*-hydroxy acid B8 (0.77 g.), m.p. 176–177°; λ_{max}^{Nujol} (μ) 2.95 (w), 5.87 (s).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67; O, 22.51. Found: C, 71.44; H, 5.79; O, 22.58.

Acknowledgment —Grateful appreciation is due Mr. W. H. Washburn for the infrared spectra; Dr. T. F. Page, Jr., Battelle Memorial Institute, Dr. R. W. Mattoon, and Dr. J. Tadanier for the n.m.r. spectra and for aid in their interpretation; and Mr. E. F. Shelberg and Mr. O. Kolsto for the microanalyses.

The Reaction of Oxalyl Chloride with Amides. II. Oxazolidinediones and Acyl Isocyanates

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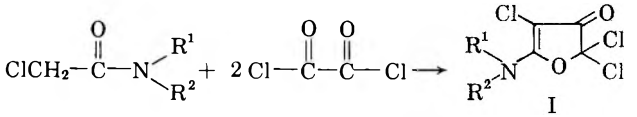
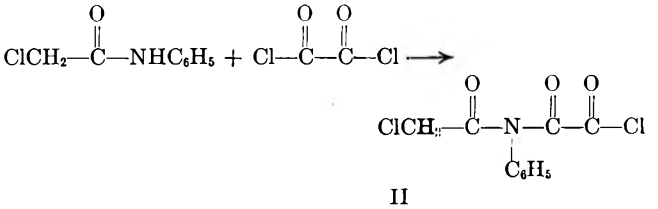
The reaction of oxalyl chloride with N-monosubstituted amides has been shown to yield acyloxamic acid chlorides or 2-methyleneoxazolidine-4,5-diones depending on the structure of the amide and experimental conditions. Treatment of primary amides with oxalyl chloride was found to be a general preparation of acyl isocyanates. A mechanism for the reaction of oxalyl chloride with various amides is discussed.

The reaction of oxalyl chloride with N,N-disubstituted chloroacetamides has been shown to yield trichlorofuranone amines I.[1]



I

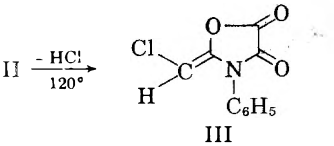
Since the formation of furanone amines would be very unlikely from N-monosubstituted chloroacetamides and oxalyl chloride, it was of interest to determine the course of this reaction. Interaction of α-chloroacetanilide and oxalyl chloride in carbon tetrachloride at 60° for twenty-four hours led to the isolation of N-chloroacetyloxanilic acid chloride (II).



II

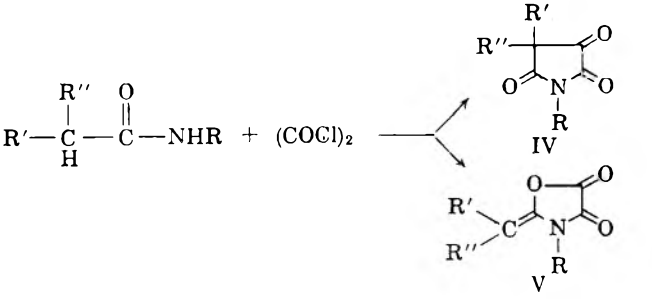
It exhibited carbonyl absorption at 1855, 1840, and 1765 cm.$^{-1}$ (Nujol) but none in the NH region. Treatment of II with methanol gave methyl N-chloroacetyl oxanilate which absorbed in the infrared at 1768, 1748, and 1720 cm.$^{-1}$ (chloroform). N.m.r. spectrum of the ester showed the presence of five protons with a complex aromatic absorption centered at 2.55 τ, two protons in a singlet at 5.90 τ, and three protons in a singlet at 6.11 τ.

On heating II at 120° for 5 min., hydrogen chloride was evolved and III was isolated. III had infrared absorption at 1827, 1745, and 1682 cm.$^{-1}$ (Nujol) with bands indicative of a vinyl proton at 3100 and 862 cm.$^{-1}$. Ultraviolet maxima were found at 235 mμ (log ϵ 3.62) and 300 mμ (log ϵ 3.82). Its n.m.r. spectrum showed the five aromatic protons centered at 2.43 τ and a singlet, perhaps due to a vinyl proton, at 4.75 τ. On the basis of the foregoing data, the structure of the compound is formulated as 2-chloromethylene-3-phenyloxazolidine-4,5-dione (III).



III

The reaction of oxalyl chloride with N-monosubstituted acetamide derivatives has led to some controversy. Figee[2] first reported that the products were pyrrolidinetriones IV without apparent justification or consideration of isomeric structures. Since the product from the reaction of oxalyl chloride and acetanilide was easily hydrolyzed to acetic acid and oxanilic acid, Stolle and Luther[3] considered the product to be the



IV V

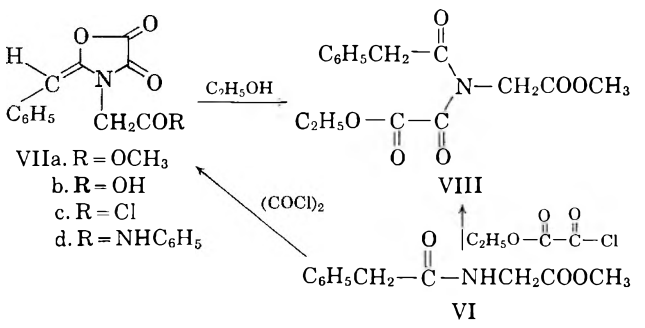
(1) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 4361 (1962).

(2) T. Figee, *Rec. trav. chim.*, **34**, 289 (1915).

(3) R. Stolle and M. Luther, *Ber.*, **53**, 314 (1920).

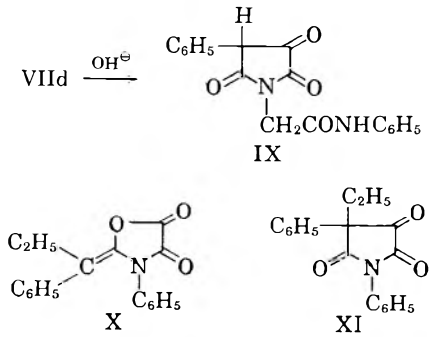
oxazolidinedione V (R′ = R″ = H, R = C_6H_5) rather than the alternate pyrrolidinetrione IV.

Spielman[4] reported that ethanolysis of the reaction product from oxalyl chloride and methyl phenaceturate (VI) led to VIII which was identical with the compound produced from VI and ethoxalyl chloride. The oxalyl chloride reaction product VIIa was assigned, therefore, the oxazolidinedione structure.

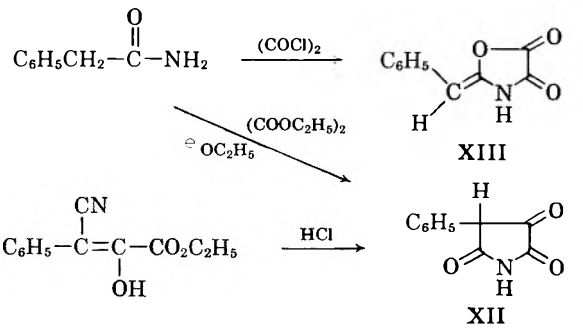


A series of twenty-five compounds was prepared by Skinner and Perkins[5] by the action of oxalyl chloride on amides. The assignment of the pyrrolidinetrione structure was based on infrared absorption at 5.6, 5.8, and 6.0 μ (1786, 1724, and 1667 cm.$^{-1}$) interpreted as three carbonyl bands. In addition, the reaction of oxalyl chloride with 2-phenylbutyranilide led to two crystalline isomers having similar infrared absorption. These were reported as multifunctional *cis–trans* isomers of 1,4-diphenyl-4-ethylpyrrolidinetrione.

Sheehan and Corey,[6] in the course of their work on penicillin synthesis,[7] examined the infrared spectra of several derivatives of the product (type VII) from the reaction of phenaceturic acid and oxalyl chloride. They felt that the absorptions at 5.50, 5.73, and 5.95 μ (1818, 1745, and 1681 cm.$^{-1}$) were in better agreement with oxazolidinediones than pyrrolidinetriones. Treatment of the anilide VIId with aqueous sodium hydroxide solution gave a compound isomeric with the starting material. The isomeric product was formulated as the pyrrolidinetrione IX because it possessed two bands at 5.62 and 5.88 μ (1779 and 1701 cm.$^{-1}$). It was further suggested that the "multifunctional *cis–trans* isomers" of Skinner and Perkins[5] were actually the oxazolidinedione X and the pyrrolidinetrione XI, since the former showed a band at 6.0 μ (1667 cm.$^{-1}$) and the latter did not.



Skinner[8] acknowledged that the previously reported pyrrolidinetriones[5] were in reality oxazolidinediones but stated that the formation of isomers having different reaction characteristics is not absolute proof of the structure of either. He then demonstrated that the pyrrolidinetrione XII, prepared from ethyl β-cyano-α-hydroxycinnamate and hydrogen chloride or from phenylacetamide and ethyl oxalate, was not identical with the oxazolidinedione XIII prepared from phenylacetamide and oxalyl chloride.

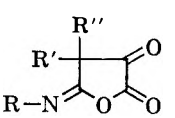


In most instances, including the 2-ethylbutyranilide case, the crude oxalyl chloride reaction products were recrystallized from ethanol. The isomerization of a series of oxazolidinediones to pyrrolidinetriones by boiling in ethanol subsequently was reported.[9]

Although the preceding work indicates that the oxazolidinedione structure is reasonable for the products of the reaction of amides with oxalyl chloride, conclusive proof is lacking. Hydrolysis data are not convincing since, in some cases,[9] pyrrolidinetriones and oxazolidinediones yield the same amides. For example, we have observed that the isomeric products formed on interaction of 2-ethylbutyranilide and oxalyl chloride both give 2-ethylbutyranilide on alkaline hydrolysis. The isolation of oxamic and acetic acid derivatives on hydrolysis of the oxalyl chloride reaction products substantiates the oxazolidinedione structure since the formation of these products from a pyrrolidinetrione would involve the unlikely cleavage of a carbon–carbon bond. However, the pyrrolidinetrione ring represents an especially reactive 1,3-dicarbonyl system and unexpected hydrolysis behavior could conceivably occur.[6] Finally, the facile isomerization of oxazolidinediones in ethanol makes it difficult to determine which isomer is present in hydroxylic solvents. The alcoholysis experiments[4] are, therefore, also inconclusive.

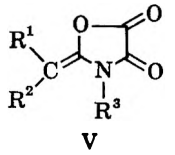
The infrared evidence is compelling but the differences between two carbonyl groups and a carbon–carbon double bond (oxazolidinediones) and three carbonyl groups (pyrrolidinetriones) appear to be subtle and misinterpreted easily.

The isolation of isomers[6,8] as a proof of structure must be rejected regardless of their method of synthesis. They could be *cis-trans* isomers of oxazolidinediones rather than isomeric five-membered rings.[6] The ketoimine XIV has not been considered by previous



(4) M. A. Spielman, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 239.
(5) G. S. Skinner and J. F. Perkins, *J. Am. Chem. Soc.*, **72**, 5569 (1950).
(6) J. C. Sheehan and E. J. Corey, *ibid.*, **74**, 360 (1952).
(7) J. C. Sheehan, E. L. Buble, E. J. Corey, G. D. Laubach, and J. J. Ryan, *ibid.*, **72**, 3828 (1950).
(8) G. S. Skinner and C. B. Miller, *ibid.*, **75**, 977 (1953).
(9) G. S. Skinner and R. E. Ludwig, *ibid.*, **78**, 4656 (1956).

TABLE I
2-METHYLENEOXAZOLIDINE-4,5-DIONES



V

	R¹	R²	R³	M.p., °C	$\nu_{C=O}$[a] (cm.⁻¹) (Nujol)	$\nu_{C=C}$ (cm.⁻¹) (Nujol)	λ_{max}[b] (log ε) ether
a.	C_2H_5	C_2H_5	C_6H_5	71–72	1805, 1735	1687	235 (3.57), 310 (4.00)
b.	(III)Cl	H	C_6H_5	162–163	1825, 1745	1681	235 (3.62), 300 (3.82)
c.	Cl	Cl	4-$CH_3C_6H_4$	132–133	1838, 1745	1672	230 (3.87), 307 (3.54)
d.	C_6H_5	C_6H_5	C_2H_5[9]	164–165	1820, 1733	1654	242 (4.20), 330 (4.13)

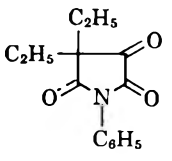
[a] Beckman IR 5A. [b] Beckman DK2.

investigators but a rational mechanism for its formation can be written for both the basis condensation and the oxalyl chloride reaction. The latter could find precedent in our work with N,N-disubstituted amides.

Since the oxazolidinediones–pyrrolidinetriones appear to be easily isomerized[6,8] and since the proof of structure is based mainly on infrared data,[6] the formation of isomers,[6,8] and somewhat inconclusive hydrolysis,[3] aminolysis,[5] and alcoholysis[4] experiments, a conclusive structure proof seemed in order. This is particularly true for the product from chloroacetanilide and oxalyl chloride since it was formed at a higher temperature than those previously reported and was prepared from an isolated intermediate (II). It also contains a chloride atom—the effect of which is unknown.

The enamine chromophore of an oxazolidinedione, fortified by the ester oxygen atom, should provide a significant and conclusive absorption in the ultraviolet. Conversely, the pyrrolidinetriones should not exhibit significant absorption above 220 mμ.

The —N—C—C— system (in ethyl N,N-dimethyloxamate) does not absorb above 220 mμ. Ultraviolet data of the products from the reaction of several amides with oxalyl chloride are shown in Table I.

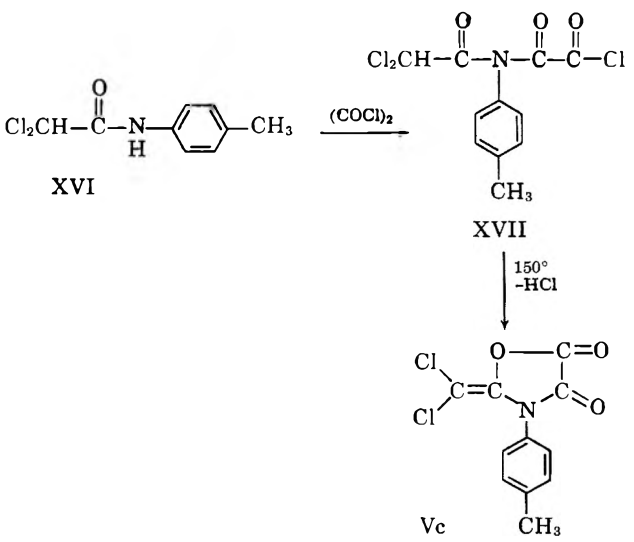


XV

The ultraviolet spectrum of the oxazolidinedione Va (λ_{max} 235 mμ, log ε 3.57, λ_{max} 310 mμ, log ε 4.00) from the reaction of oxalyl chloride with 2-ethylbutyranilide[5,9] compares very favorably with the values of the chloroacetanilide product Vb (III) (λ_{max} 235 mμ, log ε 3.62, λ_{max} 300 mμ, log ε 3.82). The pyrrolidinetrione XV, prepared by the method of Skinner[9] from Va, exhibited only a maximum at 272 mμ (log ε 3.46).

The n.m.r. spectrum of the oxazolidinedione Va should exhibit nonequivalent ethyl groups since one is shielded by the phenyl group (absorption at higher field) and the other is not (lower field). The product of the reaction showed complex aromatic absorption of five protons centered at 2.55 τ, one ethyl group as a quadruplet at 7.75 τ and a triplet at 8.98 τ and the second ethyl group as a quadruplet at 8.46 τ and a triplet at 9.32 τ. The coupling constants for methyl and methylene groups were 7.5 C/S. Clearly the presence of two *nonequivalent* ethyl groups confirm the oxazolidinedione structure Va. The comparable ultraviolet spectra also confirm that the chloroacetanilide product Vb is an oxazolidinedione. The n.m.r. spectrum of the compound produced by boiling Va in ethanol[9] exhibited complex aromatic absorption of five protons centered at 2.85 τ, absorption of four protons in a quadruplet at 8.15 τ (coupling constant 7.5 C/S), and of six protons in a triplet at 9.04 τ (coupling constant 7.5 C/S). The ethyl groups of this compound are, therefore, equivalent as would be expected for the pyrrolidinetrione XV.

The reaction was extended to monosubstituted dichloroacetamides. Treatment of N-*p*-tolyl-2,2-dichloroacetamide (XVI) with oxalyl chloride at 60° for twenty-four hours gave N-dichloroacetyl-N-*p*-tolyloxamic acid chloride (XVII).



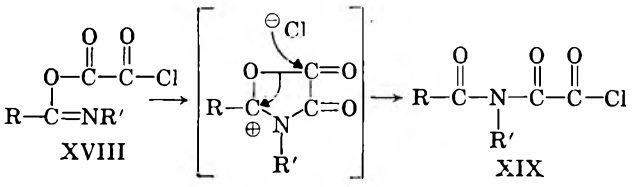
XVI XVII Vc

Acid hydrolysis of XVII led to N-*p*-tolyloxamic acid. The cyclization of XVII occurred less readily than the α-monochloro derivative, 150° for one hour being required.

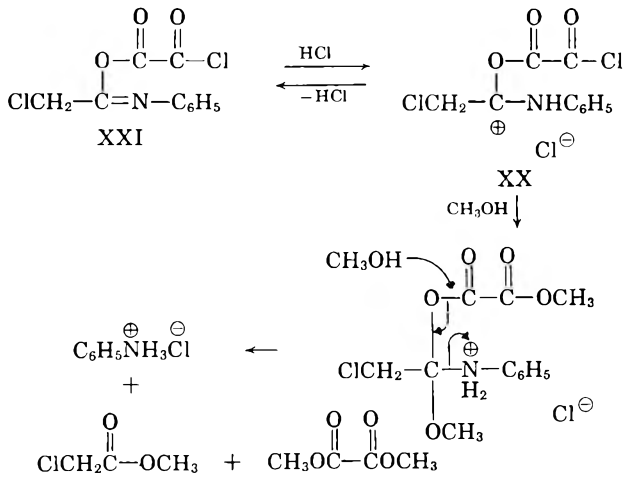
Protonation,[10,11] alkylation,[12,13] and acylation[14] of amides have been shown to occur primarily at the oxygen atom. The formation of acyl oxamic acid chlorides, however, indicates that acylation could also occur at the

(10) W. D. Kumler, *J. Am. Chem. Soc.* **83**, 4983 (1961).
(11) A. R. Katritsky and R. A. Y. Jones, *Chem. Ind.* (London), 722 (1961).
(12) M. Matsui, *Mem. Coll. Sci. Eng. Kyoto*, **2**, 37 (1909–1910).
(13) *Brit. Chem. Abstr.*, **98** (1), 695 (1910).
(14) H. K. Hall, *J. Am. Chem. Soc.*, **78**, 2717 (1956).

nitrogen atom. With oxalyl chloride, the initially formed O-acylated product XVIII can rearrange to the N-acylated product XIX.

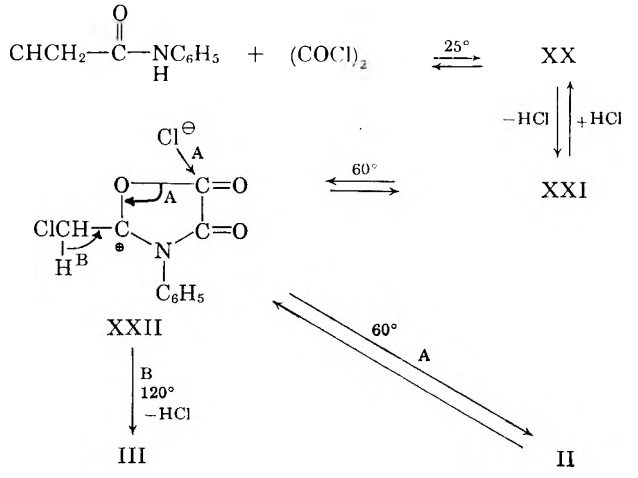


In order to determine where the initial acylation of α-chloroacetanilide occurred, the amide was treated with oxalyl chloride at room temperature and then an excess of methanol was added. The products were methyl oxalate, methyl chloroacetate, and aniline hydrochloride. These must have been formed by way of the O-acylated adduct XX.



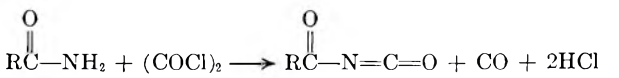
As stated earlier, treatment of the N-acylated II with ethanol gave the ester, methyl N-chloroacetyloxanilate.

The over-all reaction of N-monosubstituted acetamides with oxalyl chloride is visualized as shown for α-chloroacetanilide.



The interaction of oxalyl chloride and chloroacetanilide leads to the O-acylated product XX which loses hydrogen chloride reversibly to form XXI. Cyclization of XXI by N-acylation gives the cyclic intermediate XXII. Attack of chloride ion on the ester carbonyl carbon atom of XXII would open the ring to give the N-acylated product II (path A). At higher temperatures II could react by intramolecular acylation of the amide carbonyl oxygen atom to regenerate XXII which could lose hydrogen chloride irreversibly to produce the oxazolidinedione III (path B). This formulation would explain why α-chloroamides undergo the cyclization with more difficulty than α-alkylamides. The acylation step (II → XXII) would occur more easily with a more nucleophilic carbonyl oxygen atom. Electron-withdrawing chlorine atoms on the α-carbon atom of the amide would reduce the nucleophilicity of the oxygen atom and would thus retard the intramolecular acylation. The formation of the oxazolidinedione from N-ethyl-α,α-diphenylacetamide at temperatures similar to those for the α,α-diethylamide indicates that in the former the oxazolidinedione Vd may be formed directly from an intermediate similar to XXII by the loss of hydrogen chloride (path B) and that the N-acylated product (similar to II) may not be formed at all. This could be explained on the basis of the high acidity of the α-hydrogen atom in the diphenyl case and in the resonance stability of the product. Cyclization in the diphenyl case could also occur *via* the enol.

The reaction was further extended to unsubstituted acetamides. The reaction of chloroacetamide with oxalyl chloride at 80° for twenty-four hours led to the isolation of chloroacetyl isocyanate in 64% yield. This was shown by a strong isocyanate absorption in the infrared spectrum of the product at 2250 cm.$^{-1}$ and by the formation of N-chloroacetyl-N′-(3,4-dichloro-



phenyl)urea on treatment with 3,4-dichloroaniline. Reaction of chloroacetyl isocyanate with water gave chloroacetamide. The formation of acyl isocyanates from primary amides and oxalyl chloride appears to be general and thus constitutes a new and convenient synthesis of acyl isocyanates (Table II).

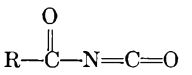
The isocyanates were, in general, too reactive toward atmospheric moisture to be analyzed and were, therefore, characterized as derivatives of 3,4-dichloroaniline. Small yields of diacylureas were isolated as by-products in the preparations of trichloroacetyl and benzoyl isocyanate. These must have been formed by the reaction of the isocyanate with the starting amide. The isolation of diacyl ureas from the reaction of amides with oxalyl chloride has been reported by Bornwater[15] by interaction of one mole of oxalyl chloride with two moles of the amide. The diacylureas, however, may be converted to acyl isocyanates by pyrolysis. For example, the pyrolysis of 1,3-bis(trichloroacetyl)-urea led to trichloroacetyl isocyanate and trichloroacetamide. An attempt to recrystallize 1,3-bis(trichloroacetyl)urea from methanol gave trichloroacetylurea. Authentic samples of trichloroacetylurea and 1,3-bis(trichloroacetyl)urea were prepared by the trichloroacetylation of urea. Attempts to prepare 1,3-dibenzoylurea by treatment of urea with benzoyl chloride led only to the monobenzoyl derivative.

In the reaction of phenylacetamide and diphenylacetamide with oxalyl chloride, yellow solids were isolated which on pyrolysis gave the isocyanates. Skinner[9] also reported the isolation of these intermediates and

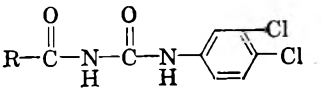
(15) M. J. Bornwater, *Rec. trav. chim.*, **31**, 118 (1912).

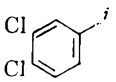
TABLE II

ACYL ISOCYANATES

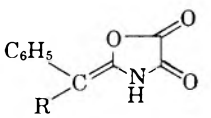


Derivative

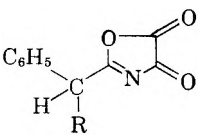


R	Yield, %	B.p., °C. (mm.)	$n_D(T°)$	ν_{NCO} (cm.$^{-1}$) pure liquid	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl
$ClCH_2$–	64[b]	50–55 (20)	1.4580 (21.5)	2250	160[g]	38.39	2.51	9.95	37.78	38.81	2.48	9.94	37.72
Cl_2CH–	68	135 (35)	1.4600 (25)	2250	157–159[g]	34.21	1.91	8.86	44.88	34.71	2.05	8.90	45.25
Cl_3C–	60	80–85 (20)	1.4755 (25)	2250	175[g]	30.84	1.44	8.00	50.59	30.86	1.81	8.11	50.68
$C_6H_5CH_2$–	36[a]	85 (3)[e]	...	2250	205–206[h]	55.74	3.74	8.67	21.94	55.89	3.46	8.68	21.65
$(C_6H_5)_2CH$–	37	136–140 (1–12)	...	2225	206–207[g]	62.85	4.52	6.98	17.69	63.04	3.64	6.98	17.37
	97[c]	105.5 (1.6)	...	2275[d]	259–260.5[h]	...	..	7.41	37.22	...	..	7.33	37.28
C_6H_5–	75	97–98 (23)[f]	1.5472 (25)	2225									

[a] Over-all from two-step reaction including isolation of intermediate. [b] *Anal.* Calcd. for $C_3H_2ClNO_2$: C, 30.15; H, 1.69; N, 11.72. Found: C, 31.03; H, 2.18; N, 11.15. [c] *Anal.* Calcd. for $C_3H_3Cl_2NO_2$: C, 44.45; H, 1.39; N, 6.48; Cl, 32.90. Found: C, 44.35; H, 1.44; N, 6.26; Cl, 33.30. [d] In chloroform. [e] Reported[20] 118° (20 mm.). [f] Reported[20] 90° (20 mm.). [g] Recrystallized from methylene chloride–hexane. [h] Recrystallized from methanol. [i] Benzoylurea identical with an authentic sample (K and K Laboratories, Jamaica, N. Y.). [j] With P. J. Stoffel.



XXIIIa. R = H
b. R = C_6H_5



XXIV

assigned the benzilideneoxazolidinedione structure XXIII.

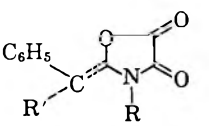
Since oxazolinedione XXIV is also possible for these compounds, their ultraviolet spectra were examined. The results appear in Table III. The similarity of the spectra of the N-substituted oxazolidinediones (R = C_2H_5 or CH_3), which must have the enamine form, to those of the unsubstituted compounds (R = H) is sufficient to conclude that the enamine form XXIII is correct. For comparison, ultraviolet data for some model enamines are given in Table IV. The spectra of the oxazolidinediones XXIII are comparable to those of the enamines. The bathochromic shift of 30 mμ produced by the ester oxygen atom of the oxazolidinediones is not unusual.[16]

The oxalyl chloride method appears superior to the only other reported preparation of acyl isocyanates which involves the reaction of acyl chlorides with silver cyanate.[20] This new method should be superior to the silver cyanate method when compounds sensitive to silver salts are involved (*i.e.*, α-halo carbonyl compounds).

The preparation of alkyl or aryl isocyanates from the reaction of amines with phosgene is not applicable to the preparation of acyl isocyanates since the reaction of primary amides with phosgene has been shown to yield nitriles[21] and complex mixtures. O-Acylation

TABLE III

ULTRAVIOLET SPECTRA OF BENZILIDENEOXAZOLIDINE-4,5-DIONES

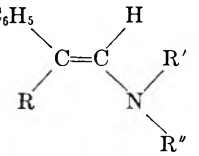


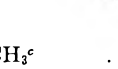
R'	R	λ_{max} (log ε) ether
H	H	240 (4.12), 330 (4.16)
C_6H_5	H	244 (4.20), 338 (4.11)
C_6H_5	C_2H_5	242 (4.20), 330 (4.13)
H	CH_3	... 330 (4.13)[a]

[a] See ref. 4.

TABLE IV

ULTRAVIOLET SPECTRA OF STYRYLAMINES



R	R'	R''	λ_{max} (log ε)	Solvent
H		$(CH_2)_5$[a]	225 (4.04), 295 (4.39)	...
C_6H_5	CH_3	CH_3[b]	... 305 (4.19)	Cyclohexane
C_6H_5	H		... 277 (4.30)	Ether

[a] See ref. 17. [b] See ref. 18. [c] See ref. 19.

(16) E. A. Braude, *Ann. Rept. Progr. Chim.* (*Chem. Soc. London*), **42**, 105 (1945).

(17) R. Dulou, E. Elkik, and A. Veillard, *Bull. soc. chim.*, 967 (1961).

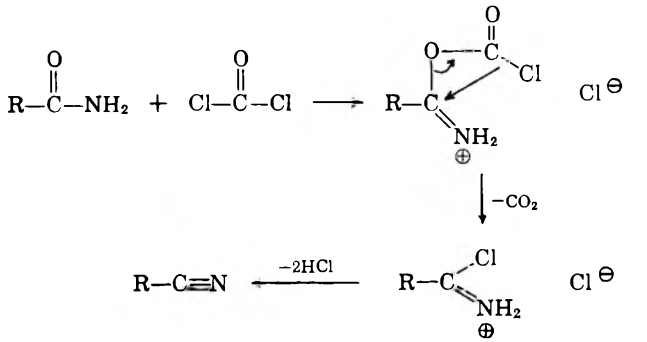
(18) J. A. Kampmeier, Ph.D. thesis, University of Illinois, 1960.

(19) We are indebted to Professor David Y. Curtin for a sample of this material.

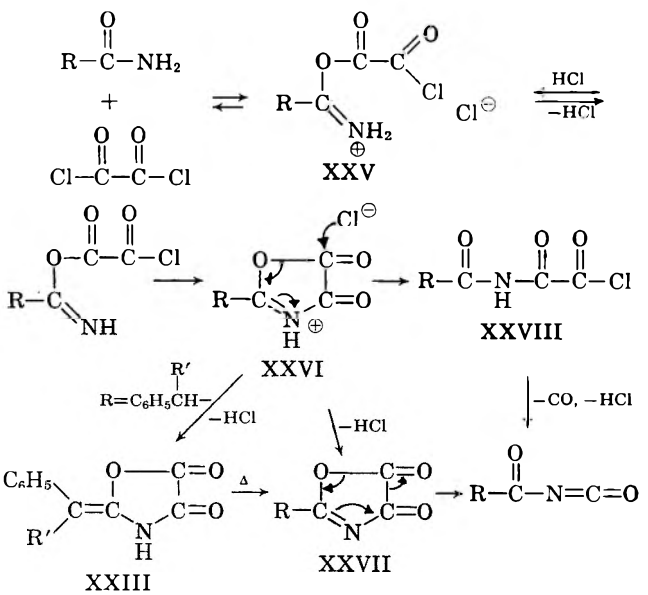
(20) A. J. Hill and W. M. Degnan, *J. Am. Chem. Soc.*, **62**, 1595 (1940).

(21) R. Greenhalgh (to Imperial Chemical Industries, Ltd.), British Patent 488,036 (June 29, 1938).

of the amide with phosgene followed by loss of carbon dioxide yields the imidoyl chloride hydrochloride which is converted to the nitrile by loss of two moles of hydrogen chloride.



This O-acylation occurs also in the reaction of oxalyl chloride with amides, but the initially formed product XXV can rearrange, by way of the cyclic intermediate XXVI. With α-phenyl- and α,α-diphenylacetamides, the α-hydrogen atom is acidic enough to be lost as hydrogen chloride yielding the benzilideneoxazolidinediones XXIII. On pyrolysis the latter may tautomerize to yield XXVII which may, by way of a reverse Diels–Alder type of reaction, yield the isocyanate and carbon monoxide. In the case of derivatives other than the α-phenylacetamides, the hydrogen atom attached to nitrogen may be lost directly giving the isocyanate again by way of the oxazoline XXVII or, alternately, attack of chloride ion could open the ring giving the acyloxamic acid chloride XXVIII which can decompose to yield the isocyanate. There is no evidence for the latter reaction, but since acyl oxamic acid chlorides are formed from reaction of N-monosubstituted amides with oxalyl chloride, they may also be formed with primary amides. An oxanilic acid chloride will indeed yield an isocyanate on pyrolysis. Treatment of oxanilic acid with thionyl chloride (presumably yielding oxanilic acid chloride) led to phenyl isocyanate on distillation.



Some evidence for the initial O-acylation was found in the reaction of chloroacetamide with oxalyl chloride. In this case the reaction was run at low temperature and methanol was added shortly after the oxalyl chloride. The products were ammonium chloride and methyl chloroacetate. These must have been formed from XXV by a mechanism similar to that in the case of chloroacetanilide.

As stated earlier, in the case of monosubstituted amides (*e.g.*, chloroacetanilide) compounds of the type XXVIII (R = $ClCH_2$–, H = C_6H_5) may be isolated and these give the acyloxamic acid ester on treatment with methanol.

Experimental[22]

N-Chloroacetyloxanilic Acid Chloride (II).—A mixture of α-chloroacetanilide (34.3 g., 0.20 mole), oxalyl chloride (28.8 g., 0.23 mole), and carbon tetrachloride (200 ml.) was stirred and heated at 60° for 24 hr. The resulting solution was cooled and evaporated to a semisolid residue. The residue was dissolved in methylene chloride and the solution was treated with charcoal. The addition of hexane caused a yellowish solid to separate. Two recrystallizations from methylene chloride–hexane gave N-chloroacetyloxanilic acid chloride (33.2 g., 0.12 mole, 60%), m.p. 107–109°; $\nu_{C=O}$ ($cm.^{-1}$) 1855, 1840, 1765 in Nujol.

Anal. Calcd. for $C_{10}H_7Cl_2NO_3$: N, 5.39. Found: N, 5.39.

2-Chloromethylene-3-phenyloxazolidine-4,5-dione (III).—N-Chloroacetyloxanilic acid chloride (3.0 g., 0.012 mole) was heated at 120° for 5 min. and was allowed to cool. The solid residue was recrystallized (with charcoal) from methylene chloride–hexane. This produced 2-chloromethylene-3-phenyloxazolidine-4,5-dione (2.1 g., 0.0093 mole, 78%), m.p. 162–163°.

Anal. Calcd. for $C_{10}H_6ClNO_3$: C, 53.72; H, 2.70; N, 6.26; Cl, 15.85. Found: C, 53.28; H, 2.77; N, 6.33; Cl, 16.06.

Reaction of α-Chloroacetanilide with Oxalyl Chloride and Methanol.—A solution of α-chloroacetanilide (17.0 g., 0.10 mole) in methylene chloride (50 ml.) was stirred while oxalyl chloride (25.4 g., 0.20 mole) was added dropwise. The solution was stirred for 4 hr. at room temperature and methanol (110 ml.) was added. The solution was evaporated to dryness and benzene (100 ml.) was added. Filtration separated aniline hydrochloride (10.0 g., 0.077 mole, 77%), m.p. 198°; reported[23] m.p. 198°. Its infrared spectrum was identical with that of an authentic sample.[24] The filtrate was placed on a column of alumina packed wet with hexane. Elution with benzene gave liquid fractions. Distillation of the recombined fractions gave methyl chloroacetate (6.2 g., 0.057 mole, 57%). The infrared spectrum was identical with that of an authentic sample.[24] Recrystallization of the distillation residue (with charcoal) from acetone–water gave dimethyl oxalate (11.1 g., 0.103 mole, 52%). The infrared spectrum was identical with that of an authentic sample.[24]

Methyl N-Chloroacetyloxanilate.—Methanol (0.32 g., 0.01 mole) was added to a solution of N-chloroacetyloxanilic acid chloride (2.6 g., 0.01 mole) in methylene chloride (25 ml.) and the solution was allowed to stand for 1 hr. The methylene chloride was evaporated and recrystallization of the residue from carbon tetrachloride gave methyl N-chloroacetyloxanilate (0.45 g., 0.0018 mole, 18%), m.p. 94°; $\nu_{C=O}$ ($cm.^{-1}$) 1768, 1748, 1720 in chloroform.

Anal. Calcd. for $C_{11}H_{10}ClNO_4$: C, 51.67; H, 3.94; N, 5.48; Cl, 13.87. Found: C, 51.62; H, 3.92; N, 5.44; Cl, 13.84.

N-Dichloroacetyl-N-*p*-tolyloxamic Acid Chloride (XVII).—A mixture of N-dichloroacetyl-*p*-toluidine (15.93 g., 0.073 mole) and benzene (75 ml.) was stirred and heated at 60° while oxalyl chloride (11.5 g., 0.0905 mole) was added dropwise. The mixture was stirred and heated at 60° for 24 hr. The benzene and excess oxalyl chloride were removed *in vacuo* and the residue was recrystallized from methylene chloride–hexane. This produced N-dichloroacetyl-N-*p*-tolyloxamic acid chloride (19.33 g., 0.0625 mole, 86%), m.p. 112.5–114°; $\nu_{C=O}$ ($cm.^{-1}$) 1850, 1765 in chloroform.

Anal. Calcd. for $C_{11}H_8Cl_3NO_3$: C, 42.81; H, 2.62; N, 4.54; Cl, 34.47. Found: C, 42.97; H, 2.67; N, 5.21; Cl, 34.16.

Hydrolysis of N-Dichloroacetyl-N-*p*-tolyloxamic Acid Chloride.—A solution of N-dichloroacetyl-N-*p*-tolyloxamic acid chloride (0.8 g., 0.0026 mole) in acetone (20 ml.) and 20% hydrochloric acid (1 ml.) was allowed to stand for 72 hr. The addition of

(22) Melting and boiling points are uncorrected.
(23) F. Ullmann, *Ber.*, **31**, 1699 (1899).
(24) Eastman Kodak Co., Rochester, N. Y.

water and chilling caused separation of N-*p*-tolyloxamic acid (0.34 g., 0.0019 mole, 73%), m.p. 170°; reported[25] m.p. 168–170°. The infrared spectrum was identical with that of an authentic sample.[25]

2-Dichloromethylene-3-*p*-tolyloxazolidine-4,5-dione (Vc).—N-Dichloroacetyl-N-*p*-tolyloxamic acid chloride (3.0 g., 0.00975 mole) was heated at 150° for 1 hr. and the resulting solid was recrystallized (with charcoal) from methylene chloride–hexane. An additional recrystallization from methylene chloride–hexane gave 2-dichloromethylene-3-*p*-tolyloxazolidine-4,5-dione (1.16 g., 0.0043 mole, 44%), m.p. 132–133°.

Anal. Calcd. for $C_{11}H_7Cl_2NO_3$: C, 48.55; H, 2.59; N, 5.15. Found: C, 49.04; H, 2.64; N, 5.16.

2-Diethylmethylene-3-phenyloxazolidine-4,5-dione (Va.)—A mixture of 2-ethylbutyranilide (38.2 g., 0.20 mole) and benzene (150 ml.) was stirred at 60° while oxalyl chloride (27.0 g., 0.215 mole) was added dropwise. The mixture was refluxed for 24 hr. and the benzene was removed *in vacuo*. Distillation produced a yellowish liquid, b.p. 161–164° (0.4–0.45 mm.), which solidified on standing. Recrystallization from methylene chloride–hexane gave 2-diethylmethylene-3-phenyloxazolidine-4,5-dione (39.9 g., 0.163 mole, 81%), m.p. 71–72°; reported[9] m.p. 70–71°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.62; H, 5.93; N, 5.76.

Acyl Isocyanates.—A mixture of the amide (1 mole) and ethylene dichloride was stirred while oxalyl chloride (1.25 moles) was added rapidly. The mixture was stirred and refluxed for 16 hr. The ethylene dichloride was distilled *in vacuo* and the acyl isocyanate was isolated by distillation under reduced pressure (see Table II).

1,3-Dibenzoylurea.—The distillation residue from the reaction of benzamide (12.1 g., 0.10 mole) and oxalyl chloride was dissolved in hot acetone and the solution was treated with charcoal. On cooling the solution a white solid precipitated. Recrystallization from methanol–benzene produced 1,3-dibenzoylurea (2.5 g., 0.009 mole, 9%), m.p. 228–230°; reported[26] m.p. 221–222°, ν_{NH} (cm.$^{-1}$) 3225, $\nu_{C=O}$ 1754, 1689, 1664 in Nujol.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 66.72; H, 4.06; N, 10.13.

1,3-Bis(trichloroacetyl)urea.—A. From Trichloroacetamide and Oxalyl Chloride.—During the reaction of 2,2,2-trichloroacetamide (8.1 g., 0.05 mole) and oxalyl chloride a white solid precipitated. An equal volume (50 ml.) of hexane was added and the white solid was separated by filtration. Recrystallization from methylene chloride–hexane gave 1,3-bis(trichloroacetyl)urea (3.5 g., 0.01 mole, 20%), m.p. 167–169°; ν_{NH} (cm.$^{-1}$) 3200, $\nu_{C=O}$ 1792, 1718 in Nujol.

Anal. Calcd. for $C_5H_2Cl_6N_2O_3$: C, 17.11; H, 0.62; N, 7.98; Cl, 60.61. Found: C, 17.32; H, 0.82; N, 7.95; Cl, 60.76.

An attempt to recrystallize 1,3-bis(trichloroacetyl)urea from methanol gave trichloroacetylurea, m.p. 158–159°; reported[27] m.p. 150°; ν_{NH} (cm.$^{-1}$) 3365, 3310, 3225, $\nu_{C=O}$ 1724, 1701 in Nujol.

Anal. Calcd. for $C_3H_3Cl_3N_2O_2$: C, 17.54; H, 1.47; N, 13.64; Cl, 51.78. Found: C, 17.67; H, 0.99; N, 13.40; Cl, 51.74.

B. From Urea and Trichloroacetyl Chloride.—A mixture of urea (6.0 g., 0.1 mole), trichloroacetyl chloride (36.4 g., 0.2 mole), and ethylene dichloride (170 ml.) was refluxed for 24 hr. Most of the ethylene dichloride was distilled *in vacuo* and the addition of hexane caused separation of a white solid. Recrystallization from methylene chloride–hexane gave 1,3-bis(trichloroacetyl)urea (23.7 g., 0.088 mole, 88%), m.p. 167–169°. The infrared spectrum was identical with that of the sample prepared as described previously.

Pyrolysis of 1,3-Bis(trichloroacetyl)urea.—When 1,3-bis(trichloroacetyl)urea (8.0 g., 0.03 mole) was heated at 180–190° under reduced pressure (*ca.* 35 mm.), trichloroacetyl isocyanate distilled (1.2 g., 0.0064 mole, 21%). The infrared spectrum was identical with that of a sample prepared as described previously. The distillation residue was treated with hot methylene chloride and filtered to remove a white solid (0.27 g.), m.p. >300°. The filtrate was evaporated to a small volume and the addition of hexane precipitated trichloroacetamide (2.6 g., 0.016 mole, 53%). The infrared spectrum was identical with that of an authentic sample.[24]

Trichloroacetylurea.[27]—A mixture of urea (6.0 g., 0.1 mole), trichloroacetyl chloride (18.2 g., 0.1 mole), and ethylene dichloride (70 ml.) was refluxed for 3 hr. and the ethylene dichloride was removed *in vacuo*. Recrystallization of the residue from methanol gave trichloroacetylurea (6.24 g., 0.03 mole, 30%), m.p. 158–159°. The infrared spectrum was identical with that of the sample prepared as described previously.

Reaction of Chloroacetamide with Oxalyl Chloride and Methanol.—A mixture of α-chloroacetamide (4.7 g., 0.05 mole) and methylene chloride (50 ml.) was stirred for 3 hr. while oxalyl chloride (12.7 g., 0.1 mole) was added dropwise. The solution was refluxed for 1 hr. and the methylene chloride was removed *in vacuo*. The residue was dissolved in methanol and the solution on standing deposited ammonium chloride (1.9 g., 0.035 mole, 70%). Distillation of the filtrate gave methyl chloroacetate (1.5 g., 0.014 mole, 28%). The infrared spectrum was identical with that of an authentic sample.[23]

Reaction of Phenylacetamide and Oxalyl Chloride (XXIIIa).—A mixture of phenylacetamide (13.5 g., 0.1 mole) and ethylene dichloride (75 ml.) was stirred at 0° while oxalyl chloride (13.5 g., 0.103 mole) was added rapidly. The mixture was refluxed for 24 hr. and a yellow solid separated. The yellow solid was isolated by filtration, recrystallized from acetone, and identified as 2-benzilideneoxazolidine-4,5-dione (13.6 g., 0.072 mole, 72%), m.p. 182–184°; reported[8] m.p. 166–167°.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.61; H, 3.63; N, 7.29.

Phenylacetyl Isocyanate.—When 2-benzilideneoxazolidine-4,5-dione (3.3 g., 0.017 mole) was heated *in vacuo* at *ca.* 190–200°, phenylacetyl isocyanate distilled (1.38 g., 0.0086 mole, 50%), b.p. 85° (3 mm.); reported[20] b.p. 118° (20 mm.); $\nu_{N=C=O}$ (cm.$^{-1}$) 2250.

Derivative: N-phenylacetyl-N′-(3,4-dichlorophenyl)urea, from methanol, m.p. 205–206°.

Anal. Calcd. for $C_{15}H_{12}Cl_2N_2O_2$: C, 55.74; H, 3.74; N, 8.67; Cl, 21.94. Found: C, 55.89; H, 3.46; N, 8.68; Cl, 21.65.

2-Diphenylmethyleneoxazolidine-4,5-dione (XXIIIb).—A mixture of 2,2-diphenylacetamide (1.23 g., 0.0058 mole), oxalyl chloride (0.91 g., 0.0072 mole), and benzene (15 ml.) was refluxed for 2 hr. and the benzene was removed *in vacuo*. The solid residue was dissolved in methylene chloride and the solution was treated with charcoal. Chilling and the addition of hexane caused separation of a yellow solid. Recrystallization from methylene chloride–hexane gave 2-diphenylmethyleneoxazolidine-4,5-dione (1.1 g., 0.0043 mole, 74%), m.p. 176–178°; reported[9] 159–160°.

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.13; H, 4.40; N, 5.53. Found: C, 71.92; H, 4.15; N, 5.19.

Pyrolysis of the product yielded 2,2-diphenylacetyl isocyanate. The infrared spectrum was identical with that of a sample prepared as described previously. Slow crystallization of the product from methylene chloride–hexane produced a lighter yellow dimorphic form, m.p. 169–172°. The Nujol infrared spectrum of the dimorph, m.p. 169–172°, is not identical with that of the dimorph, m.p. 176–178°. The infrared spectra of the dimorphs in chloroform and their ultraviolet spectra in ether are identical. The dimorph, m.p. 169–172°, may be converted to the dimorph, m.p. 176–178°, by rapid crystallization from methylene chloride–hexane.

3,3-Diethyl-1-phenylpyrrolidine-2,4,5-trione (XV).—Prepared by the method of Skinner.[9] A white solid, from ethanol–hexane, m.p. 61–62°; reported[9] m.p. 60–61°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 69.34; H, 6.20; N, 5.80.

2-Diphenylmethylene-3-ethyloxazolidine-4,5-dione (Vd).—Prepared by the method of Skinner.[5] A yellow solid from methylene chloride–hexane, m.p. 165–166°; reported[9] m.p. 165–166°.

Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 72.98; H, 4.95; N, 4.70.

Reaction of Oxanilic Acid and Thionyl Chloride.—A mixture of oxanilic acid (8.2 g., 0.05 mole), thionyl chloride (6.0 g., 0.05 mole), and chloroform (70 ml.) was refluxed for 20 hr. The chloroform was removed *in vacuo* and vacuum distillation gave phenyl isocyanate (2.62 g., 0.022 mole, 44%). The infrared spectrum was identical with that of an authentic sample.[24]

(25) H. Klinger, *Ann.*, **184**, 286 (1876).
(26) H. Biltz, *ibid.*, **391**, 181 (1912).
(27) I. A. Pearl and W. M. Dehn, *J. Am. Chem. Soc.*, **61**, 1377 (1939).

Preparation and Reactions of N-Cyanoamidines

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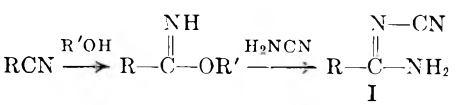
Several N-cyanoamidines were prepared by the reaction of imidates with cyanamide or of amidine hydrochlorides with monosodium cyanamide. Various methods were examined for the conversion of simple N-cyanoamidines to *s*-triazines and other heterocyclic products. Some related reactions of N-carbamoylamidines are reported also.

N-Cyanoamidines (I) rarely have been examined as synthetic intermediates, despite their close structural similarity to cyanoguanidine (I. R = NH_2), a compound which has been extensively studied for over a century.[1] The reaction of N-cyanoformamidine with guanidine to give a good yield of 2,4-diamino-*s*-triazine is apparently the only reported direct conversion of an N-cyanoamidine to a heterocyclic product.[2] The present paper contains the results of an exploratory survey of the preparation of these compounds and their utility as intermediates for the synthesis of nitrogen heterocycles.

Compounds of structure I have been obtained previously from the action of cyanide ion upon N-haloamidines[3] or by treatment of an amidine with cyanogen bromide.[3] N-Cyanoformamidine has been prepared in high yield from the reaction of cyanamide with formamidine[2] or *s*-triazine.[4]

We have prepared several N-cyanoamidines in good yields by the reaction of imidates with cyanamide, a method which has heretofore been reported only for isolated examples of N′-substituted-N-cyanoamidines.[5,6] Simplification of this procedure was possible when R contained an appropriately situated electron-withdrawing group, in that the imidate could then be prepared from the corresponding nitrile by base-catalyzed addition of alcohol.[7] Addition of cyanamide to this solution produced the N-cyanoamidine directly. In

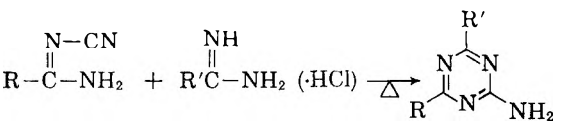


addition to the simple N-cyanoamidines (I. R = CH_3, C_6H_5) employed in the synthetic studies, several other compounds were obtained by this procedure, as shown in Table I.

N-Cyanoacetamidine and N-cyanobenzamidine were also prepared in good yields by the interaction of monosodium cyanamide with the corresponding amidine hydrochloride in aqueous solution. This appears to be an equally good preparative method, notably for cases in which the first procedure would require preparation and isolation of an imidate by the Pinner method.[8]

The N-cyanoamidines were characterized by analyses and infrared absorption spectra. The products showed three strong bands attributed to the amino group at 2.9–3.0, 3.1–3.2, and near 6.0 μ; carbon–nitrogen double bond absorption at 6.3–6.5 μ; and strong nitrile absorption, usually in the form of a doublet centered near 4.55 μ.

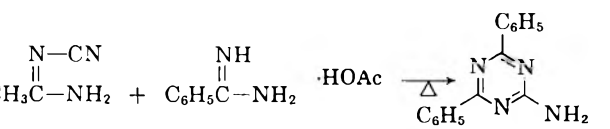
A convenient route to 2,4-diamino-*s*-triazines involves the reaction of cyanoguanidine with nitriles or amidine salts.[9] By analogy, it appeared that N-cyanoamidines might similarly function as useful intermediates for the preparation of monoamino-*s*-triazines. These reactions did occur as anticipated, although isolation of pure products was sometimes difficult.



IIa. R = R′ = C_6H_5
b. R = R′ = CH_3
c. R = CH_3, R′ = C_6H_5
d. R = H, R′ = C_6H_5
e. R = CH_3, R′ = NH_2
f. R = C_6H_5, R′ = NH_2

2-Amino-4,6-diphenyl-*s*-triazine (IIa) was obtained by treating N-cyanobenzamidine with benzonitrile in the presence of sodium hydroxide in refluxing 1-butanol, benzamidine in hot ethanol, or benzamidine hydrochloride at 175° in the absence of solvent, but yields in all three cases were around 15%. Compounds IIb, IIc, and IId were obtained in better yields (25–40%) from reactions using the appropriate combination of an N-cyanoamidine with an amidine hydrochloride at 150–175°. This procedure was found to be the most generally applicable for the conversion of I to monoamino-*s*-triazines, whereas diamino-*s*-triazines (IIe and IIf) were obtained conveniently from N-cyanoamidines with free guanidine in alcoholic solution.

Substitution of benzamidine acetate for benzamidine hydrochloride in the reaction with N-cyanoacetamidine resulted in formation of 2-amino-4,6-diphenyl-*s*-triazine (IIa), rather than the expected 4-methyl-6-phenyl analog. Although there are several possible mechanisms for this transformation, it is evident that the elements of cyanamide must have been lost from the starting N-cyanoamidine at some point.



IIa

(1) See "The Chemistry of Dicyandiamide," American Cyanamid Company, New York, N. Y., 1949.
(2) K. Shirai, K. Odo, and K. Sugino, *J. Org. Chem.*, **23**, 100 (1958).
(3) J. Goerdeler and D. Loevenich, *Ber.*, **86**, 890 (1953).
(4) Unpublished results obtained in this laboratory by I. Hechenbleikner.
(5) W. J. Comstock and H. L. Wheeler, *Am. Chem. J.*, **13**, 514 (1891).
(6) G. Pellizzari, *Gazz. chim. ital.*, **41**, 93 (1911).
(7) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).
(8) A. Pinner, "Die Imidoäther und ihre Derivate," Robert Oppenheim (Gustav Schmidt), Berlin, 1892.
(9) (a) E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience Publishers, Inc., New York, N. Y., 1959, p. 229; (b) E. J. Modest, "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 650.

TABLE I

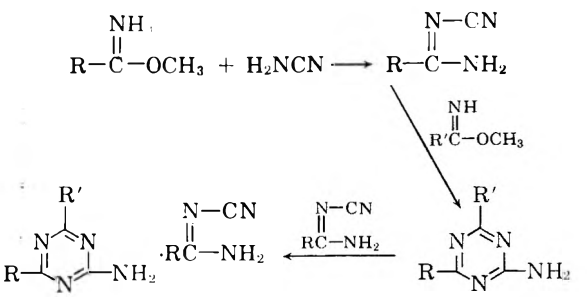
PREPARATION OF N-CYANOAMIDINES FROM IMIDATES AND CYANAMIDE

R	Time at 25°	Yield, %	M.p., °C.	Recrystallization solvent	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	15 min.	72	135–137	C_2H_5OH	$C_3H_5N_3$	43.36	6.07	50.57	43.59	5.96	50.59
C_6H_5	12 hr.	72	142–142.5[a]	C_2H_5OH/H_2O	$C_8H_7N_3$						
C_2H_5	30 min.	53	78.5–80	C_2H_5OAc	$C_4H_7N_3$	49.46	7.27	43.27	49.27	7.50	42.88
$ClCH_2$	4 hr.	59[b]	110.5–111.5	CH_3CN	$C_3H_4N_3Cl$	30.65	3.43	35.75	31.14	3.40	35.99
Cl_3C	3 hr.	43[b]	166.5–168	CH_3CN	$C_3H_2N_3Cl_3$	19.33	1.08	22.54	19.44	1.38	22.94
p-NO_2–C_6H_5	15 min.[c]	52[b]	233–234 dec.[d]	...	$C_8H_6N_4O_2$						
2-C_5H_4N	16 hr.	83[b]	224–226	CH_3OH	$C_7H_6N_4$	57.52	4.14	38.34	57.52	4.04	38.38

[a] Ref. 3 gives m.p. 142.5°. [b] Yield calculated on basis of nitrile. Imidate was not isolated. [c] At 50°. [d] Ref. 3 reports m.p. 263° dec.

Reaction of N-cyanoacetamidine with methyl acetimidate in refluxing methanol gave a product, $C_8H_{13}N_7$, which upon treatment with hydrochloric acid and subsequent neutralization afforded 2-amino-4,6-dimethyl-*s*-triazine (IIb). This same material was formed in high yield upon recrystallization of an equimolar mixture of N-cyanoacetamidine and 2-amino-4,6-dimethyl-*s*-triazine, thus establishing the structure as IIIa. The reaction of N-cyanoacetamidine with methyl propionimidate gave the homolog IIIb containing one ethyl group in the ring.

Since the N-cyanoamidines were originally prepared by treatment of imidates with cyanamide, it appeared that interaction of cyanamide with an excess of an imidate under more strenuous conditions would convert the initially formed N-cyanoamidine to the aminotriazine.



IIIa. R = R′ = CH_3
b. R = CH_3, R′ = C_2H_5

II
IIg. R = R′ = CCl_3

This reaction sequence occurred as predicted with methyl acetimidate and a 42% yield of IIIa was obtained. With methyl benzimidate, however, the reaction did not proceed beyond the first step, since N-cyanobenzamidine was the only product found. On the other hand, when methyl trichloroacetimidate was used as the starting material, the reaction proceeded to give a 29% yield of 2-amino-4,6-bis(trichloromethyl)-*s*-triazine (IIg). Apparently, the amino group in this compound is not basic enough to form a salt with the N-cyanoamidine. It should be pointed out that this synthesis of IIg is essentially a cotrimerization of cyanamide with trichloroacetonitrile as the imidate was prepared and used *in situ*.

Other methods of ring closure to form the *s*-triazine system were investigated briefly using N-cyanobenzamidine as the cyanoamidine component and acetic anhydride, formamide, and thioacetamide[10] as cyclizing agents. These are shown in Chart 1.

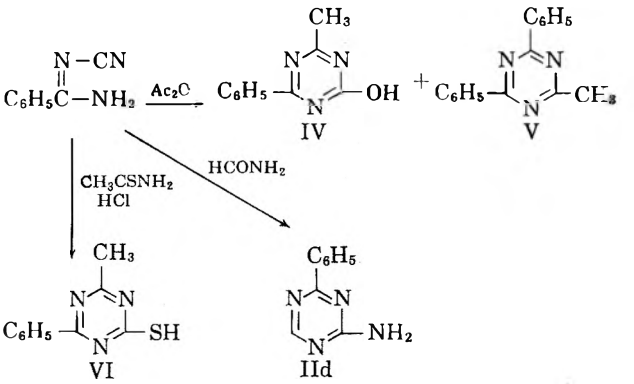
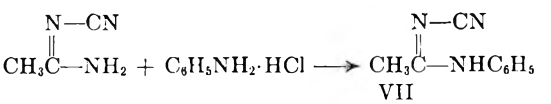


CHART 1

Although the expected product was obtained in each case, yields were again rather low (<20%). 2-Methyl-4,6-diphenyl-*s*-triazine was the major product from N-cyanobenzamidine and acetic anhydride, again demonstrating loss of cyanamide from an N-cyanoamidine during the course of a reaction. This tendency to lose cyanamide, either through dissociation or displacement, together with the somewhat lower reactivity of the nitrile groups in the N-cyanoamidines, may account for the inferior yields in many of these reactions when compared to the corresponding reactions of cyanoguanidine.

A striking example of this difference in reactivity was observed in the attempted reaction of N-cyanoamidines with aniline hydrochloride in hot aqueous solution. Although cyanoguanidine readily affords phenylbiguanide in high yield,[11] N-cyanobenzamidine did not react under these conditions, while N-cyanoacetamidine gave only a small yield of N-cyano-N′-phenylacetamidine (VII) rather than undergoing addition at the nitrile group.



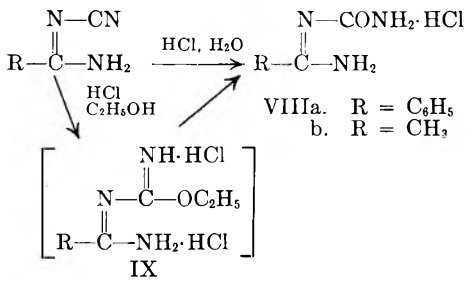
As is the case with cyanoguanidine, the nitrile groups of N-cyanoamidines are readily hydrolyzed under strongly acidic conditions.[3,6,12] In the present work, N-carbamoylamidine hydrochlorides (VIII) were isolated in good yields upon addition of N-cyanoami-

(10) *Cf.* E. C. Taylor and J. A. Zoltewicz, *J. Am. Chem. Soc.*, **83**, 248 (1961).

(11) G. Cohn, *J. prakt. Chem.*, [2] **84**, 394 (1911).

(12) G. Palazzo and G. Strani, *Gazz. chim. ital.*, **91**, 216 (1916).

dines to cold concentrated hydrochloric acid or treatment of the cyano compounds with excess dry hydrogen chloride in ethanol. The latter conditions presumably involve formation of an intermediate such as IX, which then loses ethyl chloride to give VIII.



Attempts to convert N-carbamoylbenzamidine (VIIIa) to 2-hydroxy-*s*-triazines by various methods were unsuccessful. The only products isolated were those from which the carbamoyl group had been lost (Chart 2). Presumably, the manner of decomposition of these compounds is similar to, but easier than, that occasionally found with the N-cyanoamidines, although mechanisms have not been established for these reactions.

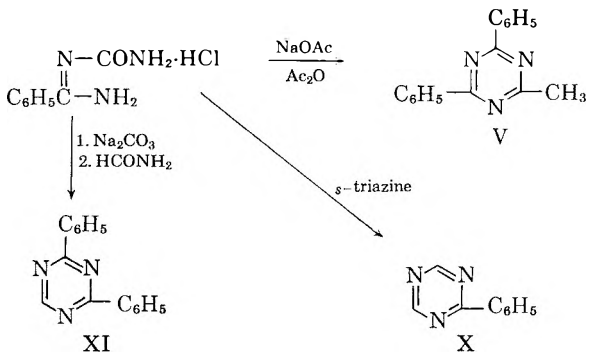
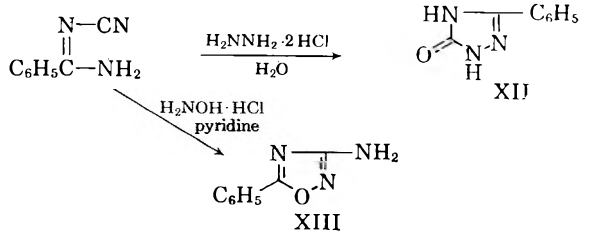


CHART 2

Recently, the preparation of N-carbamoylbenzamidine and its reaction with benzoyl chloride to give 2-hydroxy-4,6-diphenyl-*s*-triazine was reported.[12]

The use of N-cyanoamidines for the synthesis of five-membered heterocycles was demonstrated by formation of compounds XII and XIII from N-cyanobenzamidine with hydrazine dihydrochloride and hydroxylamine hydrochloride, respectively.



It is interesting that the reaction of hydroxylamine with the related methyl N-cyanobenzimidate leads to the isomer of XIII in which the positions of the amino and phenyl groups are reversed.[13]

(13) K. R. Huffman and F. C. Schaefer, *J. Org. Chem.*, **28**, 1816 (1963).

Experimental[14]

Reagents.—Crystalline cyanamide was obtained by evaporation of the commercially available 50% aqueous solution. It was purified before each reaction by dissolution in ether, filtration of the insoluble cyanoguanidine, and evaporation of the filtrate.

All imidates and amidines were prepared by standard methods.[7,8,15]

Reaction of Imidates with Cyanamide. General.—N-Cyanoamidines listed in Table I were prepared by the following general procedure. To 0.1 mole of imidate was added slowly with swirling a solution of 0.1 mole of freshly purified cyanamide in 20 ml. of methanol. The reaction mixture was cooled in an ice bath if necessary to keep the temperature below 50°. After the specified length of time, the product was isolated by filtration or by evaporation of the methanol and crystallization of the residue from the appropriate solvent.

When the imidate could be prepared *in situ*, the following procedure was effective. A solution of 0.1 mole of the nitrile in 25 ml. of methanol was treated with 0.005 mole of sodium methoxide using the previously described conditions.[7] After imidate formation was essentially complete, the solution was neutralized with 0.005 mole of acetic acid and then treated with cyanamide and worked up as before.

N-Cyanobenzamidine.—A mixture of 25.0 g. of benzamidine hydrochloride dihydrate (0.13 mole) and 11.0 g. of 75% monosodium cyanamide[16] (0.13 mole) in 75 ml. of water was stirred until the starting materials had dissolved and the product began to crystallize. After 2 hr. it was filtered to give 11.6 g. of white crystalline product, m.p. 135–137.5°. Another 2.2 g., m.p. 139–141°, crystallized from the filtrate after several more hours, for a total of 13.8 g. (74%). Recrystallization from ethanol–water raised the m.p. to 141–142° (lit.[3] m.p. 142.5°).

N-Cyanoacetamidine.—Acetamidine hydrochloride, 94.5 g., 1.0 mole, was mixed with 69.5 g. of 92% monosodium cyanamide (1.0 mole) in 100 ml. of water. After 2 hr., the mixture was chilled and filtered, and the resulting white solid was extracted with hot acetone. Sodium chloride was removed by filtration and the acetone solution was concentrated and chilled to give 38.5 g. of white crystals, m.p. 134–136°, and a second crop of 6.0 g., m.p. 125–133°. The original aqueous filtrate was evaporated and worked up as before to give another 7.7 g., m.p. 125–130°, for a total of 52.2 g. (63%). This material was identical with that described in Table I.

2-Amino-4,6-diphenyl-*s*-triazine (IIa). A.—A mixture of 1.05 g. (0.0072 mole) of N-cyanobenzamidine and 1.15 g. (0.0074 mole) of benzamidine hydrochloride was fused at 175° for 2.5 hr. Crystallization of the resulting mixture from ethanol–water afforded 0.30 g. (17%) of the triazine, m.p. 167–169° (lit.[17,18] m.p. 172° and 168–170°.

B.—A solution of 0.016 mole of benzamidine, prepared from 2.50 g. of benzamidine hydrochloride and 0.85 g. of sodium methoxide in 10 ml. of ethanol, was filtered and mixed with 2.30 g. (0.016 mole) of N-cyanobenzamidine. The resulting solution was refluxed for 2 hr. and stored overnight. The product was collected by filtration. The yield was 0.60 g. (15%), m.p. 168–170°.

C.—A solution of 2.0 g. (0.014 mole) of N-cyanobenzamidine, 1.4 g. (0.014 mole) of benzonitrile, and 20 mg. of powdered sodium hydroxide in 10 ml. of 1-butanol was refluxed for 4 hr. The mixture was filtered to remove traces of solid and evaporated to an oily residue which was crystallized from ethanol–water yielding 0.60 g. (17%) of crude IIa, m.p. 135–160°. Two recrystallizations from ethanol afforded pure material, m.p. 167–170°.

D.—Fusion of a mixture of 1.0 g. of N-cyanoacetamidine (0.012 mole) and 2.2 g. of benzamidine acetate (0.012 mole) at 160–165° for 3.5 hr. yielded an oil which was partially crystallized from water. Several recrystallizations from aqueous ethanol gave pure IIa, m.p. 169–171°, identical with the samples described previously.

(14) Melting points are uncorrected. N. B. Colthup aided in interpretation of the infrared spectra.

(15) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

(16) R. A. Vingee and L. J. Christmann, U. S. Patent 2,656,256 (October 20, 1953); *Chem. Abstr.*, **48**, 2996 (1954).

(17) J. Ephraim, *Ber.*, **26**, 2226 (1893).

(18) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **72**, 4922 (1950).

2-Amino-4,6-dimethyl-s-triazine (IIb).—A mixture of 4.15 g. (0.050 mole) of N-cyanoacetamidine and 4.8 g. (0.051 mole) of acetamidine hydrochloride in 6 ml. of 2-methoxyethanol was heated at a bath temperature of 155° for 4 hr. The solid which separated on cooling was filtered and recrystallized from water to give 2.55 g. (41%) of IIb, m.p. 160–166°. After one additional recrystallization from acetonitrile the m.p. was 167–169° (lit.[19,20] m.p. 170° and 171°.

2-Amino-4-methyl-6-phenyl-s-triazine (IIc).—A mixture of 1.6 g. of benzamidine hydrochloride dihydrate (0.0083 mole) and 0.85 g. of N-cyanoacetamidine (0.010 mole) was fused at 150° for 3 hr. The resulting oil was cooled and treated with 10 ml. of water which caused crystallization of a tan solid, 0.40 g. (26%), m.p. 148–152°. This crude material was identified by infrared comparison with pure IIc, m.p. 155–156°, obtained as described in the following paper.[13]

2-Amino-4-phenyl-s-triazine (IId). **A.**—A solution of 2.0 g. of N-cyanobenzamidine in 5 ml. of formamide was heated at 180° for 2 hr. Upon cooling, a tan solid separated. It was recrystallized from ethanol to give 0.35 g. (15%) of crude material, m.p. 187–195°. Two additional recrystallizations afforded white flakes, m.p. 203–204°.

Anal. Calcd. for $C_9H_8N_4$: C, 62.77; H, 4.68; N, 32.54. Found: C, 62.39; H, 4.63; N, 32.44.

B.—A mixture of 1.0 g. (0.0145 mole) of N-cyanoformamidine[2] and 2.3 g. of benzamidine hydrochloride (0.015 mole) was fused at 160° for 30 min. The resulting solid was triturated successively with water and hot ethanol to give 0.70 g. of IId as tan crystals, m.p. 201–204°. The ethanol solution yielded another 0.07 g., m.p. 195–198°, for a total of 0.77 g. (31%).

2,4-Diamino-6-methyl-s-triazine (IIe).—A solution of guanidine was prepared from 3.1 g. of guanidine hydrochloride and 1.75 g. of sodium methoxide in 20 ml. of methanol. This was filtered and 2.5 g. of N-cyanoacetamidine was added. After refluxing for 6 hr., the solution was chilled and filtered to give 2.0 g. (53%), m.p. 275–276°, identical with an authentic sample.

2,4-Diamino-6-phenyl-s-triazine (IIf).—Application of the above procedure to N-cyanobenzamidine afforded a 19% yield of IIf, m.p. 219–223°, compared with an authentic sample.

2-Amino-4,6-dimethyl-s-triazine, N-Cyanoacetamidine Salt (IIIa). **A.**—A solution of 2.1 g. (0.050 mole) of cyanamide in 10 ml. of ethanol was added slowly with swirling to 7.4 g. (0.10 mole) of methyl acetimidate. The resulting warm solution was refluxed for 6 hr. and stored at room temperature overnight, during which time the product crystallized. The yield was 2.2 g. (42%), m.p. 179–182°. Two recrystallizations from methanol gave an analytical sample, m.p. 182–183.5°.

Anal. Calcd. for $C_8H_{13}N_7$: C, 46.36; H, 6.32; N, 47.32. Found: C, 46.68; H, 5.90; N, 47.38.

This compound was converted to the hydrochloride of 2-amino-4,6-dimethyl-s-triazine by treatment with excess dry hydrogen chloride in ethanol. Addition of the salt to aqueous bicarbonate gave the free base, m.p. 166–167°, identical with the sample prepared earlier.

B.—A solution of 1.65 g. (0.020 mole) of N-cyanoacetamidine and 1.50 g. (0.020 mole) of methyl acetimidate in 5 ml. of methanol was refluxed for 6 hr. and chilled. The crystalline IIIa was filtered; yield, 1.05 g. (51%), m.p. 182–184°.

C.—Recrystallization of a mixture of 0.30 g. (0.0024 mole) of 2-amino-4,6-dimethyl-s-triazine and 0.20 g. (0.0024 mole) of N-cyanoacetamidine from methanol afforded 0.35 g. (70%) of pure IIIa, m.p. 183–184.5°, identical with the samples described previously.

2-Amino-4-ethyl-6-methyl-s-triazine, N-Cyanoacetamidine Salt (IIIb).—A solution of 2.5 g. of N-cyanoacetamidine (0.030 mole) and 2.85 g. of 94% methyl propionimidate (0.031 mole) in 5 ml. of ethanol was refluxed for 5.5 hr. and chilled to give 1.50 g. (45%) of white solid, m.p. 148–155°. An analytical sample, m.p. 158–159°, was obtained after three recrystallizations from methanol.

Anal. Calcd. for $C_9H_{15}N_7$: C, 48.85; H, 6.83; N, 44.32. Found: C, 48.97; H, 6.72; N, 44.08.

2-Amino-4,6-bis(trichloromethyl)-s-triazine (IIg).—A cold solution of 7.4 g. (0.051 mole) of trichloroacetonitrile in 20 ml. of methanol was treated with 0.15 g. of sodium methoxide and kept at room temperature for 30 min. It was then treated successively with 0.20 g. of acetic acid and 1.05 g. (0.025 mole) of cyanamide and then refluxed for 4.5 hr. The resulting solution was evaporated to a dark oil from which there was obtained, by crystallization and recrystallization from ethanol–water, 2.4 g. (29%) of the triazine as dirty white prisms, m.p. 163–165.5°. Further recrystallization raised the m.p. to 165–167° (lit.[21] m.p. 165–166°). A mixture melting point with N-cyano-2,2,2-trichloroacetamidine, m.p. 166.5–168°, was strongly depressed. No nitrile band was apparent in the infrared spectrum.

Reaction of N-Cyanobenzamidine with Acetic Anhydride.—A solution of 1.0 g. of N-cyanobenzamidine in 4 ml. of acetic anhydride was refluxed for an hour. The resulting yellow solid was recrystallized from acetonitrile to give 0.18 g. (14%) of **2-hydroxy-4-methyl-6-phenyl-s-triazine** (IV), m.p. 239–241°. Another recrystallization afforded material, m.p. 243–245°.

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.13; H, 4.58; N, 22.79.

The acetic anhydride solution was then distilled and the oily residue was crystallized from water and recrystallized from ethanol–water yielding 0.25 g. (29%) of **2-methyl-4,6-diphenyl-s-triazine** (V), m.p. 94–102°. After another recrystallization the m.p. was 107–108°. The structure was confirmed by comparison with an authentic sample.[22]

2-Mercapto-4-methyl-6-phenyl-s-triazine (VI).—A solution of 0.75 g. (0.0052 mole) of N-cyanobenzamidine and 0.40 g. (0.0053 mole) of thioacetamide in 5 ml. of acetone was treated with excess dry hydrogen chloride. An orange gum was quickly formed. The acetone was decanted and 5 ml. of water was added, causing crystallization of a bright yellow solid. The yield was 0.20 g. (19%), m.p. 208–213°. Two recrystallizations from ethanol raised the m.p. to 230.5–233°.

Anal. Calcd. for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.68; S, 15.77. Found: C, 59.46; H, 4.54; N, 20.75; S, 16.07.

N-Cyano-N′-phenylacetamidine (VII).—A solution of 0.85 g. (0.010 mole) of N-cyanoacetamidine and 1.3 g. (0.010 mole) of aniline hydrochloride in 5 ml. of water was heated on the steam bath for 3 hr. Addition of dilute sodium hydroxide to the cooled solution caused separation of an oil which partially crystallized on standing. Recrystallization from ethanol gave 0.08 g. of VII, m.p. 190–192° (lit.[6] m.p. 193°).

N-Carbamoylbenzamidine Hydrochloride (VIIIa).—Addition of excess dry hydrogen chloride to 1.0 g. of N-cyanobenzamidine in 10 ml. of absolute ethanol, while cooling in an ice bath, produced a white crystalline solid which was filtered and washed with ether. The yield of VIIIa was 1.2 g. (87%), m.p. 192–194°, in agreement with the lit.[12] m.p. 192–194°.

N-Carbamoylacetamidine Hydrochloride (VIIIb). **A.**—Application of the previous procedure to 0.40 g. of N-cyanoacetamidine gave 0.40 g. (60%) of VIIIb, m.p. 167–170°. The melting point was raised to 170–172° by recrystallization from ethanol.

Anal. Calcd. for $C_3H_7N_3O \cdot HCl$: C, 26.18; H, 5.86; N, 30.54. Found: C, 26.41; H, 5.83; N, 30.79.

B.—When 0.50 g. of N-cyanoacetamidine was mixed with 3 ml. of cold concentrated hydrochloric acid a vigorous reaction occurred with formation of a clear solution. Evaporation to dryness and crystallization from ethanol afforded 0.65 g. (78%) of VIIIb, m.p. 163–165° dec. Further recrystallization gave a sample identical with that described earlier.

Reaction of N-carbamoylbenzamidine with Acetic Anhydride.—A mixture of 1.0 g. of VIIIa and 0.41 g. of sodium acetate in 5 ml. of acetic anhydride was refluxed for an hour. The cooled solution was poured into water and neutralized with sodium bicarbonate. Extraction with ether gave a dark oil which slowly crystallized on drying under vacuum. Recrystallization from ethanol–water gave 0.30 g. (48%) of **2-methyl-4,6-diphenyl-s-triazine** (V), m.p. > 100°, in two crops. Further recrystallization from ethanol gave pure material, m.p. 108–108.5°, identical with an authentic sample.[22]

2-Phenyl-s-triazine (X).—A solution of 1.0 g. of N-carbamoylbenzamidine hydrochloride (0.0050 mole) and 0.43 g. of s-triazine[15] (0.0053 mole) in 10 ml. of absolute ethanol was refluxed for 2.5 hr. Removal of the ethanol left a colorless oil which was partially crystallized from methanol–acetonitrile to give 0.25 g. of an unidentified hydrochloride, m.p. 77–79°. The mother liquor was evaporated to dryness leaving an oil which crystallized upon addition of water. This material, 0.47 g., m.p. 62–63°, was identified as 2-phenyl-s-triazine (X) by comparison with an authentic sample[23]; yield, 59%.

(19) N. Tscherven-Iwanoff, *J. prakt. Chem.*, [2] **46**, 142 (1892).

(20) H. Schroeder and C. Grundmann, *J. Am. Chem. Soc.*, **78**, 2447 (1956).

(21) A. Weddige, *J. prakt. Chem.*, [2] **33**, 76 (1886).

(22) A. Pinner, *Ber.*, **25**, 1624 (1892).

(23) F. C. Schaefer and G. A. Peters, *J. Am. Chem. Soc.*, **81**, 1470 (1959).

2,4-Diphenyl-s-triazine (XI).—A solution of 1.1 g. of N-carbamoylbenzamidine,[12] m.p. 130–132°, in 3 ml. of formamide was heated at 180–185° for an hour. The white solid which crystallized on cooling was extracted into petroleum ether. This solution was decanted from some insoluble oil and evaporated to give 0.10 g. (13%) of XI, m.p. 68–72°. Recrystallization from aqueous ethanol gave a sample which had m.p. 73–75° and an infrared spectrum identical with that of an authentic sample.[23]

3-Phenyl-1,2,4-triazolin-5-one (XII).—A mixture of 1.0 g. (0.007 mole) of N-cyanobenzamidine and 0.75 g. (0.007 mole) of hydrazine dihydrochloride in 15 ml. of 50% aqueous methanol and was refluxed for 3 hr. Most of the methanol was distilled. Upon cooling 0.30 g. (30%) of the starting material crystallized. A little sodium bicarbonate was added to the aqueous filtrate, from which XII slowly crystallized during 24 hr. The yield was 0.25 g. (23%), m.p. > 300°. It was recrystallized from 50% aqueous ethanol; m.p. 322–325° (lit.[24,25] m.p. 321° and 324°).

In another run, under slightly more strenuous conditions, a 15% yield of **benzoylurea**,[8] m.p. 210–212°, was isolated in addition to a lesser amount of XII.

3-Amino-5-phenyl-1,2,4-oxadiazole (XIII).—A solution composed of 1.0 g. of N-cyanobenzamidine, 0.50 g. of hydroxylamine hydrochloride, 3 ml. of ethanol, and 2 ml. of pyridine was refluxed for 30 min. and filtered hot to remove ammonium chloride. The filtrate was chilled to give 0.35 g. (31%) of XIII, m.p. 156–160°. One recrystallization from ethanol raised the m.p. to 164–165.5° (lit.[26,27] m.p. 164° and 164–165°).

(24) H. Gehlen, *Ann.*, **563**, 185 (1949).
(25) E. Hoggarth, *J. Chem. Soc.*, 1918 (1949).
(26) H. Wieland and H. Bauer, *Ber.*, **40**, 1680 (1907).
(27) P. Adams, D. W. Kaiser, and G. A. Peters, *J. Org. Chem.*, **18**, 934 (1953).

N-Cyanoimidates

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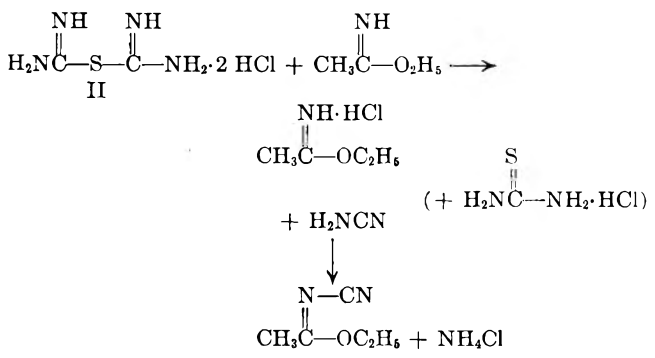
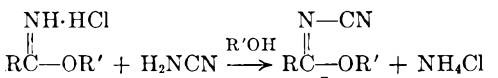
Alkyl N-cyanoimidates, a new class of reactive intermediates, have been prepared by reaction of cyanamide with ortho esters or imidate hydrochlorides. The N-cyanoimidates react with amidines to give 2-amino-s-triazines, with amidoximes to give 2-amino-s-triazine 1-oxides, with hydroxylamine to give 5-amino-1,2,4-oxadiazoles, and with hydrazine to give 3-amino-1,2,4-triazoles. Interaction of monosodium cyanamide with N-cyanoimidates gives N,N′-dicyanoamidine salts, which cyclize to 2-amino-s-triazines upon treatment with dry hydrogen chloride.

As an extension of the work reported in the previous paper[1] concerning the use of N-cyanoamidines as intermediates for the synthesis of certain nitrogen heterocycles, we have investigated the chemistry of the related N-cyanoimidates (I), with the expectation that the more easily displaceable alkoxy group would allow more efficient reactions with nucleophilic reagents. Although N-cyanoimidates have apparently not been reported in the literature, various N-carbamoylimidates[2] and N-acylimidates[3,4] are known. Moreover, they have been reported to react well with amines to give N-acylamidines.[2,5] An N-cyanopseudourea (I. R = NH_2) has also been prepared,[6] but its reactions were apparently not investigated.

We first obtain ethyl N-cyanoacetimidate as an unexpected product from attempted cotrimerization[7a] of ethyl acetimidate with thiodiformamidine dihydrochloride (II). Consideration of the probable mechanism of this reaction suggested that this N-cyanoimidate resulted from reaction of the imidate hydrochloride with cyanamide, the latter arising from dissociation of the starting material. Although imidates generally react with amino compounds with displacement of alcohol to give amidines, in many cases use of the imidate hydrochloride shifts the reaction to give formation of the N-substituted imidate by loss of ammonium chloride.[8] Thus, while reaction of cyanamide with imidates rapidly gave N-cyanoamidines,[1] it appeared that the corresponding reaction of the imidate salt might lead to N-cyanoimidates.





The first results were immediately encouraging when it was found that ethyl and methyl N-cyanoacetimidates (I. R = CH_3, R′ = C_2H_5 or CH_3) could be prepared in 60–65% yields according to the equation shown. The procedure consisted simply of mixing the imidate hydrochloride with cyanamide in alcoholic solution, filtering the ammonium chloride after a few hours, and isolating the product by distillation. The somewhat slower reaction of imidate hydrochlorides with alcohols to give ortho esters[8] did not appear to be interfering to any appreciable extent.

Unfortunately, this method failed to give pure isolable N-cyanoimidates when the group R was made more complex than alkyl. The use in this reaction of alkyl imidates containing α- or β-chloro, α-hydroxy, or α-cyano groups led to complex mixtures or different products.

(1) K. R. Huffman and F. C. Schaefer, *J. Org. Chem.*, **28**, 1812 (1963).
(2) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **77**, 5872 (1955).
(3) H. L. Wheeler and P. T. Walden, *Am. Chem. J.*, **19**, 129 (1897).
(4) H. L. Wheeler, P. T. Walden, and H. F. Metcalf, *ibid.*, **20**, 64 (1898).
(5) H. L. Wheeler and P. T. Walden, *ibid.*, **20**, 568 (1898).
(6) W. Madelung and E. Kern, *Ann.*, **427**, 1 (1922).
(7) (a) F. C. Schaefer, *J. Org. Chem.*, **27**, 3608 (1962); (b) F. C. Schaefer and G. A. Peters, *ibid.*, **26**, 2778 (1961).
(8) For examples, see R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

TABLE I

PREPARATION OF N-CYANOIMIDATES FROM CYANAMIDE AND ORTHO ESTERS

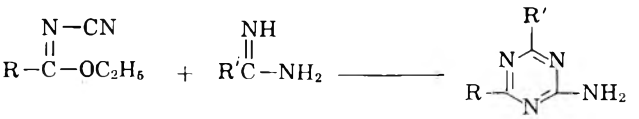
$$RC(OR')_3 + H_2NCN \xrightarrow{2Ac_2O} RC(=N-CN)-OR'$$

R	R′	Temp., °C.	Time	Yield, %	B.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	C_2H_5	140	1 hr.	90	90–95 (20 mm.)	$C_5H_8N_2O$	53.55	7.19	24.99	53.56	7.52	24.61
H	C_2H_5	140	1 hr.	90	58–63 (0.1 mm.)	$C_4H_6N_2O$	48.97	6.17	28.56	49.26	6.18	28.37
$C_2H_5O_2CCH_2$[a]	C_2H_5	150	15 min.	74	103–106 (0.2 mm.)	$C_8H_{12}N_2O_3$	52.16	6.57	15.21	52.22	6.39	14.85
C_6H_5	CH_3	150	20 min.	61	115–125 (0.3 mm.)	$C_9H_8N_2O$	67.48	5.03	17.49	67.18	4.99	17.34
$ClCH_2$	CH_3	130	30 min.	75	76–80 (0.3 mm.)	$C_4H_5N_2OCl$[b]	36.24	3.80	...	36.54	3.88	...
$ClCH_2$	C_2H_5	145	30 min.	65	87–90 (0.2 mm.)	$C_5H_7N_4OCl$[c]	34.40	4.04	32.09	34.36	4.01	32.25

[a] The ketene acetal (III) was used with one equivalent of acetic anhydride. [b] Calcd.: Cl, 26.75. Found: Cl, 26.46. [c] Calcd.: Cl, 20.31. Found: Cl, 20.43.

TABLE II

PREPARATION OF 2-AMINO-*s*-TRIAZINES IN METHANOL AT 25°



R	R′	Reaction time (hr.)	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3[a]	CH_3	3	84	170–171[b]	$C_5H_8N_4$	...	...	...	...	...	...
CH_3[a]	C_6H_5	3	76	156.5–158	$C_{10}H_{10}N_4$	64.50	64.32	5.41	5.39	30.09	30.26
CH_3	NH_2	0.5	77	276–277	$C_4H_7N_5$	...	...	...	...	...	...
CH_3	$CH_3O_2CCH_2$[c]	2[d]	38[e]	117.5–119.5	$C_7H_{10}N_4O_2$	46.15	46.04	5.52	5.41	30.76	30.22
CH_3	$C_2H_5O_2CCH_2$	18[f]	27	125–126	$C_8H_{12}N_4O_2$	48.97	48.92	6.17	6.16	28.56	28.62
CH_3	CH_3O	2	45	257–259[g]	$C_5H_8N_4O$	42.85	43.00	5.75	6.00	39.98	39.77
CH_3	*p*-NO_2-C_6H_5	2[d]	60	267–268	$C_{10}H_9N_5O_2$	51.94	52.24	3.92	4.32	30.29	30.50
H	NH_2	1	...[h]	>300[h]	$C_3H_5N_5$	...	...	...	...	...	...
H	C_6H_5	0.5	29	203.5–204.5[i]	$C_9H_8N_4$	...	...	...	...	...	...
$ClCH_2$	C_6H_5	0.5	23	145–147	$C_{10}H_9N_4Cl$[j]	54.43	54.66	4.11	4.16	25.39	25.46
$ClCH_2$	CH_3O	0.25	63	164–165	$C_5H_7N_4OCl$[k]	34.40	34.36	4.04	4.01	32.09	32.25
C_6H_5[l]	CH_3	1	54[e]	156–158	$C_{10}H_{10}N_4$[m]	...	...	...	...	...	...

[a] Starting material was *methyl* N-cyanoacetamidate. [b] N. Tscherven-Iwanoff, *J. prakt. Chem.*, [2] **46**, 147 (1892), reports m.p. 170°. [c] Ethyl ester was used as starting material. Ester interchange occurred during course of reaction. [d] At 50°. [e] Yield of crude product. [f] In ethanol. [g] Purified by trituration with hot water. [h] See Experimental. [i] Ref. 1 gives m.p. 203–204°. [j] Calcd.: C, 16.07. Found: Cl, 15.83. [k] Calcd.: Cl, 20.31. Found: Cl, 20.43. [l] Starting material was methyl N-cyanobenzimidate. [m] Identical with second entry in this table.

Methyl benzimidate hydrochloride also did not react smoothly with cyanamide, although a small amount of methyl N-cyanobenzimidate was obtained.

Investigation of a second method for synthesis of N-cyanoimidates was based on the known reaction of amino compounds with ortho esters to give alkoxymethylene derivatives. Such a reaction has been used successfully by Whitehead and Traverso[2] to convert substituted ureas to N-carbamoylimidates, but there is no report of the use of cyanamide as the amine component. Accordingly, this route to N-cyanoimidates was tried and was found to work quite well in most cases. Table I lists the compounds prepared by this procedure, which consisted simply of heating the reagents in two equivalents of acetic anhydride at 130–150° for periods of fifteen minutes to one hour, while distilling the by-products, acetic acid and alkyl acetate. The pure N-cyanoimidates were then isolated by distillation.

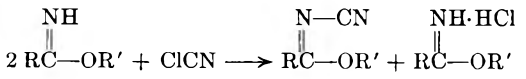
$$RC(OR')_3 + H_2NCN + 2Ac_2O \longrightarrow \underset{\text{I}}{RC(=N-CN)-OR'} + 2\,R'OAc + 2HOAc$$

In order to obtain an example of an N-cyanoimidate containing a potentially active methylene group, the ketene acetal III was prepared and treated with cyanamide in the presence of one equivalent of acetic anhydride. This variation of the usual procedure produced the N-cyanoimidate Ic in 74% yield.

$$C_2H_5O_2CCH{=}C(OC_2H_5)_2 \quad \underset{\text{III}}{} + H_2NCN \xrightarrow{Ac_2O} C_2H_5O_2CCH_2C(=N-CN)-OC_2H_5$$

Ic

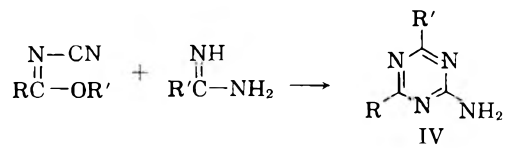
A few experiments directed at the preparation of N-cyanoimidates by reaction of imidates with cyanogen chloride were also carried out. Although it has long been known that imidates could be acylated with acid chlorides,[3,4] addition of cyanogen chloride to two equivalents of methyl benzimidate in ether gave little or no reaction, while the same procedure applied to methyl acetimidate afforded only a 23% yield of methyl N-cyanoacetimidate. In the latter case the major product was 2,4,6-trimethyl-*s*-triazine, resulting from acid-catalyzed trimerization of the imidate.[7b] Low yields of crude methyl N-cyanobenzimidate and methyl N-cyanoacetimidate were obtained by treatment of the imidates with cyanogen chloride in aqueous solution in the presence of calcium hydroxide.



The N-cyanoimidates prepared during this investigation were all colorless liquids characterized primarily by analyses and by infrared absorption spectra. These compounds exhibit strong nitrile bands near 4.5 μ and strong C=N bands near 6.2 μ, with no absorption in the N—H or carbonyl region. Chemical confirmation of the assigned structures was obtained by their reaction with amino compounds resulting, in most cases, in ready displacement of the alkoxyl group.

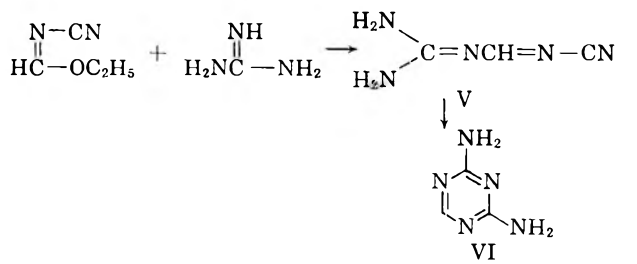
In contrast to the strenuous conditions required to convert N-cyanoamidines to aminotriazines,[1] N-cyanoimidates were found to react smoothly with amidines in alcoholic solution to give 2-amino-*s*-triazines (IV).

Compounds of type IV prepared by this method are listed in Table II. The R′ group of the amidine was



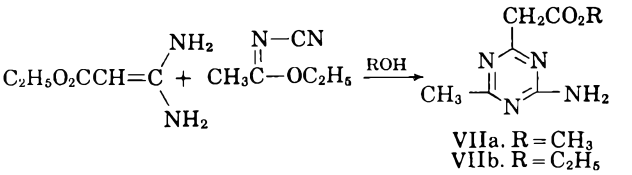
varied successfully among such groups as methyl, phenyl, *p*-nitrophenyl, amino, methoxy, and carbethoxymethyl. While the best yields were obtained with N-cyanoacetimidates, the other N-cyanoimidates, with the exception of compound Ic, were also converted to triazines by this procedure. This new method appears to be the best available for synthesis[9] of monoamino-*s*-triazines containing dissimilar R groups.

In one case, the reaction of guanidine with an excess of ethyl N-cyanoformimidate, an open chain intermediate V was isolated. This compound was identified by analysis, infrared spectrum (strong nitrile band, absence of ring band at 12.4 μ), and by its quantitative conversion to the isomeric 2,4-diamino-*s*-triazine (VI) upon recrystallization from water. Equivalent amounts of the starting materials produced a mixture of V and VI in high conversion. Intermediates similar to V are probably formed in the other cases also, but are normally too soluble and too reactive to be isolated.

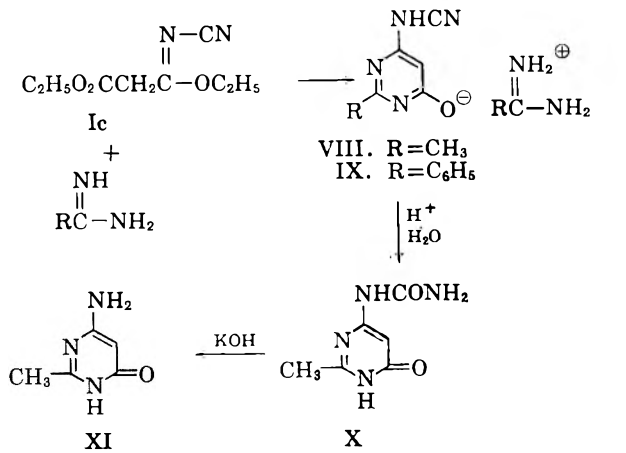


The reaction of 2-carbethoxyacetamidine with ethyl N-cyanoacetimidate in methanol was accompanied by interchange with the solvent to afford the methyl ester VIIa.

The similar product VIIb was not formed, however, upon reaction of acetamidine with ethyl 2-carbethoxy-N-cyanoacetimidate. Instead, the product was a high

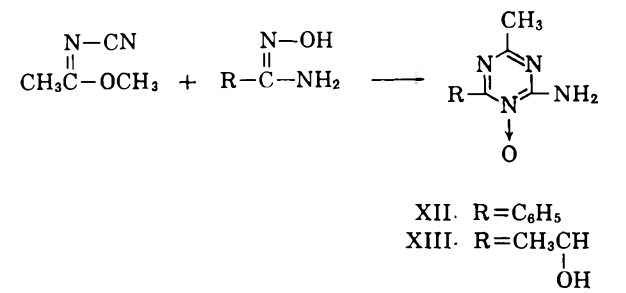


melting solid which still contained a nitrile group but no ester group, indicating that ring closure had occurred in an alternative manner to give a pyrimidine derivative. Structure VIII was assigned to this material on the basis of the infrared spectrum and rather erratic analytical data. This structure was confirmed by acid hydrolysis to the ureido derivative X, which upon treatment with strong base gave the known 4-amino-6-hydroxy-2-methylpyrimidine (XI). Treatment of Ic with benzamidine similarly led to the phenyl derivative IX.



Methyl N-cyanoacetimidate reacted with benzamidoxime and lactamidoxime to give the 2-amino-*s*-triazine 1-oxides XII and XIII, respectively.

These products were characterized by analysis, for-



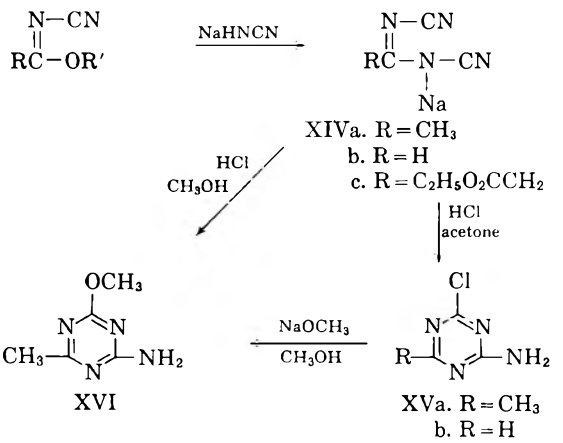
mation of a red color with ferric chloride,[10] and, in the case of the phenyl derivative XII, by reduction with phosphorus trichloride to 2-amino-4-methyl-6-phenyl-*s*-triazine. Although these results establish the presence of the triazine N-oxide system, they do not rule out the isomeric 4-amino 1-oxide structure. The assignment of structures XII and XIII is based primarily on the infrared spectral correlation with 2-aminopyridine N-oxide, in which one of the N—H stretching bands and the N—O band are shifted to appreciably longer wave lengths than normal, presumably due to hydrogen bonding between the adjacent groups. Similar shifts to longer wave lengths were shown by the two triazine derivatives, in which the N—O band ap-

(9) For previous syntheses of monoamino-*s*-triazines see E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience Publishers Inc., New York, N. Y., 1959, p. 217.

(10) J. T. Shaw, *J. Org. Chem.*, **27**, 3890 (1962).

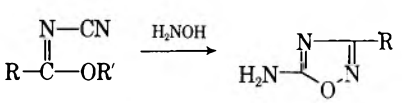
peared near 8.75 μ, well outside the normal range of 7.7–8.3 μ quoted for normal heterocyclic N-oxides.[11]

Treatment of N-cyanoimidates with monosodium cyanamide led to the formation of N,N′-dicyanoamidine sodium salts (XIV) in excellent yields, although the products were not obtained analytically pure in all cases. Compounds of type XIV have been prepared previously by reaction of amidines with cyanogen chloride.[10] Cyclization of the dicyanoamidines XIVa and XIVb to 2-amino-4-chloro-*s*-triazines (XV) was effected by treatment with dry hydrogen chloride in acetone. Alternatively, when the dicyanoacetamidine salt XIVa was cyclized in methanol, the product was the methoxytriazine XVI. The latter was also prepared by displacement of the chlorine of XVa with sodium methoxide in methanol.



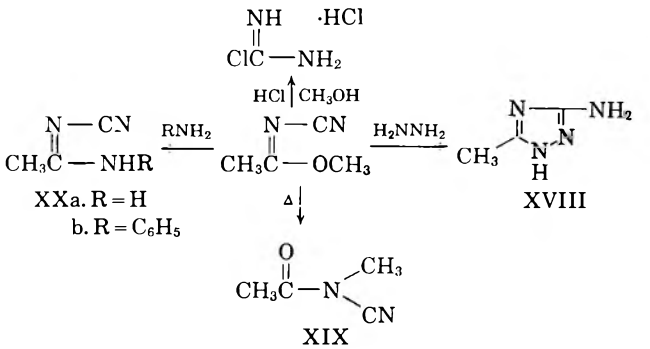
This new route to the *s*-triazine system is analogous to the known cyclization of potassium dicyanoguanidine to 2,4-diamino-6-chloro-*s*-triazine.[12] In view of the ease of displacement of the chlorine atom, compounds of type XV should be useful as intermediates for the synthesis of a variety of monoamino-*s*-triazines.

N-Cyanoimidates were also found to be useful as precursors of 1,2,4-oxadiazoles and 1,2,4-triazoles. When N-cyanoimidates were mixed with hydroxylamine hydrochloride in methanol, in the presence of triethylamine, an exothermic reaction occurred with formation of a 5-amino-1,2,4-oxadiazole (XVII). The isomeric 3-amino-1,2,4-oxadiazoles could be ruled out as possible structures for these products as the 3-amino-5-methyl-[13] and 3-amino-5-phenyl-1,2,4-oxadiazole[1,14,15] are known compounds having melting points different from our products. Moreover, the phenyl derivative, XVIId, had properties in agreement with the known material.[16,17]



XVIIa. R = CH_3
c. R = $C_2H_5OCCH_2$-
d. R = C_6H_5
e. R = $ClCH_2$

Methyl N-cyanoacetimidate reacted vigorously with hydrazine to give 3-amino-5-methyl-1,2,4-triazole (XVIII). Additional reactions tried with this N-cyanoimidate included treatment with dry hydrogen chloride in methanol, which led to cleavage of the molecule with formation of 1-chloroformamidine hydrochloride, and displacement of the methoxy group with ammonia and aniline to form the N-cyanoamidines XXa and XXb. N-Cyano-N′-substituted amidines have been obtained previously by reaction of the N-substituted imidate with cyanamide.[18,19]



Methyl N-cyanoacetimidate was stable to distillation at reduced pressure, as were the other compounds of type I, but upon heating at 165° at atmospheric pressure it slowly underwent the Chapman rearrangement[8] to give the isomeric N-cyano-N-methylacetamide (XIX).

Experimental[20]

Reagents.—Cyanamide was obtained and purified as before.[1] Monosodium cyanamide[21] was purified by extracting the crude material with boiling methanol, filtering the insoluble impurities, and evaporating to dryness at reduced pressure. All amidine salts were prepared by standard methods.

Trimethyl orthobenzoate was prepared by a literature procedure.[22] Trimethyl and triethyl 2-chloroorthoacetates[23] were prepared by allowing the corresponding imidate hydrochlorides to stand in methanol or ethanol at 25° for 1–3 days. 2-Carbethoxyketene diethyl acetal[24,25] was obtained following the procedure of McElvain and Schroeder[26] for the preparation of triethyl 2-carbethoxyorthoacetate and redistilling the product from *p*-toluenesulfonic acid.

N-Cyanoimidates from Ortho Esters and Cyanamide. General Procedure.—In general, equivalent amounts of cyanamide and ortho ester were dissolved in 2 equivalents of acetic anhydride and the resulting solution was heated to 130–140°, at which point the alkyl acetate began to distil rapidly. The oil bath was removed until the initial vigorous reaction subsided and then heating was continued at 135–150°, until most of the alkyl acetate and acetic acid had distilled. The residual liquid was then distilled under vacuum. The N-cyanoimidates prepared by this procedure are listed in Table I.

Reaction of Thiodiformamidine Dihydrochloride with Ethyl Acetimidate.—A suspension of 20.0 g. (0.10 mole) of thiodiformamidine dihydrochloride[27] in 20 ml. of methanol at 55–60° was treated dropwise with 29.0 g. of ethyl acetimidate (0.31 mole) during 20 min. The reaction mixture was heated at 65° for an

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(12) J. J. Roemer and D. W. Kaiser, U. S. Patent 2,658,893 (November 10, 1953); *Chem. Abstr.*, **48**, 12813 (1954).
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(16) G. Ponzio, *Gazz. chim. ital.*, **62**, 854 (1932).
(17) G. Palazzo and G. Strani, *ibid.*, **90**, 1290 (1960).
(18) W. J. Comstock and H. L. Wheeler, *Am. Chem. J.*, **13**, 514 (1891).
(19) G. Pellizzari, *Gazz. chim. ital.*, **41**, 93 (1911).
(20) Melting points and boiling points are uncorrected. Microanalyses were by J. Deonarine and associates.
(21) R. A. Vingee and L. J. Christmann, U. S. Patent 2,656,246 (October 29, 1953); *Chem. Abstr.*, **48**, 2996 (1954).
(22) S. M. McElvain and J. T. Venerable, *J. Am. Chem. Soc.*, **72**, 1661 (1950).
(23) F. Beyerstedt and S. M. McElvain, *ibid.*, **59**, 1273 (1937).
(24) H. Reitter and A. Weindel, *Ber.*, **40**, 3358 (1907).
(25) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).
(26) S. M. McElvain and J. P. Schroeder, *ibid.*, **71**, 40 (1949).
(27) B. H. Chase and J. Walker, *J. Chem. Soc.*, 4443 (1955).

additional hour at which point it was cooled and diluted with ether. The ethereal solution was decanted from insoluble material and distilled to give 12.0 g. of liquid, b.p. 120–130° (40 mm.). This crude product was shown to contain approximately 65% ethyl N-cyanoacetimidate and 18% methyl N-cyanoacetimidate by infrared and mass spectroscopic comparison with samples obtained as before. The combined yield was approximately 85%.

Methyl N-Cyanoacetimidate.—To a solution of 19.6 g. (0.47 mole) of freshly purified cyanamide in 70 ml. of dry methanol was added 51.1 g. (0.47 mole) of methyl acetimidate hydrochloride.[28] The resulting mixture was shaken for a few minutes and allowed to stand at room temperature for 3 hr. After filtration of the ammonium chloride the methanol was stripped from the filtrate and the product was distilled rapidly. Redistillation gave 30.1 g. (66%) of methyl N-cyanoacetimidate, b.p. 98–99° (25 mm.).

Anal. Calcd. for $C_4H_6N_2O$: C, 48.97; H, 6.17; N, 28.56. Found: C, 49.23; H, 6.50; N, 28.60.

Ethyl N-cyanoacetimidate was prepared according to the previous procedure using ethyl acetimidate hydrochloride[7b] in ethanol. The yield was 65%, b.p. 95–96° (15 mm.). The infrared spectrum was identical with that of the sample prepared as in Table I.

Reaction of Methyl Acetimidate with Cyanogen Chloride.—A solution of 14.6 g. (0.20 mole) of methyl acetimidate[29] in 100 ml. of ether was stirred in an ice bath while 6.2 g. (0.10 mole) of cyanogen chloride was distilled into the solution. The flask was stoppered and kept at 0° for 6 hr. and then at room temperature overnight. Filtration at this point yielded 3.5 g. (32%) of methyl acetimidate hydrochloride. Removal of the ether and distillation afforded 3.5 g. (43%) of 2,4,6-trimethyl-*s*-triazine,[7b] b.p. to 63° (20 mm.), which solidified in the condenser, and 2.3 g. (23%) of **methyl N-cyanoacetimidate**, b.p. 90–92° (20 mm.).

Preparation of 2-Amino-*s*-triazines. General Procedure.—The 2-amino-*s*-triazines listed in Table II were prepared by the following procedure. A solution of 0.020 mole of sodium methoxide in 20 ml. of methanol was treated with 0.021 mole of the amidine hydrochloride. The mixture was shaken for a few minutes and then filtered into 0.020 mole of the N-cyanoimidate while stirring and cooling the reaction mixture in an ice bath, if necessary. In most cases the product crystallized directly from the reaction mixture. If crystallization did not occur, the solvent was evaporated after an appropriate length of time and the residue was crystallized from ethyl acetate and then recrystallized from ethanol.

N-Cyano-N′-guanylformamidine (V).—A solution of guanidine in 15 ml. of methyl alcohol was prepared from 1.90 g. of guanidine hydrochloride (0.020 mole) and 1.1 g. of sodium methoxide (0.020 mole). This was filtered and 2.20 g. (0.022 mole) of ethyl N-cyanoformimidate was added. The solution became warm with crystallization of a white solid, which after an hour was filtered and washed with ethanol. This was the open chain product V, 0.95 g. (43%), m.p. >300°.

Anal. Calcd. for $C_3H_5N_5$: C, 32.43; H, 4.54; N, 63.04. Found: C, 32.17; H, 4.42; N, 62.76.

The infrared spectrum of this material showed a strong nitrile band near 4.55 μ. Recrystallization from water resulted in near-quantitative conversion to the isomeric 2,4-diamino-*s*-triazine (VI), m.p. >300°, which could not be detected in the spectrum of the original material.

In another run using the standard procedure for reaction of N-cyanoimidates with amidines a mixture of V and VI crystallized from the solution in a combined yield of 87%. Pure VI was then obtained by recrystallization of this mixture from water.

4-Cyanoamino-6-hydroxy-2-methylpyrimidine, Acetamidine Salt (VIII).—A solution of 0.021 mole of acetamidine, prepared from 2.15 g. of the hydrochloride and 1.15 g. of sodium methoxide in 20 ml. of methanol, was filtered into 2.0 g. (0.011 mole) of ethyl 2-carbethoxy-N-cyanoacetimidate and the resulting solution was heated at 50° for 3 hr. while a pale yellow solid slowly crystallized. The solid was filtered and triturated with fresh methanol to give 1.20 g. (53%) of VIII, m.p. >250 dec.

Anal. Calcd. for $C_6H_6N_4O \cdot C_2H_6N_2$: C, 46.14; H, 5.81; N, 40.36. Found: C, 45.57; H, 5.71; N, 39.80.

Reaction of acetamidine with the N-cyanoimidate in a 1:1 ratio also gave VIII as the only solid product.

A 0.25-g. sample of VIII was heated with 3 ml. of 6 *N* hydrochloric acid for 30 min. on the steam bath. The resulting hydrochloride salt was neutralized with aqueous bicarbonate to give **4-hydroxy-2-methyl-6-ureidopyrimidine (X)**, m.p. >275°, which upon treatment with aqueous potassium hydroxide for 2 hr. at 90° was converted to **4-amino-6-hydroxy-2-methylpyrimidine (XI)**, m.p. 298–300° dec. The infrared spectrum of this material was identical with that of an authentic sample prepared by a literature procedure.[30] Lit.[30] m.p. 295–297°.)

4-Cyanoamino-6-hydroxy-2-phenylpyrimidine, Benzamidine Salt (IX).—A solution of 1.85 g. (0.010 mole) of ethyl 2-carbethoxy-N-cyanoacetimidate and an equivalent amount of benzamidine in 15 ml. of methanol was warmed at 35–40° for 3 hr. Evaporation of the solvent gave a gum which was crystallized from ethanol–ethyl acetate. The yield of IX, m.p. 191–192° dec., was 1.1 g. (66% based on the amidine). Recrystallization from water afforded off-white crystals, m.p. 192–193° dec.

Anal. Calcd. for $C_{11}H_8N_4O \cdot C_7H_8N_2$: C, 65.04; H, 4.85; N, 25.29. Found: C, 64.53; H, 4.60; N, 25.91.

2-Amino-4-methyl-6-phenyl-*s*-triazine 1-Oxide (XII).—A solution of 1.0 g. (0.010 mole) of methyl N-cyanoacetimidate and 1.4 g. (0.010 mole) of benzamidoxime[31] in 5 ml. of ethanol was refluxed for 4 hr. and chilled. The white crystalline product was filtered and washed with ether, 0.65 g., m.p. 209–215°. After standing for a week the filtrate had deposited another 0.30 g., m.p. 216–219°, for a total of 0.95 g. (45%). Trituration with ethanol raised the m.p. to 219–221°.

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. Found: C, 58.99; H, 5.02; N, 27.47.

This compound exhibited a bright red color with ethanolic ferric chloride. Treatment of a small sample with refluxing phosphorus trichloride gave 2-amino-4-methyl-6-phenyl-*s*-triazine, m.p. 155.5–156.5°, identical with the sample prepared as in Table II.

2-Amino-4-methyl-6-(1-hydroxyethyl)-*s*-triazine 1-Oxide (XIII).—A solution of 1.95 g. (0.020 mole) of methyl N-cyanoacetimidate and 2.10 g. (0.020 mole) of lactamidoxime[32] in 5 ml. of methanol was refluxed for 2.5 hr. and evaporated to dryness. Recrystallization of the solid residue from acetonitrile gave 1.05 g. of tan solid, m.p. 153–158°. Two further recrystallizations from methanol gave an analytical sample of XIII, m.p. 172–173°.

Anal. Calcd. for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.44; H, 6.22; N, 32.66.

The yield of crude product was 31%. This compound also gave a bright red color test with ferric chloride in ethanol.

Sodium N,N′-Dicyanoacetamidine (XIVa).—To a solution of 10.0 g. (0.10 mole) of methyl N-cyanoacetimidate in 50 ml. of methanol was added 6.5 g. (0.10 mole) of purified monosodium cyanamide. Upon shaking a clear warm solution formed. After an hour at 40° the methanol was removed at reduced pressure and the pale yellow solid residue was washed with cold ethanol. The yield of crude XIVa was 10.45 g. (79%), m.p. 244–245° dec. Lit.[10] m.p. 262–263°).

Anal. Calcd. for $C_4H_3N_4Na$: C, 36.93; H, 2.32; N, 43.07. Found: C, 36.34; H, 2.31; N, 42.12.

Sodium N,N′-Dicyanoformamidine (XIVb).—A solution of 1.0 g. of ethyl N-cyanoformimidate in 10 ml. of methanol was treated with 0.65 g. of monosodium cyanamide and worked up as before. This gave 1.10 g. (93%) of crude XIVb, m.p. 253–255° dec.

Anal. Calcd. for C_3HN_4Na: C, 31.05; H, 0.87; N, 48.28. Found: C, 30.33; H, 2.22; N, 46.07.

Sodium 2-Carbethoxy-N,N′-dicyanoacetamidine (XIVc).—To a solution of 0.70 g. of 90% monosodium cyanamide (0.010 mole) in 10 ml. of methanol was added 1.8 g. of ethyl 2-carbethoxy-N-cyanoacetimidate. The solution was kept at 45–50° for 10 min. and then evaporated under vacuum. The resulting gum crystallized upon prolonged scratching with a glass rod. The solid was washed with ether, dissolved in acetonitrile, filtered to remove a small amount of insoluble material, and again evaporated to a gum. The latter crystallized upon treatment with hot benzene giving 1.60 g. (80%) of XIVc, m.p. 155–165° dec.

(28) A. Pinner, "Die Imidoäther und ihre Derivate," Robert Oppenheim (Gustav Schmidt), Berlin, 1892.

(29) Prepared according to procedure for ethyl acetimidate in ref. 7b.

(30) A. Maggiolo, A. P. Phillips, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 106 (1951).

(31) F. Tiemann and P. Kruger, *Ber.*, **17**, 1685 (1884).

(32) H. Schiff, *Ann.*, **321**, 357 (1902).

Anal. Calcd. for $C_7H_7N_4O_2Na$: C, 41.59; H, 3.49; N, 27.72. Found: C, 41.84; H, 3.28; N, 27.75.

2-Amino-4-chloro-6-methyl-s-triazine (XVa).—A suspension of 6.5 g. of sodium N,N′-dicyanoacetamidine in 100 ml. of acetone was treated with a large excess of dry hydrogen chloride while cooling occasionally in an ice bath. The white insoluble solid was filtered, washed with ether, and added in portions with stirring to 75 ml. of cold 5% sodium bicarbonate. The aqueous mixture was filtered and the solid product was washed with a little cold water. The yield of XVa was 6.5 g. (90%), m.p. 202–203° dec. The analytical sample was recrystallized from ethylene dichloride, raising the m.p. to 206–207°.

Anal. Calcd. for $C_4H_5N_4Cl$: C, 33.23; H, 3.49; Cl, 24.53. Found: C, 33.34; H, 3.59; Cl, 24.69.

2-Amino-4-chloro-s-triazine (XVb).—Application of the above procedure to 0.90 g. of sodium N,N′-dicyanoformamidine gave 0.60 g. (60%) of 2-amino-4-chloro-s-triazine, m.p. >300°, which could not be recrystallized.

Anal. Calcd. for $C_3H_3N_4Cl$: C, 27.60; H, 2.32; N, 42.92; Cl, 27.16. Found: C, 27.73; H, 2.72; N, 42.60; Cl, 26.95.

2-Amino-4-methoxy-6-methyl-s-triazine (XVI). A.— A solution of 1.0 g. of sodium N,N′-dicyanoacetamidine in 10 ml. of methanol was treated with excess dry hydrogen chloride while cooling in an ice bath. The reaction mixture was worked up as before to give 0.70 g. (65%) of XVI, m.p. 259–261°, identical with a sample prepared from methyl N-cyanoacetimidate and methylpseudourea (Table II).

B.—To 0.30 g. (0.0055 mole) of sodium methoxide in 10 ml. of dry methanol was added 0.72 g. (0.0050 mole) of 2-amino-4-chloro-6-methyl-s-triazine. The reaction mixture was shaken for 10 min., warmed gently on the steam bath for 5 min., and then chilled and filtered. The resulting white solid was extracted with cold water leaving 0.57 g. (81%) of XV, m.p. 258–260°, identical with the sample described previously.

5-Amino-3-methyl-1,2,4-oxadiazole (XVIIa).—A stirred mixture of 1.40 g. (0.020 mole) of hydroxylamine hydrochloride and 2.0 g. of triethylamine (0.020 mole) in 10 ml. of ethanol was treated dropwise with 1.95 g. (0.020 mole) of methyl N-cyanoacetimidate. Toward the end of the addition the reaction mixture was cooled to keep the temperature below 40°. After 30 min. the now clear solution was evaporated to dryness and the residue was recrystallized from water to give 1.35 g. (69%) of XVIIa as white needles, m.p. 153–157°. Two additional recrystallizations raised the m.p. to 159–160.5°.

Anal. Calcd. for $C_3H_5N_3O$: C, 36.36; H, 5.09; N, 42.41. Found: C, 36.23; H, 5.28; N, 42.62.

5-Amino-3-phenyl-1,2,4-oxadiazole (XVIId).—To 3 ml. of methanol was added 0.40 g. of methyl N-cyanobenzimidate, 0.18 g. of hydroxylamine hydrochloride, and 0.25 g. of triethylamine. The mixture became warm and a clear solution formed on shaking. After an hour the methanol was removed and the residue was recrystallized from water to give 0.35 g. (88%) of XVIId, m.p. 146–147°. After a second recrystallization from benzene the m.p. was 147–148° (lit.[16,17] m.p. 153–154°).

5-Amino-3-chloromethyl-1,2,4-oxadiazole (XVIIe).—The procedure used for preparation of the 3-methyl compound, when applied to 2.65 g. of methyl 2-chloro-N-cyanoacetimidate (0.020 mole), gave an oily residue which was crystallized from water to give 1.20 g., m.p. 110–120°. Extraction of the mother liquor with ether yielded more product, which after two recrystallizations from benzene weighed 0.40 g., m.p. 116–121°; total yield of crude product, 1.60 g. (60%). Two additional recrystallizations from benzene afforded colorless prisms, m.p. 125.5–127.5°.

Anal. Calcd. for $C_3H_4ClN_3O$: C, 26.98; H, 3.02; N, 31.47; Cl, 26.55. Found: C, 27.41; H, 2.95; N, 31.13; Cl, 26.34.

This compound is a strong vesicant and should be handled cautiously.

5-Amino-1,2,4-oxadiazole-3-acetic Acid, Ethyl Ester (XVIIc).—Ethyl 2-carbethoxy-N-cyanoacetimidate, 1.85 g., was treated with hydroxylamine as before. After the methanol had been removed, the mushy residue was dissolved in water and extracted twice with ether. Evaporation of the dried extracts afforded an oil which crystallized on standing overnight. The yield of XVIIc was 1.20 g. (70%), m.p. 61–65°. This material was recrystallized once from water and once from benzene–petroleum ether; m.p. 68–70°.

Anal. Calcd. for $C_6H_9N_3O_3$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.09; H, 5.08; N, 24.33.

3-Amino-5-methyl-1,2,4-triazole (XVIII).—A solution of 1.95 g. of methyl N-cyanoacetimidate in 5 ml. of methanol was treated dropwise with 0.65 g. of 98% hydrazine while stirring and cooling in an ice bath. After the addition, during which a vigorous reaction occurred, the solution was allowed to warm to room temperature and then evaporated to dryness. The solid residue was recrystallized from acetonitrile to give 1.30 g. (67%) of the triazole as a white solid, m.p. 147–148° (lit.[33] m.p. 148°).

N-Cyanoacetamidine (XXa).—A solution of 4.2 g. of methyl N-cyanoacetimidate in 10 ml. of methanol was cooled in an ice bath while 1.5 g. of gaseous ammonia was added. After an hour at room temperature the solvent was removed. Recrystallization of the residue from ethanol gave 2.4 g. of N-cyanoacetamidine,[1] m.p. 132–135°. A second crop of 0.35 g., m.p. 122–130°, made a total of 2.75 g. (77% yield).

N-Cyano-N′-phenylacetamidine (XXb).—A solution of 2.0 g. of methyl N-cyanoacetimidate and 1.9 g. of aniline in 5 ml. of ethanol was refluxed for 12 hr. and chilled. The white crystalline product was filtered and washed with ether. The yield was 2.25 g. (70%), m.p. 189.5–192°. Upon recrystallization from ethanol the melting point was increased to 191.5–193.5° (lit.[19] m.p. 193°).

N-Cyano-N-methylacetamide (XIX).—Methyl N-cyanoacetimidate was heated in an oil bath at 160–165° for 5 hr. and then distilled. Two fractions were collected: A, b.p. 87–91° (25 mm.), and B, b.p. 95–97° (25 mm.). Fraction A partially crystallized on being chilled. The crystalline material was filtered, washed with a 2:1 petroleum ether–ether mixture, and then recrystallized twice from ether–petroleum ether to give a pure sample of XIX, m.p. 51.5–52.5°.

Anal. Calcd. for $C_4H_6N_2O$: C, 48.97; H, 6.17. Found: C, 49.16; H, 6.13.

This compound was quite unstable in storage and decomposed after a few days in a closed vial.

Fraction B was identified as unchanged starting material by its infrared spectrum.

Reaction of Methyl N-Cyanoacetimidate with Hydrogen Chloride.—A cold solution of 0.70 g. of methyl N-cyanoacetimidate in 5 ml. of ethanol was treated with an excess of dry hydrogen chloride. The white solid which formed weighed 0.50 g., m.p. 177–179° dec. It was identified as chloroformamidine hydrochloride (61% yield) by infrared comparison with an authentic sample.[34]

Acknowledgment.—The authors wish to acknowledge the technical assistance of Mr. Ronald Phillips and the aid in interpretation of the infrared spectra of Mr. N. B. Colthup.

(33) J. Thiele and K. Hedenreich, *Ber.*, **26**, 2598 (1893).

(34) H. Z. Lecher and C. L. Kosloski, U. S. Patent 2,727,922 (December 20, 1955); *Chem. Abstr.*, **50**, 15578 (1956).

Percyanophospholes

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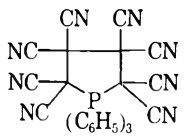
Tetracyanoethylene and dicyanoacetylene reacted with phosphines with spontaneous dimerization to give percyanophospha heterocycles or polymeric derivatives.

The reaction of acetylene dicarboxylic ester with aromatic phosphines is known to occur with the formation of a nonisolable unstable phosphole as intermediate which rearranges subsequently to a stable butadiene derivative.[1-3] Triphenylarsine and acetylene dicarboxylic ester gave a stable arsole derivative[2] and the larger size of the arsenic atom was proffered as a tentative explanation for the difference in stability between the phosphole and the arsole compounds. The present investigation suggests this to be of minor importance, however. No stable phosphole derivatives have been reported thus far which were formed from olefins or acetylenes directly.

The facile addition of triphenylphosphine to cyano-substituted ethylenic double bonds such as in tetracyano-7-oxabicyclohexa-2,5-diene which gave a stable ylid[4] invited further investigation of this type of reaction.

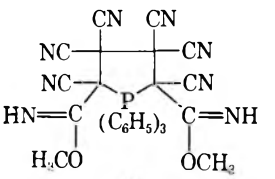
Aromatic phosphines react exothermically with two moles of tetracyanoethylene to give a stable, colorless, crystalline derivative of octacyano(triphenyl)phospholidine (I) (octacyano-P,P,P-triphenylphosphacyclopentane).



I

The reaction is best carried out in acetonitrile, but other solvents may be used successfully as long as they are unreactive toward tetracyanoethylene. The reaction also proceeded easily on diluting the two components with sodium chloride and subjecting the mixture to about 10,000 p.s.i. of external pressure. The reactants are probably brought in close contact with each other at the applied pressure, and exist in small droplets and in this state the reaction is facilitated. Different methods of preparation gave yields varying from 80 to 100%.

The structure of I as a percyanophospholidine is supported by the following results: it gave no indication of a zwitterion and failed to show the typical color test of tetracyanoethylene.[5] Decomposition occurred at about 230° with the ejection of some tetracyanoethylene and formation of a black polymeric product which still contained the triphenylphosphine unit as evidenced by the strong absorption at 9.0 μ and the three intensive absorption bands in the 13–15-μ region.



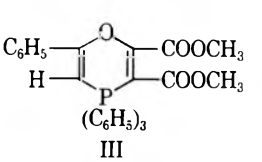
II

Reflux in methanol yielded a bisimino ether for which structure II is proposed.

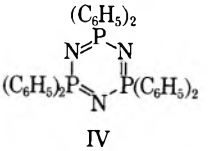
Hydrolysis with concentrated hydrochloric acid at 140–150° yielded butanetetracarboxylic acid as a mixture of the high and low melting form and triphenylphosphine oxide. The acidic component was further characterized by conversion into the tetramethyl ester whose infrared spectrum was superimposable on that of an authentic specimen. Further confirmation was obtained by conversion to its bisanhydride. These results indicated that two tetracyanoethylene units had been linked together.

Strong evidence for the phosphole structure of I was given by the nuclear magnetic resonance spectrum. The phosphorus chemical shifts in some compounds including I are given in Table I. It has been reported by several investigators[6-9] that in compounds of the general structure $\diagdown\!\!\diagup P{=}O$ and $\diagdown\!\!\diagup P{=}N$ the resonance of phosphorus generally lies above that of phosphoric acid. In cases where phosphorus is attached to a larger number of oxygen or nitrogen atoms somewhat lower chemical shifts have been reported.

The shift of 0.0 ± 1.0 p.p.m. for $(C_6H_5)_3P{=}N{-}C_6H_5$ is in good agreement with the previous observations in similar compounds. In III where there is little doubt about the structure[1] the chemical shift is −17.0 ± 1.0



III



IV

p.p.m. which is quite different from the others. The chemical shift in IV which is a very stable compound[10] is very much in agreement with other similar compounds of this basic structure.[11] This slightly low field shift in contrast to the compounds of the structure $\diagdown\!\!\diagup P{=}N\!\!\diagdown\!\!\diagup$

(1) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 2018 (1961).

(2) J. B. Hendrickson, R. E. Spenger, and J. J. Sims, *Tetrahedron Letters*, 477 (1961).

(3) A. W. Johnson and J. C. Tebby, *J. Chem. Soc.*, 2126 (1961).

(4) C. D. Weis, *J. Org. Chem.*, **27**, 3520 (1962).

(5) B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and H. F. Mower, *J. Am. Chem. Soc.* **80**, 2806 (1958).

(6) J. R. Van Wazer, C. F. Callis, J. N. Shovlery, and R. C. Jones, *ibid.*, **78**, 5715 (1956).

(7) K. John, T. Moeller, and L. F. Audrieth, *ibid.*, **82**, 5616 (1960).

(8) K. John, T. Moeller, and L. F. Audrieth, *ibid.*, **83**, 2608 (1961).

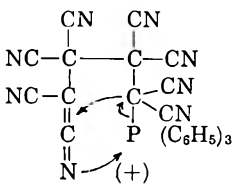
(9) E. Fluck, *Chem. Ber.*, **94**, 1388 (1961).

(10) K. Freudenberg and H. Richtzenhain, *Ann.*, **552**, 126 (1942). We are indebted to G. Nichols for a sample of this compound.

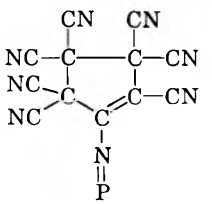
(11) M. Becke-Goehring, K. Kohn, and E. Fluck, *Z. anorg. allgem. Chem.*, **302**, 103 (1959).

could be due to either the second nitrogen or anisotropy effect of the phosphonitrile ring.[12-14] The two possible structures for the product are I and VI. In I the phosphorus atom is bonded as in III and in VI it is like $(C_6H_5)_3P{=}N{-}C_6H_5$. The vast difference in the chemical shifts of these compounds (see Table I) arises from the nature of the bonding rather than from the substituents. The chemical shift of I is −22.0 p.p.m. and is close to that of III in which the phosphorus is attached to five carbon atoms. To the extent the phosphorus chemical shifts are invariably positive in compounds of the type $-P{=}N$ this low chemical shift suggests the structure to be I rather than VI. It was thought that n.m.r. studies of C^{13} nuclei should give an unambiguous assignment of I based on its symmetry, but solubility did not permit observance of C^{13} resonance in natural abundance.

Structure VI conceivably might have been formed by migration of triphenylphosphine from carbon to the nitrogen on the other end of the percyanoalkane chain. (V–VI). Acidic cleavage of the P–N bond of VI, followed by hydrolysis of the imino compound formed to give a β-ketone and its subsequent cleavage would also afford butanetetracarboxylic acid.



V



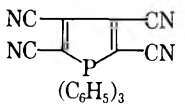
VI

Triphenylarsine or stibine did not react with tetracyanoethylene, as was observed previously for the oxabicycloderivative.

A possible explanation is that the *d*-orbital of the phosphorus overlaps partially the π-electron field of the alpha cyano substituents and contributes thus to the stability of I while the arsine atom is large enough to frustrate this interaction. The stability of IX compared with the corresponding tetraester[2,3] derived from it is attributed to the same effect.

ortho- and *para*-methyl-substituted triphenylphosphines (VII, VIII) underwent the same type of reaction. Tris(*p*-methoxyphenylphosphine), however, gave a tarry product only. Tributylphosphine gave a dark-colored polymeric product of low molecular weight. The 2:1 ratio of tetracyanoethylene to phosphine indicates that the same type of reaction occurred as with aromatic phosphines with the formation of an unstable phospholidine. Analysis suggested that the product, apparently during the work-up procedure, lost two cyano groups which were given off as hydrogen cyanide. No reaction was observed with fumaronitrile.

Dicyanoacetylene and triphenylphosphine reacted in acetonitrile with the formation of tetracyano(triphenyl)phosphole (IX) (tetracyano-P,P,P-triphenylphosphacyclopentadiene). The orange-colored compound



IX

is rather insoluble in organic solvents. The assignment of its structure is based on analytical results and the similarity of the pattern of its infrared spectrum with the spectrum of I. Thermal decomposition at 245° gave carbonized product and triphenylphosphine. There was no indication of a zwitterionic structure such as was proposed for the analogous methylphosphole tetracarboxylate[2,3] or any rearranged product thereof.[2]

Experimental[15]

Octacyano-P,P,P-triphenylphospholidine. A.—Triphenylphosphine (5.8 g., 0.022 mole) was added slowly to a slurry of tetracyanoethylene (5.2 g., 0.04 mole) in acetonitrile (15 ml.). The temperature was maintained at 25–35° by external cooling. After the addition was completed stirring was continued for 10 min. and then the crystalline product (8.4 g., 80%) filtered from the ice-cold solution. Recrystallization of the buff-colored material from benzene yielded colorless crystals, m.p. 168.5–170°. The compound turned slightly red on melting.

Anal. Calcd. for $C_{30}H_{15}N_8P$: C, 69.50; H, 2.92; N, 21.61; P, 5.97. Found: C, 69.78; H, 3.15; N, 21.52; P, 5.89.

Mol. wt. (benzene) calcd.: 518; found: 512, 527. The infrared spectrum showed characteristic absorptions for CN at 4.41 μ (w) and 4.52 μ (w) with a ratio of the size of the bands about 1:2. The aromatic vibration bands were at 6.22 μ (vs), 6.32 μ (m), 6.92 μ (m), 7.20 μ (m). The absorption at 8.93 μ (s) was found to be characteristic of all aromatic phosphine compounds usually ranging from 8.9 to 9.2 μ. Further characteristic absorptions are at 9.98 μ (w); 10.95 μ (m); 13.12 μ (m); 13.31 μ (w); 13.72 μ (s); 14.40 μ (s). The triple sequence of medium to strong sized absorption bands in the 13.3–14.5-μ region was found to be very characteristic of five bonded phosphorus compounds and aromatic phosphonium compounds in general. The ultraviolet spectrum showed absorptions at $\lambda_{max}^{dioxane}$, 300 mμ (ε 15,700); shoulder at 276 mμ (ε 10,480); shoulder at 269 mμ (ε 9960).

N.m.r. Spectra. All the spectra were obtained on a Varian Associates high resolution spectrometer operating at 15.1 Mc./sec. The solvent was dioxane in all cases and saturated solutions were used. Calibrations were carried out by superposition technique with 85% orthophosphoric acid in a capillary as reference. All the chemical shifts are expressed in parts per million with respect to 85% orthophosphoric acid.

B.—Tetracyanoethylene (2.56 g., 0.002 mole) and triphenylphosphine (2.71 g., 0.001 mole) were well mixed with sodium chloride (5 g.) and the mixture placed in a die and subjected to 10,000-p.s.i. pressure. The pellet obtained was powdered and added to water (30 ml.). Buff-colored crystals (5.1 g., 97%) were filtered off, m.p. 168°, whose infrared spectrum was superimposable to the spectrum of the previously obtained sample.

Octacyano-P,P,P-tri-*o*-tolylphospholidine (VII).—Tri-*o*-tolylphosphine (3.04 g., 0.01 mole) was added to a suspension of tetracyanoethylene (.256 g., 0.02 mole) in acetonitrile (15 ml.). The slurry was heated to 50° whereupon a sudden change in color occurred. Subsequent filtration of the ice-cold solution gave buff-colored crystals (4.37 g., 78%). Recrystallization from benzene afforded colorless crystals, m.p. 235–237°.

Anal. Calcd. for $C_{33}H_{21}N_8P$: C, 70.70; H, 3.78; N, 19.98; P, 5.50. Found: C, 70.65; H, 3.88; N, 19.85; P, 5.49.

Octacyano-P,P,P-tri-*p*-tolylphospholidine (VIII).—*p*-Tolylphosphine (3.04 g., 0.01 mole) and tetracyanoethylene (2.56 g., 0.02 mole) were added to acetonitrile (15 ml.). The crystals went into solution with moderate evolution of heat, and crystals deposited after a few minutes. Further cooling of the solution furnished buff-colored crystals (3.7 g., 66.5%). Recrystallization from acetonitrile and subsequently from benzene gave colorless crystals, m.p. 205–206°.

Anal. Calcd. for $C_{33}H_{21}N_8P$: C, 70.70; H, 3.78; N, 19.98; P, 5.53. Found: C, 71.01; H, 4.02; N, 19.73; P, 5.38.

(12) J. H. Goldstein and G. S. Reddy, *J. Chem. Phys.*, **36**, 2644 (1962).
(13) K. Ito, *J. Am. Chem. Soc.*, **80**, 3502 (1958).
(14) J. S. Waugh and R. W. Fessenden, *ibid.*, **79**, 846 (1957).
(15) Melting points are uncorrected.

The infrared spectrum exhibited the same absorption pattern as I, except for the additional CH_3 bands.

Hexacyanobis(imidic Acid, Methyl Ester)-P,P,P-triphenylphospholidine (II).—A solution of octacyano-P,P,P-triphenylphospholidine (5 g., 0.096 mole) in methanol (40 ml.) was refluxed for 10 min. Filtration of the ice-cold mixture gave off-colored crystals (2 g., 35.5%). Recrystallization from acetonitrile gave colorless crystals, m.p. 215–220° dec. The compound turned slightly brown at about 180°.

Anal. Calcd. for $C_{32}H_{23}N_8O_2P$: C, 65.98; H, 3.98; N, 19.23; P, 5.32. Found: C, 65.70; H, 4.37; N, 19.78; P, 5.36.

The infrared spectrum exhibited principal absorption bands at 3.01 μ (m); 4.63 μ (w); 6.03 μ (s); 6.35 μ (s); 6.43 μ (s).

Hydrolysis of I.—Octacyano-P,P,P-triphenylphospholidine (50 g., 0.0965 mole) was suspended in concentrated hydrochloric acid (210 ml.) and the mixture heated in an autoclave to 140° for 3 hr. The product was diluted with 500 ml. of water and allowed to stand for 12 hr. Filtration gave impure triphenylphosphine oxide (30.3 g., theoretical yield 25 g.), identified by the superimposability of the infrared spectrum of a recrystallized sample on that of a known specimen. The filtrate was evaporated to dryness on a steam bath. The residue (55.7 g.) was extracted with ether in a Soxhlet for 24 hr. Concentration of the ethereal extract (50 ml.) yielded a white crystalline precipitate (11.9 g., 53%) of crude 1.2.3.4 butanetetracarboxylic acid as a mixture of the low and high melting forms. It was filtered and washed with a few milliliters of cold ether. An analytical sample was recrystallized from water, m.p. 235°.[16] (It melted at 192°, resolidified, and melted finally at 235°.) Crude butanetetracarboxylic acid (1.5 g., 0.0064 mole) was treated with an excess of diazomethane in ether. Recrystallization of the tetramethyl ester from petroleum ether gave a mixture of the low and high melting form, m.p. 45–62°.

Anal. Calcd. for $C_{21}H_{188}O$: C, 49.68; H, 6.25. Found: C, 49.88; H, 6.35.

The infrared spectrum was superimposable with the one of an authentic sample of methyl 1.2.3.4-butanetetracarboxylate. The mixture of the butanetetracarboxylic acids (1 g., 0.0043 mole) was refluxed in acetic anhydride (8 ml.) for 3 min. The precipitate of butanetetracarboxylic acid dianhydride was filtered and identified by the superimposability of the infrared spectrum and the m.p. 248°, with a specimen which was prepared according to the literature.[17]

Thermal Decomposition of I.—Octacyano-P,P,P-triphenylphospholidine (1 g., 0.0019 mole) was heated in a test tube to 220–250° for 8 min. Tetracyanoethylene sublimed to the cold part of the tube and was identified by its infrared spectrum. The dark-colored residue showed still the typical absorption pattern of the triphenylphosphine unit as shown by its absorption at 9.1 μ and the three strong bands between 13 and 15 μ.

Tetracyanoethylene and Tributylphosphine.—Tributylphosphine (10 g., 0.05 mole) was added slowly to a suspension of tetracyanoethylene (12.5 g., 0.1 mole) in acetonitrile (30 ml.) which was immersed in an ice bath. The dark-colored solution was allowed to stand at room temperature for 30 min. and then the solvent was removed under reduced pressure. The dry, dark-colored residue (20 g., 88%) was extracted with ether in a Soxhlet for 8 hr. The product (insoluble in ether) softened at 190–230°.

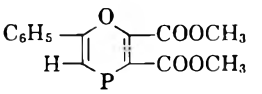
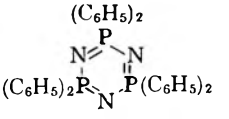
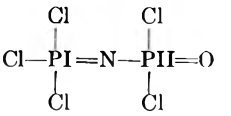
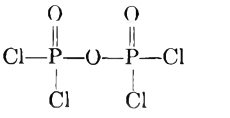
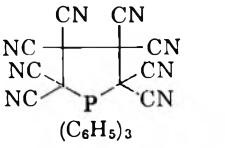
Anal. Calcd. for $C_{22}H_{29}N_6PO_2$: C, 59.98; H, 6.63; N, 19.08; P, 7.03. Found: C, 60.43; H, 6.71; N, 18.52; P, 7.22.

(16) W. Bertram, *Ber.*, **36**, 3295 (1903).

(17) A. J. Viorlew and W. J. Mur, "Syntheses of Organic Compounds," Ved Verlat Technik, Berlin, 1959, p. 29.

TABLE I

P^{31} N.M.R. CHEMICAL SHIFTS IN SOME ORGANO-PHOSPHOROUS COMPOUNDS

Compound	Lit.	P^{31} chemical shift, p.p.m.
$(C_6H_5)_3P{=}N{-}C_6H_5$		0.0 ± 1.0
		
$(C_6H_5)_3$	1	−17.0 ± 1.0
$(C_6H_5)_4PBr$		−22.0 ± 1.0
	10	−9.0 ± 2.0
	9	(PI) + 0.1 ± 1.0 (PII) + 14.3 ± 1.0
	9	+10.0 ± 1.0
		−22.0 ± 1.0

Mol. wt. in dimethyl sulfoxide: 4953, 5084. The only characteristic absorption in the infrared spectrum was the CN absorption at 4.50 μ.

Tetracyano-P,P,P-triphenylphosphole (IX).—All reactants were carefully purified and kept under nitrogen during the experiment. A solution of dicyanoacetylene[18] (3.0 g., 0.040 mole) in acetonitrile (6 ml.) was added to a solution of triphenylphosphine (5.2 g., 0.02 mole) in acetonitrile (50 ml.) at 25–30°. The deep purple-colored solution was allowed to stand for 12 hr. Filtration gave light brown crystals (1.12 g., 13.6%). Several recrystallizations from pyridine gave orange-colored crystals, m.p. 237–239° (dec.).

Anal. Calcd. for $C_{26}H_{15}N_4P$: C, 75.35; H, 3.65; N, 13.52; P, 7.48. Found: C, 75.52; H, 4.00; N, 12.52, 13.10; P, 7.47.

The infrared spectrum showed absorption at 4.50 μ (w); 4.56 μ (m); 4.62 μ (m); 6.73 μ; 6.80 μ; 6.98 μ; 7.33 μ; 7.60 μ; 9.30 μ; 13.30 μ; 13.82 μ; 14.45 μ. Absorption in the ultraviolet occurred at $\lambda_{max}^{dioxane}$, 485 mμ and 378 mμ. The deep blue mother liquor yielded upon evaporation a blue-colored, apparently polymeric residue.

Thermal Decomposition of IX.—Tetracyano-P,P,P-triphenylphosphole (0.2 g., 0.00048 mole) was heated in a sublimation apparatus to 250–260° at 0.5 mm. for 4 hr. The sublimed triphenylphosphine (0.095 g., 75%) was identified by comparison of its infrared spectrum with that of an authentic sample. The carbonaceous residue weighed 0.70 g.

(18) E. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

Chemistry of Isocyanic Acid. I. Reactions of Isocyanic Acid with Carbonyl Compounds

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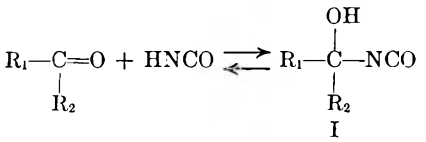
Received January 7, 1963

A number of α-hydroxy isocyanates, a new class of compounds, have been synthesized from isocyanic acid and carbonyl compounds such as formaldehyde, chloral, s-dichlorotetrafluoroacetone, trifluoroacetaldehyde, and perfluorocyclobutanone. These novel isocyanates undergo most of the normal isocyanate reactions. They can be converted readily to 1,3,5-oxadiazine-2,4-diones and to α-chloro isocyanates, an unusually reactive class of compounds. α-Chloromethyl isocyanate, obtained from hydroxymethyl isocyanate and thionyl chloride, was found to react with styrene to give cinnamyl isocyanate and 3-chloro-3-phenylpropyl isocyanate, with *m*-xylene to give 2,4-dimethylbenzyl isocyanate, and with phenols to give 1,3-oxazinones.

Previously reported chemistry of isocyanic acid, a long known compound,[1] has involved reactions with amines to form ureas[2] and with alcohols to form urethanes[3] and allophanates.[4] Reactions of isocyanic acid with chloral have given cyclic products.[5] The addition of isocyanic acid to Schiff's bases[6] and azines[7] has given heterocyclic structures.

Our studies have led to new chemistry of isocyanic acid which will be reported in this and subsequent papers. In this paper, the addition of isocyanic acid to certain carbonyl compounds to give the hitherto unknown α-hydroxy isocyanates (I) is discussed.



I

Previous attempts[8] to prepare compounds of this type by the Lossen rearrangement have been unsuccessful.

The formation of hydroxy isocyanates has been found to occur with such carbonyl compounds as formaldehyde, s-dichlorotetrafluoroacetone, trifluoroacetaldehyde, 5*H*-perfluoropentanal, perfluorocyclobutanone, chloral, dichloroacetaldehyde, and perfluoroacetone. It appears that most carbonyl compounds capable of forming hydrates undergo this reaction. In general, the carbonyl compounds have electronegative substituents in the α position.

Because of the high reactivity of hydroxy isocyanates, it is usually best to prepare them at temperatures of 0° or below. The extent of the formation of the hydroxy isocyanate on mixing a carbonyl compound with isocyanic acid can be determined readily by near-infrared spectrophotometry. As the reaction proceeds, the absorption band at 1.47 μ (NH of HNCO) decreases, and a band at 1.42–1.44 μ appears as a result of the formation of hydroxyl groups.

Hydroxymethyl Isocyanate (II).—We have found that the addition of monomeric formaldehyde to ethereal solutions of isocyanic acid at about −70° gives

$$CH_2O + HNCO \longrightarrow HOCH_2NCO$$

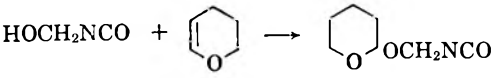
II

hydroxymethyl isocyanate in essentially quantitative yield. Upon removal of the solvent at low temperatures under reduced pressure, hydroxymethyl isocyanate is isolated and is found to melt at about −50°. Infrared examination of this product at −50° showed strong absorption at 2.9 μ (OH) and 4.43 μ (NCO), but none at 5.4 μ to 5.5 μ (CO). This spectrum is consistent with the $HOCH_2NCO$ structure but not with an alternative cyclic structure.

Hydroxymethyl isocyanate polymerizes with explosive violence above 0°. Solutions in diethyl ether are somewhat more stable and remain clear for as long as an hour at room temperature. The formation of a slight turbidity signals an incipient rapid polymerization. No additives were found which would increase the stability of the ether solutions.

Spontaneous polymerization of hydroxymethyl isocyanate gave a friable solid insoluble in water. The elemental analyses of this solid indicated that carbon dioxide was lost during polymerization. The polymers formed with either a basic or acidic catalyst at low temperatures showed a loss of formaldehyde during polymerization. Most of the polymers obtained were of low molecular weight and in no case could be represented by the formula $(HOCH_2NCO)_x$.

Hydroxymethyl isocyanate forms adducts with α,β-unsaturated ethers, such as dihydropyran and butyl vinyl ether, as illustrated by the following reaction.



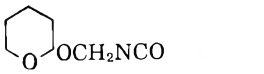
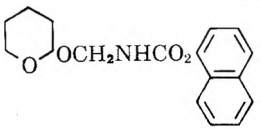
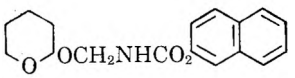
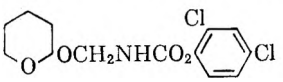
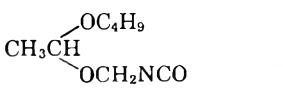
This reaction proceeds readily at room temperature with an acidic catalyst such as *p*-toluenesulfonic acid. These adducts are relatively stable, distillable liquids that can be converted to the expected isocyanate derivatives (see Table I).

In general, amines promote the rapid polymerization of hydroxymethyl isocyanate. To obtain good yields of hydroxymethylureas it is necessary to add the hydroxymethyl isocyanate to a solution of amine at low temperature. For example, when an ethereal solution of hydroxymethyl isocyanate was added slowly to an ethereal solution of aniline at −30° N-hydroxymethyl-N′-phenylurea was obtained in high yield. This compound has also been obtained from phenylurea and formaldehyde.[9] On the other hand, when aniline was

(1) F. Wöhler, *Ann. Chim. et Phys., Ser. 2*, **27**, 196 (1824).
(2) M. Bogert and G. Scatchard, *J. Am. Chem. Soc.*, **38**, 1606 (1916).
(3) J. Johnson and L. Ferstandig, *Science*, **110**, 441 (1949).
(4) M. A. Spielman, J. D. Barnes, and W. J. Close, *J. Am. Chem. Soc.*, **72**, 2520 (1950); H. W. Blohm and E. I. Becker, *ibid.*, **72**, 5342 (1950).
(5) C. Bischoff, *Ber.*, **5**, 86 (1872).
(6) W. J. Hale and N. A. Lange, *J. Am. Chem. Soc.*, **41**, 379 (1919).
(7) J. R. Bailey and N. H. Moore, *ibid.*, **39**, 279 (1917).
(8) L. W. Jones and D. H. Powers, *ibid.*, **46**, 2518 (1924).
(9) G. Zigeuner, W. Knierzinger, and K. Voglar, *Monatsh.*, **82**, 847 (1951).

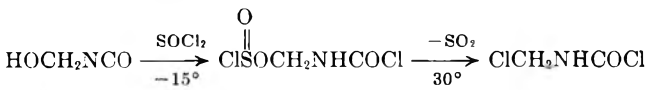
TABLE I

DERIVATIVES OF HYDROXYMETHYL ISOCYANATE

Structure	M.p., °C.	B.p., °C. (mm.) ($n^{25}D$)	Anal. (calcd.)/found C	H	N
		87–88 (15) (1.4499)	(53.48) 53.99	(7.05) 7.12	(8.91) 8.91
	143–147		(54.83) 54.56	(6.02) 6.12	(9.84) 10.09
	81–82		(67.76) 67.38	(6.36) 6.55	(4.65) 4.86
	92–94		(67.76) 67.90	(6.36) 6.39	(4.65) 4.80
	98–100		(48.76) 48.07	(4.72) 4.93	(4.38) 4.44
	88–91	85–87 (16) (1.4192)	(55.47) 56.10	(8.73) 9.00	(8.95) 8.20
			(55.90) 55.64	(7.04) 6.86	(9.31) 9.33

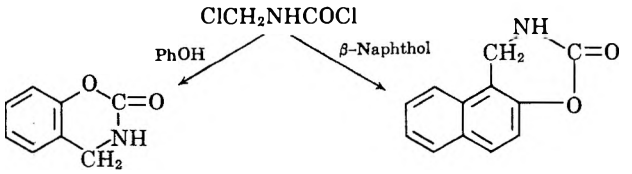
added to a solution of hydroxymethyl isocyanate a complicated mixture of products was obtained.

A new synthesis of chloromethyl isocyanate has been uncovered in the reaction of hydroxymethyl isocyanate with thionyl chloride. This reaction takes place in the cold to give first the chlorosulfite which loses sulfur dioxide on warming to room temperature.



The resulting chloromethylcarbamoyl chloride, m.p. 9–10°, was converted to the known chloromethyl isocyanate[10] by treatment with α-pinene, *d,l*-limonene, acrylonitrile or pyridine. Both chloromethylcarbamoyl chloride and chloromethyl isocyanate are very potent respiratory irritants.

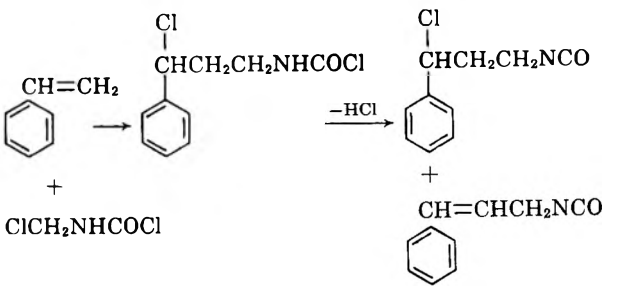
Chloromethylcarbamoyl chloride reacted with phenol and naphthol to give cyclic structures.



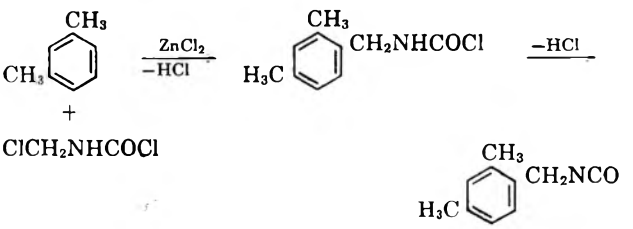
Although the product from naphthol appears to be new, the derivative[11] of phenol has been prepared by another route.

Chloromethylcarbamoyl chloride added readily to styrene in the presence of small amounts of mercuric chloride to give an adduct that lost hydrogen chloride on heating to form cinnamyl isocyanate.

Under mild conditions with zinc chloride as a catalyst, chloromethylcarbamoyl chloride reacted with *m*-xylene



to give 2,4-dimethylbenzylcarbamoyl chloride, which was converted to the corresponding isocyanate.



1-Hydroxy-2,2,2-trichloroethyl Isocyanate (III).—The reaction of chloral and isocyanic acid proceeds slowly at 0° but is complete after about seven hours.

1-Hydroxy-2,2,2-trichloroethyl isocyanate (III) is a low melting solid (m.p. 25°), recrystallizable from carbon tetrachloride. Above its melting point it is slowly converted to solid products of indefinite composition, which are soluble in acetone but insoluble in carbon tetrachloride.

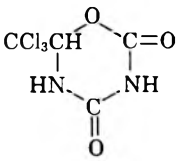
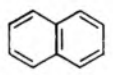
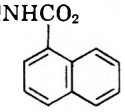
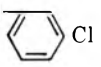
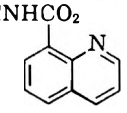
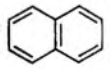
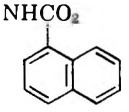
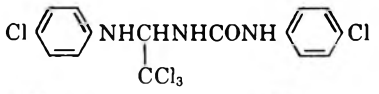
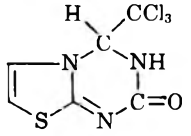
A new cyclic structure, a 1,3,5-oxadiazine-2,4-dione, was obtained on treatment of 1-hydroxy-2,2,2-trichloroethyl isocyanate with water. This compound was also made from chloral hydrate and isocyanic acid.

(10) G. Schroeter, *Ber.*, **42**, 3356 (1909).

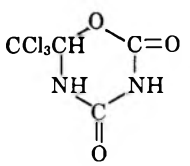
(11) H. Lindemann and W. Schultheis, *Ann.*, **464**, 248 (1928).

TABLE II

DERIVATIVES OF $CCl_3CH(OH)NCO$

Structure	M.p., °C.	Anal. (calcd.)/found C	H	N	Cl
$CCl_3CH(OH)NHCONHC_6H_5$	145			(9.88) 9.97	(37.55) 37.52
$CCl_3CH(OH)NHCONHC_6H_4Cl$-*p*	183–185			(8.80) 8.79	(44.51) 43.91
$(CCl_3CH(OH)NH)_2CO$	173–182[a]	(16.92) 16.35	(1.70) 1.81	(7.90) 8.01	(59.95) 58.75
	190–200[b]	(20.55) 20.68	(1.30) 1.76	(12.00) 12.03	(45.60) 45.50
$CCl_3CHClNCO$	58 (1)[c]			(6.71) 6.85	(67.90) 67.51
$CCl_3CHClNHCO_2CH_3$	93–94	(19.94) 20.03	(2.09) 2.24	(5.81) 5.87	(58.87) 59.10
$CCl_3CH(OCH_3)NHCO_2CH_3$	64–65	(25.39) 26.08	(3.41) 3.47	(5.92) 5.67	(44.98) 44.73
$CCl_3CHClNHCO_2$ 	158–165	(44.22) 43.91	(2.57) 2.34	(3.97) 3.88	(40.19) 39.95
$CCl_3CHClNHCO_2$ 	175–188	(44.22) 43.61	(2.57) 2.59	(3.97) 4.32	(40.19) 39.99
$CCl_3CHClNHCO_2$ 	135–139	(29.07) 28.52	(1.36) 1.10	(3.77) 3.81	(57.21) 56.90
$CCl_3CHClNHCO_2$ 	121–125			(7.91) 7.87	
$CCl_3CH(OCH_3)NHCO_2$ 	108–110			(4.02) 3.60	(30.60) 30.08
$CCl_3CH(OCH_3)NHCO_2$ 	149–151	(48.30) 48.13	(3.45) 3.42	(4.02) 4.26	
	162–164	(42.13) 41.90	(2.81) 2.90	(9.83) 9.62	
	153–156	(50.23) 49.83	(3.93) 3.95	(11.72) 11.81	
	195 dec.	(26.44) 26.75	(1.48) 1.74	(15.42) 15.25	

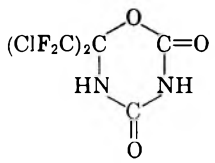
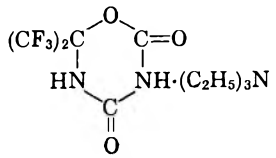
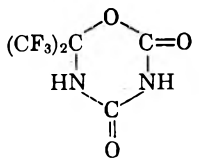
[a] Lit.[15] —190° dec. [b] Depended on the rate of heating. [c] B.p., °C. (mm.).



1-Hydroxy-2,2,2-trichloroethyl isocyanate formed the expected derivatives with aniline and *p*-chloroaniline. With thionyl chloride it gave 1,2,2,2-tetrachloroethylcarbamoyl chloride and 1,2,2,2-tetrachloroethyl isocyanate. Both of these compounds are potent respiratory irritants.

The α-chlorine in 1,2,2,2-tetrachloroethyl isocyanate is highly reactive. Thus, when this compound was treated with alcohols or amines, the first product was the expected derivative of the isocyanate, but when

TABLE III
DERIVATIVES OF VARIOUS HYDROXY ISOCYANATES

Structure	M.p., °C.	Anal. (calcd.)/found C	H	N	F
	98–99	(21.07) 21.36	(0.71) 0.99	(9.83) 9.84	(26.60) 26.35
$(ClF_2C)_2C(OH)NHCO_2C_2H_5$	44–46	(25.02) 25.09	(2.45) 2.56	(4.90) 5.20	(26.40) 26.26
$(ClF_2C)_2C(OH)NHCONHC_6H_6$[a]	75–77			(8.40) 8.84	(22.70) 22.09
$CF_3CH(OH)NHCONHC_6H_5$[a]	145–147			(11.97) 12.20	(24.40) 23.88
$HC_4F_8CH(OH)NHCONHC_6H_5$	125–126			(7.65) 7.62	(41.51) 41.22
	120–121			(11.11) 11.16	(45.22) 44.90
	110–111	(37.40) 37.65	(4.85) 5.09	(11.90) 12.12	(32.27) 31.65

[a] Contained traces of phenylurea.

excess reactant was used the α-chlorine was replaced with an alkoxy or amino group as illustrated by the reaction with methanol.

$$CCl_3CHClNCO \xrightarrow[1\ mole]{CH_3OH} CCl_3CHClNHCO_2CH_3 \xrightarrow[excess]{CH_3OH} CCl_3CH(OCH_3)NHCO_2CH_3$$

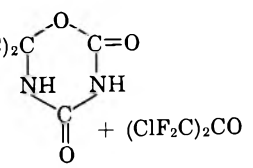
In a similar manner the reaction of 1,2,2,2-tetrachloroethyl isocyanate with water gave $(CCl_3CH(OH)NH)_2CO$.

The derivatives obtained from 1-hydroxy-2,2,2-trichloroethyl isocyanate are listed in Table II.

Bis-(chlorodifluoromethyl)-hydroxymethyl Isocyanate (IV).—Of the various α-hydroxy isocyanates prepared, bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate is one of the most stable at room temperature. It does not undergo polymerization at room temperature and can be distilled under reduced pressure. Examination by near-infrared spectrophotometry of both the product isolated by distillation and equimolar mixtures of isocyanic acid and *s*-dichlorotetrafluoroacetone showed that bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate exists in equilibrium with its precursors. These equilibrium mixtures contained nearly 100% of the hydroxy isocyanate at −20°, 98% at 0°, and 95% at 25°.

This hydroxy isocyanate reacted readily with amines and alcohols to form the expected derivatives (see Table III).

Attempts to obtain a linear polyurethane by the use of pyridine as a catalyst led instead to the cyclic structure of the type obtained from chloral.

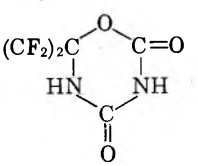
$$2(ClF_2C)_2C(OH)NCO \xrightarrow{pyridine} \text{  } + (ClF_2C)_2CO$$

Bis-(trifluoromethyl)-hydroxymethyl Isocyanate (V).

$$(CF_3)_2CO + HNCO \rightleftharpoons (CF_3)_2C(OH)NCO$$
V

—Bis-(trifluoromethyl)-hydroxymethyl isocyanate is similar to IV in stability. It can be distilled without appreciable decomposition at low temperatures under reduced pressures, but decomposes reversibly at temperatures much above 0°.

On standing in glass containers V is slowly converted to the 1,3,5-oxadiazine-2,4-dione,



an acidic compound that readily forms a salt on treatment with triethylamine in tetrahydrofuran.

Other Hydroxy Isocyanates.—Trifluoroacetaldehyde and 5*H*-perfluorovaleraldehyde reacted rapidly with isocyanic acid at 0° to form the corresponding hydroxy isocyanates. 1-Hydroxy-2,2,2-trifluoroethyl isocyanate from trifluoroacetaldehyde was stable at −20° for several days but polymerized at 0°. On the other hand,

the hydroxy isocyanate from 5*H*-perfluorovaleraldehyde was stable for at least three days at 25°. Both hydroxy isocyanates formed ureas with aniline (see Table III). 1-Hydroxy-2,2,2-trifluoroethyl isocyanate reacted slowly with refluxing ethanol to give a mixture of ethyl N-1-hydroxy-2,2,2-trifluoroethylcarbamate and ethyl carbamate.

Experimental

Preparation of Isocyanic Acid.—Isocyanic acid was prepared routinely essentially by a literature method.[12] Cyanuric acid obtained from Eastman Kodak or American Cyanamid was pyrolyzed at 400–550° under a stream of nitrogen. The crude isocyanic acid was collected in traps cooled with Dry Ice–acetone. Redistillation over phosphorus pentoxide gave high purity isocyanic acid with only trace amounts of hydrogen cyanide as indicated by gas chromatography at 22° with a column of Silicone 703 on Columpak.

The purified isocyanic acid could be kept at −50° or below for months without apparent change. However, on warming, it underwent rapid polymerization or trimerization of explosive character so that caution was necessary. By comparison with acetylene or nitrocellulose, isocyanic acid is a mild explosive.

Preparation of α-Hydroxy Isocyanates and Their Derivatives.—The general procedure for preparing α-hydroxy isocyanates comprised mixing isocyanic acid and the carbonyl compound in essentially equimolar quantities at −78° and then allowing the mixture to warm to a temperature of about 0°, depending on the stability of the product. Solvents such as diethyl ether and carbon tetrachloride were used in some cases.

The rate of adduct formation varied with the carbonyl compound. The progress of the reaction was followed by means of near-infrared spectrophotometry.

Hydroxymethyl Isocyanate.—Anhydrous formaldehyde, generated by heating 30 g. (1 mole) of α-polyoxymethylene[13] (formed by base catalysis), was passed into a stirred solution of 39.2 g. (0.91 mole) of isocyanic acid in 200 ml. of anhydrous diethyl ether at −78° over a period of 107 min. Analysis of the reaction mixture at this point by near-infrared showed a strong OH band at 1.42 μ [the optical density of a 1% carbon tetrachloride solution in a 10-cm. cell was 0.528 at room temperature, whereas the optical density at 1.47 μ (HN of HNCO) was only 0.018, indicating that virtually all of the isocyanic acid had reacted].

The solvent was removed at −30° under 0.5-mm. pressure to yield 69 g. (theory 66) of a mobile liquid. On cooling, this liquid formed a crystalline solid at about −52°. Further purification was effected by partial freezing and separation of the solid from the liquid. The resulting solid was triturated with pentane, and residual amounts of pentane were removed by distillation [−29° to −10° (0.5 mm.)]. The final product melted at about −50°. The analysis of hydroxymethyl isocyanate was difficult because of its instability.

Anal. Calcd. for $C_2H_3NO_2$: C, 32.88; H, 4.14; N, 19.17; mol. wt., 73.05. Found: C, 33.55; H, 4.34; N, 19.20; mol. wt., 79, 80 (benzene).

Infrared analysis at −50° showed −NCO (4.43 μ), OH (2.9 μ), and no carbonyl.

N-Hydroxymethyl-N′-phenylurea.—At −35°, a mixture of 26 g. of hydroxymethyl isocyanate and 30 g. of ether was added with stirring over a period of 30 min. to a solution of 47 g. of aniline in 150 ml. of ether. The mixture was allowed to warm to −10° and poured into 500 ml. of cold 5% acetic acid. The solid precipitate was washed with ether and methanol. The analytical sample was recrystallized from methanol (m.p. on rapid heating, 176–182° dec.). The infrared spectrum showed absorption at 3.0, 3.05 μ (NH); 6.08 μ (CO); 6.45 μ (amide II); and 7.6, 13.2 μ (C_6H_5NH).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.51; H, 6.12; N, 16.85.

When aniline was added to hydroxymethyl isocyanate, an unidentified mixture was obtained.

2-Tetrahydropyranyloxymethyl Isocyanate.—A mixture of 135 g. of hydroxymethyl isocyanate, 400 g. of dihydropyran, 185 g. of ether, and 0.5 g. of *p*-toluenesulfonic acid was prepared at −5°. Within a few minutes the temperature rose to 20°. After the mixture had stood about 10 days at 25°, 188 g. of 2-tetrahydropyranyloxymethyl isocyanate, b.p. 87–88° (15 mm.), was obtained (see Table I for analytical data and for information on a similar adduct with butyl vinyl ether).

2-Tetrahydropyranyloxymethyl isocyanate and the adduct from butyl vinyl ether reacted (pyridine catalysis) readily with phenols in ether solution to give a variety of urethanes and with *p*-chloroaniline (see Table I) to form ureas.

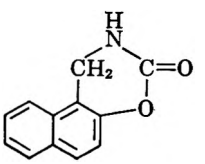
Chloromethylcarbamoyl Chloride and Chloromethyl Isocyanate.—A mixture of 115 g. of hydroxymethyl isocyanate and 100 g. of ether was added at −15° with stirring to a mixture of 205 g. of thionyl chloride, 400 ml. of pentane, and 2 ml. of pyridine. The temperature was maintained at 0° for 1 hr. and at 33–35° for 4 hr., during which time sulfur dioxide was evolved. The pentane and ether were removed under reduced pressure, and the product was recrystallized from pentane–methylene chloride (2:3). The yield of chloromethylcarbamoyl chloride, m.p. 9–10°, was 68%.

Anal. Calcd. for $C_2H_3NOCl_2$: C, 18.77; H, 2.36; N, 10.95; Cl, 55.41. Found: C, 19.41; H, 2.29; N, 11.11; Cl, 53.54.

Treatment of 194 g. of chloromethylcarbamoyl chloride in 100 ml. of xylene with 250 ml. of α-pinene resulted in a mild exothermic reaction (temperature maintained at 25–30° for 2 hr.). On distillation, 66 g. (48%) of $ClCH_2NCO$, b.p. 37–39° (158 mm.) (extrapolated 80°—lit.[10] b.p. 80–81°), $n^{25}D$ 1.4327, was obtained.

Anal. Calcd. for C_2H_2NOCl: N, 15.31. Found: N, 15.44.

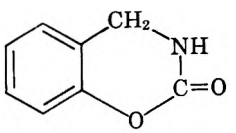
3,4-Dihydro-2*H*-naphtho[1,2-*e*]-1,3-oxazin-2-one.—On mixing



38 g. of chloromethyl isocyanate, 62 g. of pentane–ether (3:1), and 43 g. of β-naphthol at 25°, hydrogen chloride was immediately evolved. After the evolution of hydrogen chloride had ceased (1 day), the solvent was removed under vacuum, and the product extracted with methanol. The solid obtained melted at 175–192°. Recrystallization from methanol gave a 25% yield of the oxazinone, m.p. 190–194°.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.03; H, 4.73; N, 6.88.

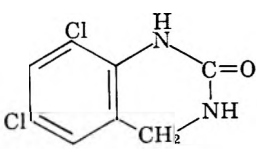
3,4-Dihydro-2*H*-benzo-1,3-oxazin-2-one.—A mixture of 38 g.



of chloromethyl isocyanate, 62 g. of pentane–ether (3:1), and 28 g. of phenol was allowed to stand 24 hr. at 25° and then refluxed 3 hr. The solid product left after removal of solvent under reduced pressure was extracted with ether in a Soxhlet apparatus, and the extracted material was recrystallized from alcohol–water, sublimed, and recrystallized from water. A 5% yield of product, m.p. 189–191° (lit.[11] m.p. 188°), was obtained.

Anal. Calcd. for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.73; H, 4.97; N, 8.72.

3,4-Dihydro-6,8-dichloro-2(1*H*)-quinazolinone.—A mixture of



8.5 g. of chloromethyl isocyanate and 25 ml. of heptane was added to a mixture of 15 g. of 2,4-dichloroaniline, 50 ml. of ether, and 100 ml. of heptane at −10°. After standing for 16 hr. at 25°, the solid (13 g.) which formed was separated by filtration and recrystallized thrice from dimethylformamide–methanol (2:1). It melted at 258–260°.

Anal. Calcd. for $C_8H_6N_2OCl_2$: C, 44.26; H, 2.79; N, 12.91; Cl, 32.67. Found: C, 44.11; H, 3.02; N, 12.76; Cl, 32.55.

The infrared spectrum showed absorption at 3.0 μ (NH), 3.23 μ (=CH), 3.36 μ (saturated CH), 6.05 μ (>CO), 6.28–6.45 μ,

(12) F. Zobrist and H. Schinz, *Helv. Chim. Acta*, **35**, 2380 (1952); M. Linhard, *Z. anorg. allgem. Chem.*, **236**, 200 (1938).

(13) I. F. Walker, "Formaldehyde," 2nd Ed., Reinhold Publishing Corp., New York, N. Y., 1953, p. 129.

6.53 μ (conjugated >C=C< and NH), and 12.12 μ (probably C–Cl) consistent with this structure.

Cinnamyl Isocyanate and 3-Chloro-3-phenylpropyl Isocyanate.—A mixture of 36 g. of chloromethylcarbamoyl chloride, 58 g. of styrene, 100 ml. of methylene chloride, and 2 g. of mercuric chloride was refluxed for 37 hr. The volatiles were removed at 45° (1 mm.). Toluene (100 ml.) was added and the mixture refluxed for 20 hr. to remove hydrogen chloride. Fractionation gave 1, b.p. 75–76° (0.35), $n^{25}D$ 1.5597, and 2, b.p. 76–83° (0.28 mm.), $n^{25}D$ 1.5408. Infrared and elemental analyses indicated that fraction 1 was 70% cinnamyl isocyanate and 30% 3-chloro-3-phenylpropyl isocyanate and fraction 2 was 15% cinnamyl isocyanate and 85% 3-chloro-3-phenylpropyl isocyanate.

2,4-Dimethylbenzylcarbamoyl Chloride and 2,4-Dimethylbenzyl Isocyanate.—A mixture of 508 g. of *m*-xylene, 300 ml. of methylene chloride, 135 g. of chloromethylcarbamoyl chloride, and 2 g. of zinc chloride was refluxed (57–58°) for 26 hr. when the evolution of hydrogen chloride had virtually ceased. The zinc chloride was removed by adding phosphorus pentoxide (2 g.), refluxing, and filtering. Removal of solvent at 50° (1 mm.) left 92 g. of crude 2,4-dimethylbenzylcarbamoyl chloride, m.p. 64–77°, after one recrystallization from heptane.

This carbamoyl chloride was refluxed for 24 hr. with 200 ml. of toluene to remove the hydrogen chloride. On distillation, 55.7 g. of 2,4-dimethylbenzyl isocyanate, b.p. 80–81° (0.2 mm.), $n^{25}D$ 1.5240, was obtained.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.57; H, 6.97; N, 9.13.

The infrared spectrum was consistent with this structure.

A mixture of 9 g. of 2,4-dimethylbenzyl isocyanate and 50 ml. of methanol gave methyl 2,4-dimethylbenzylcarbamate, m.p. 70.5–71.5°, after recrystallization from methanol.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.46; H, 7.95; N, 7.27.

The infrared spectrum was in good agreement with this structure.

1-Hydroxy-2,2,2-trichloroethyl Isocyanate.—This compound was prepared routinely in essentially quantitative yields by allowing a mixture of chloral and a 40% ethereal solution of isocyanic acid (reactants in equimolar amounts) to stand overnight. When no solvent was used, the hydroxy isocyanate was obtained as a solid at 0°. This solid melted about 25° and underwent an exothermic reaction above its melting point to give a mixture of unidentified acetone-soluble products.

Reaction of 1-hydroxy-2,2,2-trichloroethyl isocyanate with amines in ether at −10° gave the expected ureas (see Table II). The 1,3,5-oxadiazine-2,4-dione was obtained in 30% yield by stirring a mixture of 10.5 g. (0.055 mole) of hydroxy isocyanate, 1 g. (0.055 mole) of water, and 9 ml. of 1,2-dimethoxyethane at 0° for 1 hr. It was identified by its infrared spectrum (two carbonyls at 5.57 μ and 5.8 μ, NH at 3.1 μ and 3.25 μ) and elemental analysis.

1,2,2,2-Tetrachloroethylcarbamoyl Chloride, 1,2,2,2-Tetrachloroethyl Isocyanate, and Their Derivatives.—1,2,2,2-Tetrachloroethylcarbamoyl chloride was prepared by the procedure used for chloromethylcarbamoyl chloride. Conversion to the isocyanate was effected by refluxing a toluene solution. The overall yield of isocyanate from chloral was about 75%.

The isocyanate was generally quite reactive and could be converted to carbamates by refluxing in ether with an equivalent amount of alcohol. Refluxing with excess alcohol led to replacement of the α-chloro group with an alkoxy group (Table II).

Admixture of the isocyanate with amines in aromatic hydrocarbon solvents gave the corresponding ureas (Table II). With excess amine, the α-chloro group was replaced with an amine group.

The reaction of the isocyanate with 2-aminothiazole proceeded rapidly in tetrahydrofuran at room temperature to give the bicyclic derivative shown in Table II in high yield. This reaction is analogous to that reported[14] for CH_3OCF_2NCO.

The isocyanate reacted with 2,4-dichlorophenol, α-naphthol, β-naphthol, and 8-quinolinol in ether or benzene under reflux with triethylamine as a catalyst. No reaction occurred without catalyst.

The urea $(CCl_3CHOHNH)_2CO$ was obtained by treatment of the isocyanate with aqueous acetone. This compound was obtained previously from chloral and urea.[15]

Bis-(chlorodifluoromethyl)-hydroxy Isocyanate (IV).—A mixture of *s*-dichlorotetrafluoroacetone (4.5 g.) and 1.2 g. of isocyanic acid prepared at −78° was allowed to warm slowly to room temperature. Distillation of the product gave 2.4 g. of bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate, b.p. 26–27° (7 mm.). Near-infrared absorption at 1.42 μ (OH) in carbon tetrachloride, infrared absorption at 2.9 μ (OH), 4.43 μ (NCO) as well as proton and fluorine resonance data were consistent with the proposed structure.

Anal. Calcd. for $C_4HNO_2F_4Cl_2$: N, 5.80. Found: N, 6.03.

Bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate was converted to a urea by reaction with aniline. Aniline was added dropwise at −5° to a stirred mixture of 9.7 g. of bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate and 25 ml. of ether. After allowing the mixture to stand overnight, the solvent was removed under reduced pressure leaving 2.9 g. (95%) of crude 1-[bis-(chlorodifluoromethyl)-hydroxymethyl]-3-phenylurea, m.p. 60–70°. A small amount of phenylurea impurity was removed by treating the product with a diethyl ether–petroleum ether (10 ml.:40 ml.) mixture in which phenylurea is only slightly soluble. Recrystallized (from carbon tetrachloride), the product melted at 75–77°.

When a drop of pyridine was added to 1.63 g. of IV, an exothermic reaction occurred with the formation of a viscous liquid which solidified on cooling. After recrystallization from benzene, it melted at 98–99°. Elemental analyses (see Table IV) and the infrared spectrum [3.07 μ, 3.22 μ (NH), 5.58 μ, 5.78 μ (>C=O), 8.9 μ (C—F and C—O)] were in accord with the oxadiazine-2,4-dione structure.

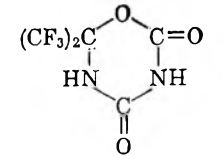
Reaction of IV with ethanol in ether occurred rapidly to form the carbamate. Proton magnetic resonance indicated the presence of NH, OH, and C_2H_5 groups. The infrared spectrum was also consistent with the carbamate structure and indicated strong internal hydrogen bonding.

Bis-(trifluoromethyl)-hydroxy Isocyanate (V).—This compound was prepared by essentially the same procedure used for IV. It distilled at about 2° (3 mm.). Some decomposition to its precursors occurred when higher pressures and temperatures were employed. The distilled product melted about −40°.

Anal. Calcd. for $C_4HF_6NO_2$: N, 6.70. Found: N, 7.12.

The proton magnetic resonance spectrum of the pure compound showed a single peak at 4.07 p.p.m. [downfield from the external standard, tetramethylsilane (5%) in carbon tetrachloride, used in these n.m.r. studies].

On standing for a week in a glass container, V was converted to



The proton magnetic resonance spectrum showed a single peak at 9.5 p.p.m.

The infrared spectrum (3.1 μ, 3.2 μ (NH's); 5.52 μ, 5.70 μ (>C=O); 8-μ region (C—F and C—O) was in good agreement with the structure.

The addition of 2.2 g. (0.02 mole) of triethylamine to a mixture of 2.5 g. (0.01 mole) of 6,6-bis-(trifluoromethyl)-1,3,5-oxadiazine-2,4-dione and 5 ml. of tetrahydrofuran at 25° gave an immediate precipitate of a 1:1 derivative. Proton magnetic resonance in "D" acetone showed broad absorption at 8 p.p.m., a quadruplet at 3.2 p.p.m., and a triplet at 1.3 p.p.m.

(14) J. C. Kauer and A. K. Schneider, *J. Am. Chem. Soc.*, **82**, 852 (1960).

(15) O. Jacobson, *Ann.*, **157**, 247 (1871).

Ozonolysis of Polycyclic Aromatics. X.[1] 7,12-Dimethylbenz[a]anthracene[2]

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Ozonization of 7,12-dimethylbenz[a]anthracene (1) in methylene chloride, 3:1 methylene chloride–methanol, and acetone gave an unstable peroxidic mixture, oxidation of which with hydrogen peroxide and silver oxide led to benz[a]anthracene-7,12-dione, 1,2-anthraquinonedicarboxylic acid, phthalic acid, 1,4-dimethyl-3-hydroxymethyl-2-phenylnapthalene-2′-carboxylic acid, and, most probably, 1,2-diacetylnaphthalene. Thus, L-region reactivity to ozone is decreased in the potent carcinogen 1, relative to benz[a]anthracene, while simultaneous K-region cleavage is increased as would be predicted from the Pullmans' K-region theory of carcinogenesis.

The quantum-mechanical (K-region) theory of carcinogenesis[3] has been an extraordinary stimulus to research in the chemical reactivity of that most important and probably most studied class of carcinogens, the unsubstituted polycyclic aromatic hydrocarbons.[4] Despite recent criticism of the theory,[5] it seems generally accepted that the observation of any consistent correlation of the carcinogenicity (or lack of it) of these polycyclic aromatic hydrocarbons, with some specific chemical reaction would necessarily be "considered as extremely significant for the process of carcinogenesis itself."[3d] All previous studies of chemical reactivity of these *unsubstituted* polycyclic aromatic hydrocarbons have concerned themselves mainly with addition or substitution reactions involving either reactive centers (L-region) or reactive bonds (K-region).[3d] It also has been predicted that "most probably no consistent general relation exists between these reactions and the carcinogenic activity of *substituted* molecules."[3e]

With ozone, work in our laboratory and others has shown that reaction occurs with all carcinogenic and noncarcinogenic, unsubstituted polycyclic aromatics examined to date, and most importantly, reaction can occur uniquely at any of the three relevant sites, K-, L-, and M-regions.

Thus ozone attacks: (i) the K-region predominantly in phenanthrene,[6a,7a,8a] chrysene,[9a] triphenylene,[9a] pyrene,[9b,10] dibenz[a,h]anthracene,[6b] dibenz[a,j]anthracene,[1,11] benzo[g]chrysene,[9a] picene,[9a] and dibenz[c,g]-phenanthrene[9a]; (ii) the L-region predominantly in anthracene,[7b,9c,12] naphthacene,[6c,9c] benz[a]anthracene,[6d,9a,12] and perylene[9d]; (iii) the L- and M-regions in benzo[a]pyrene.[6e] Where measurable, we also have demonstrated that ozone reacts predominantly at those positions in an unsubstituted polycyclic aromatic whose corresponding *o*- or *p*-quinone had the lowest corrected oxidation–reduction potential.[6f,13,14]

Strikingly fewer ozonization data are available for methyl-substituted polycyclic aromatics. The ozonization of 1- and 2-methylnaphthalenes,[17] and 2,3- and 1,4-dimethylnaphthalenes[8b] in general led to complex product mixtures, and the separable components were obtained only in poor yields. Methyl groups undoubtedly activate the ring to which they are attached,[18] but their "leaving power"[7d] to ozone attack is low, and in 9,10-dimethylanthracene, the initial zwitterionic intermediate formed by addition of ozone, stabilizes itself by forming the 9,10-transannular ozonide with ring-methyl groups intact.[7d] In this paper, we report on the ozonization of the potent (++++) carcinogen,[19] 7,12-dimethylbenz[a]anthracene (1).

Results

Ozonization of 1 dissolved in methylene chloride, 3:1 methylene chloride–methanol, and acetone was

(1) Paper IX, E. J. Moriconi, B. Rakoczy, and W. F. O'Connor, *J. Org. Chem.*, **27**, 3618 (1962).

(2) This research was supported by a grant C-3325(C4) from the U. S. Public Health Service, National Cancer Institute.

(3) (a) A. Pullman and B. Pullman, "Cancérization par les Substances Chimiques et Structure Moléculaire," Masson et Cie, Paris, 1955; summaries in "Advances in Cancer Research," Academic Press Inc., New York, N. Y.; (b) C. A. Coulson, Vol. I, 1953, p. 2; (c) G. M. Badger, Vol. II, 1954, p. 73; (d) A. Pullman and B. Pullman, Vol. III, 1955, p. 117; (e) p. 154.

(4) J. R. Sampey, *J. Chem. Educ.*, **32**, 448 (1955).

(5) "Theories of Carcinogenesis," I. Hieger in "Carcinogenesis, Mechanisms of Action," Ciba Foundation Symposium, Little, Brown and Co., Boston, Mass., 1958, pp. 3–11. See B. Pullman's reply in "Berliner Symposium über Fragen der Carcinogenese," Akademie-Verlag, Berlin, 1960, p. 69.

(6) (a) W. J. Schmitt, E. J. Moriconi, and W. F. O'Connor, *J. Am. Chem. Soc.*, **77**, 5460 (1955); (b) E. J. Moriconi, W. F. O'Connor, W. J. Schmitt, G. W. Cogswell, and B. P. Fürer, *ibid.*, **82**, 3441 (1960); (c) E. J. Moriconi, W. F. O'Connor, and L. B. Taranko, *Arch. Biochem. Biophys.*, **83**, 283 (1959); (d) E. J. Moriconi, W. F. O'Connor, and F. T. Wallenberger, *J. Am. Chem. Soc.*, **81**, 6466 (1959); (e) E. J. Moriconi, B. Rakoczy, and W. F. O'Connor, *ibid.*, **83**, 4618 (1961); (f) E. J. Moriconi, B. Rakoczy, and W. F. O'Connor, *J. Org. Chem.*, **27**, 2772 (1962).

(7) (a) P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956); (b) F. Dobinson and P. S. Bailey, *Tetrahedron Letters*, No. **13**, 14 (1960); (c) F. Dobinson and P. S. Bailey, *Chem. Ind.* (London), 632 (1961); (d) R. E. Erickson, P. S. Bailey, and J. C. Davis, Jr., *Tetrahedron*, **18**, 389 (1962).

(8) (a) J. P. Wibaut and Th. J. De Boer, *Rec. trav. chim.*, **78**, 183 (1961); (b) L. W. F. Kampschmidt and J. P. Wibaut, *ibid.*, **73**, 431 (1954).

(9) (a) P. G. Copeland, R. E. Dean, and D. McNeil, *J. Chem. Soc.*, 1232 (1961); (b) *Chem. Ind.* (London), 98 (1960); (c) *J. Chem. Soc.*, 3858 (1961); (d) *Chem. Ind.* (London), 329 (1959).

(10) H. Vollman, H. Becker, M. Corell, and H. Streeck, *Ann.*, **531**, 51, 130 (1937).

(11) Some L-region oxidation to the 7,12-quinone also occurred.

(12) Some bond cleavage products also obtained.

(13) A referee has noted that the corrected redox potential correlation does not fit anthracene in nonionic solvents.[7c] If such had been the case, it would have been both surprising and probably fortuitous since the redox potentials invariably are measured in 95% ethanolic solution. With the single exception of picene,[9a] however, all the compounds correlated[6f] have been ozonized in at least 3:1 methylene chloride–methanol (sufficient to consider the solvent polar) or acetic acid. Anthracene, when ozonized in the latter solvent (ref. 7c also mentions methylene chloride–methanol), does fit the correlation.

(14) The recent suggestion[15] that ozone reacts at the K- and L-regions with the lowest localization energies, "provided that the *p*-positions are weighted by about 0.1 unit" unfortunately overlooks a most important point. Even with this additional correction, localization energies predict predominant ozone attack at the K-region, rather than the L-region, in benz[a]anthracene. In our hands, the reverse is simply true.[6d] Dean, Copeland, and McNeil have demonstrated some measure of reactivity of the K-region under conditions different from ours.[9a] However, the sensitivity of the ozone reaction to solvent,[7b,c] and temperature demand that comparison of these theoretical indices be made with the mode of predominant ozone attack of each of these unsubstituted polycyclic aromatic hydrocarbons *under identical reaction* conditions. With these necessary limitations, L-region attack predominates in benz[a]anthracene, and the indices suggested by others,[15,16] predict the reverse.

(15) A. Streitweiser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 196-, p. 440.

(16) F. T. Wallenberger, *Tetrahedron Letters*, No. **95**, 5 (1959).

(17) R. Callighan and M. H. Wilt, *J. Org. Chem.*, **26**, 5212 (1961).

(18) There is considerable kinetic evidence for this. *Cf.* P. S. Bailey, *Chem. Rev.*, **58**, 958 (1958), for a summary of earlier work; T. W. Nakagawa, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **82**, 269 (1960).

(19) G. M. Badger, *Brit. J. Cancer*, **2**, 309 (1948).

carried out at −78° with ozone–oxygen, and ozone–nitrogen streams. Two series of experiments were made: reaction of **1** with one molar equivalent, and ozonization to saturation with 2.5 molar ozone equivalents. The resulting solution and the precipitated, unstable peroxidic mixture (**2**) defied separation and identification by chemical and physical means. Therefore, it was subjected directly to oxidative decomposition.

A number of conventional oxidants were used for decomposition of the ozonides, the most successful of which were dilute, aqueous hydrogen peroxide and freshly precipitated silver oxide. The use of the former led to the isolation of benz[*a*]anthracene-7,12 dione (**3**), 1,2-anthraquinonedicarboxylic acid (**4**), and phthalic acid (**5**). For the isolation of 1,4-dimethyl-3-hydroxymethyl-2-phenylnaphthalene-2′-carboxylic acid (**7**), in addition to **3** and **4**, it was imperative to use the mild oxidant silver oxide, and to avoid any application of heat either to reactants or products.[20]

With increasing polarity of solvent in the series methylene chloride, 3:1 methylene chloride–methanol, and acetone, the yields of **3** increased to the extent of 10% with the maximum average results of over forty runs summarized in Table I. The extraordinary difficulty encountered in the isolation of **4** and **7** precluded any discrimination between solvent effects and the difference in work-up procedures. Further, oxidation of **1** with either 10% hydrogen peroxide or alkaline silver oxide led to a 95–97% recovery of **1**. The oxidized moiety which was separated on a Florisil column did not contain **3**, nor was it soluble in alkaline solution. It was not investigated further.

TABLE I

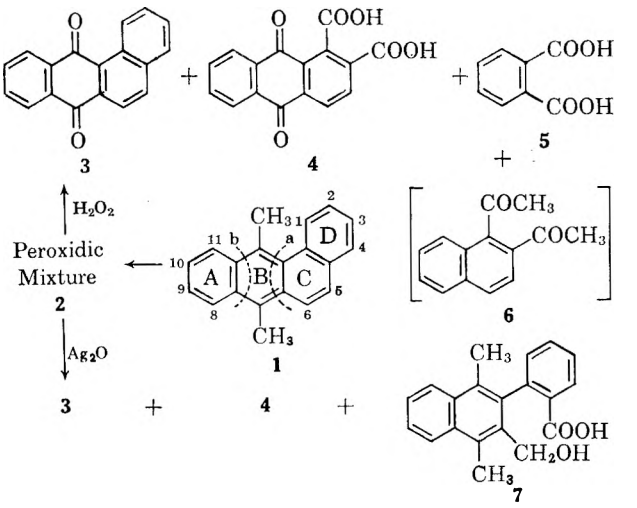
OZONIZATION PRODUCTS AND AVERAGE % YIELDS

Mole ratio ozone: 1	3[a]	4[a]	5[a]	7[b]	6[a]
1.0	23	6	..	14	*ca.* 2
2.5	29	15	11	8	..

[a] After hydrogen peroxide oxidation. [b] After alkaline silver oxide oxidation.

Vapor phase chromatography of original ozonolysis solution confirmed the presence of **3** emanating from the column at a column temperature of 310°.[22] The chromatogram also showed a shoulder at *ca.* 185°, approximately 5% of the 310° peak area. All attempts to collect the effluent samples from the 185° shoulder were fruitless.

However, when a filter paper impregnated with a glycine solution was pressed against the ejection port of the chromatograph, a blue coloration appeared on the filter paper at the point of contact. A blue color was also produced with aniline and *o*-phenylenediamine. No such coloration was observed with these amines for any other peaks observed in the chromatogram.



Riemschneider[23a] has reported the formation of a blue color in the reaction of various amino acids with compounds containing *o*-carbonyl groups, such as *o*-diacetylbenzene, *o*-diacetylcyclohexane, and *o*-dipropionylbenzene. Ozonolysis of **1** conceivably can result in four fragments which would exhibit the required *o*-carbonyl groups. Cleavage along line *a* of central ring B would yield *o*-diacetylbenzene and 1,2-naphthoquinone, while along line *b* would lead to 1,2-diacetylnaphthalene and *o*-benzoquinone. Cleavage along line *a* seems improbable due to the considerable steric hindrance of the methyl substituent on C-12 and the lateral ring D. However, *o*-benzoquinone (dec. 60–70°) and 1,2-naphthoquinone (dec. 145–147°) can be eliminated as possible causes of the 185° shoulder since both are thermally instable and decompose well below the ejection temperature. Further, an authentic sample of *o*-diacetylbenzene was desorbed from the v.p.c. column at considerably lower temperatures. Thus we believe the 185° shoulder to be 1,2-diacetylnaphthalene (**6**). Two independent approaches to the synthesis of **6** were unsuccessful.[24]

Finally, oxidation of **1** with sodium dichromate in acetic acid gave a 70% yield of **3**.

Experimental[25]

Ozonization of 7,12-Dimethylbenz[*a*]anthracene (1).—Ozone (3.5 vol. % or ozone–nitrogen) was dispersed into a solution of **1**[26] (2.0 g., 7.8 mmoles) in 300–500 ml. of methylene chloride, 3:1 methylene chloride–methanol, and acetone at −78°, until the calculated amount of ozone was absorbed. The solution ab-

(20) These mild oxidative conditions account for the lower yields of **3** and **4** obtained with this reagent. **7** readily forms the ε-lactone, and this facile lactonization is largely responsible for the difficulties encountered in the isolation of **7**.[21]

(21) H. I. Hadler and A. C. Kryger, *J. Org. Chem.*, **25**, 1896 (1960).

(22) Addition of authentic samples of **3** to the ozonolysis solution prior to its injection in the v.p.c. column lead to an increase in the 310° peak area in proportion to the amounts added.

(23) (a) R. Riemschneider, *Monatsh. Chem.*, **91**, 1034 (1960); (b) R. Riemschneider, *Ber.*, **92**, 1205 (1959); *Ann.*, **646**, 18 (1961); (c) R. Riemschneider, *Gazz. chim. ital.*, **81**, 479 (1951); (d) R. Riemschneider and K. Preuss, *Monatsh. Chem.*, **90**, 924 (1959).

(24) See Experimental.

(25) The ozonator used in this research was a Welsbach Corporation T-23 laboratory ozonator. The infrared spectra were run on a Perkin-Elmer Model 137 Spectracord.

Vapor phase chromatography separations were effected on an F and M Scientific Corp. Model 500 equipped with a 2-ft., silicone-gum rubber column, initial column temp., 50°, temperature programmed 6.4° per min., helium flow rate, 40 ml. per min. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Melting points were determined on a Kofler micro melting point apparatus and are corrected. Boiling points are uncorrected. All solvents were Fisher Scientific Co. certified grade and were used without further treatment.

(26) Eastman 5149; disposable polyethylene plastic gloves (Handgards) were used throughout this research. The fluorescence of **1** under ultraviolet light was quite useful in its surveillance. An ever present reminder for care in handling **1** was a photograph of a cluster of papillomas initiated in a mouse by 1 μg. of **1** [V. Darchun and H. I. Hadler, *Cancer Res.*, **16**, 316 (1956)].

sorbed ozone readily up to 1.5 molar equivalents. Thereafter the absorption capacity of the solution steadily declined and became negligible at saturation after absorption of 2.5 molar ozone equivalents. Approximately 3.5–4.0 molar equivalents of ozone were added before saturation was achieved. In all experiments, ozonization was terminated after absorption of 1.0 or 2.5 (±0.1) molar ozone equivalents. The solution then was flushed with dry nitrogen to remove excess ozone. Addition of petroleum ether (30–60°) precipitated a voluminous peroxidic solid (2), m.p. 110–150° dec., which darkened rapidly on filtration, and exploded on heating in an open flame. Compound 2 contained active oxygen since it liberated iodine from an acetic acid solution of potassium iodide.

Oxidation of Peroxidic Mixture (2) with Aqueous Hydrogen Peroxide.—Hydrogen peroxide (10% aqueous) (70 ml.) was added to the solution of 2 and the heterogeneous mixture was then refluxed for 20 hr. with stirring. Solvents were removed *in vacuo* to leave a viscous yellow oil which was dissolved in 50 ml. of methylene chloride. This solution was extracted repeatedly with 50-ml. portions of dilute ammonium hydroxide until the alkaline extracts were colorless. The combined alkaline extracts gave solution A.

The methylene chloride layer (B) was then washed successively with water, dilute hydrochloric acid, and water, and finally dried over anhydrous sodium sulfate. Filtration followed by evaporation of the solvent (steam bath) left an oily semisolid. This material was dissolved in a minimum amount of carbon tetrachloride, deposited on a 40 × 2 cm. Florisil-packed column, and eluted with carbon tetrachloride. The carbon tetrachloride fractions were evaporated to dryness to give an oil which resisted all attempts to crystallize. This oil gave the strong violet-blue fluorescence of unchanged 1 on irradiation with ultraviolet light. Further elution with 99% benzene:1% ether led, after solvent evaporation, to a bright yellow solid. One recrystallization from methanol gave benz[*a*]anthracene-7,12-dione (3), identified by m.p. 169–170° (lit.[6d] m.p. 169–171°), mixture melting point, and superimposable infrared spectra with an authentic sample of 3.

Alkaline layer A was successively extracted with methylene chloride, benzene, and ether, followed by acidification with dilute sulfuric acid. The resulting suspension was extracted continuously with ether for 24 hr. The ether extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to leave a semisolid material; trituration with a small amount of chloroform produced a grey-colored solid; one recrystallization of this crude material from water gave phthalic acid (5) identified by m.p. 201–203°, mixture melting point, and super-imposable infrared spectra with authentic 5.

The chloroform-soluble material was evaporated to dryness; the residue was dissolved in benzene, deposited on a Woelm's nonalkaline aluminum oxide (activity grade I) packed column, and eluted with ethyl acetate. Evaporation of the ester solvent led to crude 1,2-anthraquinonedicarboxylic acid (4). One recrystallization from dilute hydrochloric acid solution gave 4, m.p. of anhydride 320–322° (lit.[6d] m.p. 320–323°).

Oxidation of Peroxidic Mixture (2) with Alkaline Silver Oxide.—A freshly prepared suspension of silver oxide (5.0 g. of silver nitrate, dissolved in 100 ml. of water to which was added 5.0 g. of sodium hydroxide in 50 ml. of water) was added to the solution of 2 and the heterogeneous mixture was shaken mechanically overnight. The resulting black precipitate was filtered and washed thoroughly with water, methylene chloride, and ether. The combined filtrates and washings were separated into two layers, organic (A), and aqueous, alkaline (B). Portion A was washed successively with water, dilute nitric acid, and water, and then dried over anhydrous sodium sulfate. Filtration, solvent evaporation, and chromatography as described in the hydrogen peroxide oxidation led to 3.

Portion B was washed successively with methylene chloride, benzene, and ether. The aqueous dark-colored solution was cooled by addition of ice chips, and carefully acidified with dilute nitric acid. The precipitated acid mixture was extracted immediately with chloroform; the chloroform extracts were washed with water and dried over anhydrous sodium sulfate. Filtration and solvent evaporation produced a yellow semisolid which was dissolved in benzene and adsorbed on an activated silicic acid column. Elution with ether followed by evaporation of solvent gave 4, m.p. of anhydride 318–321°, after recrystallization from dilute hydrochloric acid solution. Further column elution with ethyl acetate ultimately led to 1,4-dimethyl-3-hydroxymethyl-2-phenylnaphthalene-2′-carboxylic acid (7) as colorless, hairlike needles, m.p. 166.5–167.5°, after recrystallization from acetone–hexane (lit.[21] m.p. 165–165.2°); a mixture melting point with authentic 7 showed no depression and the infrared spectra were identical.[27]

Oxidation of 1 with Sodium Dichromate in Acetic Acid.—To a solution of 1 (1.0 g., 3.9 mmoles) in 20 ml. of boiling glacial acetic acid was added a solution of 3.0 g. of sodium dichromate in 10 ml. of glacial acetic acid and 2 ml. of water. The mixture was refluxed 1 hr., cooled, and poured into 100 ml. of water. The precipitated quinone was filtered, washed successively with warm water, dilute alkali, and again with water. This crude material was dissolved in benzene, adsorbed on alumina, and eluted with benzene–ether. One final recrystallization from methanol (or ethanol) gave 3, m.p. 169–170°, in 70% yield.

Attempted Preparations of 1,2-Diacetylnaphthalene (6). From 2′-Acetonaphthone.—This synthesis was patterned after that for *o*-diacetylbenzene.[23a,b,28] 2′-Acetonaphthone (Eastman 3118) was converted in 58% yield to 2-ethylnaphthalene, b.p. 127–129° (14 mm.) [lit.[29] b.p. 127–129° (14 mm.)] *via* a modified Clemmensen reduction. Low temperature and light-insulated bromination of 2-ethylnaphthalene led in 74% yield to 1-bromo-2-ethylnaphthalene, b.p. 151–153° (7 mm.) [lit.[30] b.p. 125–126° (3 mm.)]. The Grignard of 1-bromo-2-ethylnaphthalene was converted with carbon dioxide in 60% yield to 2-ethyl-1-naphthoic acid, m.p. 117–119° (lit.[30] m.p. 118–119°). A second Grignard reaction between 2-ethyl-1-naphthoyl chloride, b.p. 158–159° (7 mm.) [lit.[30] b.p. 129–131° (2–3 mm.)] and methylmagnesium iodide led in 95% yield to 2′-ethyl-1′-acetonaphthone as a yellow oil, b.p. 158–159° (7 mm.), $\lambda_{max}^{CCl_4}$ 5.92 (s) (C=O).

Anal. Calcd. for $C_{14}H_{14}O$ (198.25): C, 84.48; H, 7.08. Found: C, 84.88; H, 6.83.

Oxidation of 2′-ethyl-1′-acetonaphthone with potassium permanganate in magnesium nitrate buffer,[23a,b] or silver permanganate in pyridine[23c] gave only a 96% recovery of unchanged 2′-ethyl-1′-acetonaphthone and trace amounts of 6. An ethereal extract of reaction products was brought into contact with a filter paper impregnated with an aqueous solution of glycine. Oven drying the paper at 75° for 30 min. produced a light purple coloration of the wetted spots.

From 1-Vinylcyclohexane and 3-Hexene-2,5-dione.—Selenious acid oxidation of 2,4-hexanedione (K and K) gave a 20% yield of 3-hexene-2,5-dione, as faint yellow needles, m.p. 73–75° (lit.[23d] m.p. 75–79°). The tedious, reported petroleum ether extraction of the dione from the reaction mixture could be supplanted by dissolving the oil in benzene and filtering the solution through a 40 × 2 cm. Florisil-packed column. Addition of petroleum ether (60–95°) precipitated the dione in pure form.

Catalytic reduction of 1-ethynyl-1-cyclohexanol (K and K) with 2% palladized strontium carbonate led in 76% yield to 1-vinylcyclohexanol, b.p. 84–86° (30 mm.) [lit.[31] b.p. 66–68° (14 mm)]. Distillation of 1-vinylcyclohexanol over freshly fused, powdered potassium hydrogen sulfate converted it in 84% yield to 1-vinyl-1-cyclohexene b.p. 141–143° (760 mm.) [lit.[31] b.p. 143–144° (760 mm.)].

A sealed tube, Diels–Alder addition of 3-hexene-2,5-dione to 1-vinyl-1-cyclohexene (stabilized with a trace of hydroquinone) at 230° for 3 hr. was attempted. The homogeneous reaction mixture was heated to 80° in a high vacuum for 2 hr. to remove excess dione. The resulting dark brown oil, presumably 1,2,3,5,6,7,8-heptahydro-1,2-diacetylnaphthalene, was dehydrogenated over 30% palladium–charcoal in refluxing *p*-cymene for 12 hr. Removal of the catalyst by filtration and of solvent by distillation under reduced pressure left a yellow oil which could not be further distilled without extensive decomposition. A small sample of this oil when spotted onto filter paper wetted with an aqueous glycine solution produced no coloration even after heating at 75° for 3 hr.

Discussion

Compound 1 is structurally similar to its noncarcinogenic, parent hydrocarbon, benz[*a*]anthracene. Ozonization of benz[*a*]anthracene has led to 3[6d,9a];

(27) We are grateful to Professor Hadler for a sample of 7.
(28) F. Weygand, *Ber.*, **89**, 994 (1956).
(29) L. F. Fieser, *J. Am. Chem. Soc.*, **61**, 3218 (1939).
(30) R. C. Fuson and D. H. Chadwick, *J. Org. Chem.*, **13**, 484 (1948).
(31) P. A. Robins and J. Walker, *J. Chem. Soc.*, 646 (1952).

oxidative work-up of the ozonolysis mixture with alkaline peroxide has produced **4**,[6d] while permanganate in aqueous pyridine oxidative decomposition has led to benzo[*d*]diphenic acid.[9a] The two methyl substituents in **1**, however theoretically, should introduce two competitive effects not present in benz[*a*]anthracene.

(i) Hyperconjugation with the aromatic moiety in **1** should enhance the electron density and, consequently, ozone attack at both the L-region, and to a lesser extent, the K-region.

(ii) Increased steric hindrance to ozone attack at the L-region should lower reaction at these sites.

On the basis of only 45% of the starting material accounted for in the 1:1 mole ratio runs, and 63% in the 2.5:1 mole ratio runs, both effects seem operative (L-region attack by ozone *is decreased* in the strongly carcinogenic **1**, relative to benz[*a*]anthracene, while simultaneous K-region cleavage *is increased*). No clean separation of these competitive factors could be derived however from the present study. Also unknown is the site of attack on that portion of **1** which is unaccounted for. The observed mode of attack on **1** by ozone, however, would be expected from Pullmans' K-region theory of carcinogenesis.

The mechanism of electrophilic ozone attack of aromatic bonds, to yield cleavage products **4**, **5**, **6**, and **7**, and reactive sites, to give **3**, has been thoroughly discussed elsewhere.[6d,e,7b,d,15,16]

Tetracyclic Phenothiazines. V. Brominations and Dehydrobrominations of Some Pyrido[3,2,1-*kl*]phenothiazines[1]

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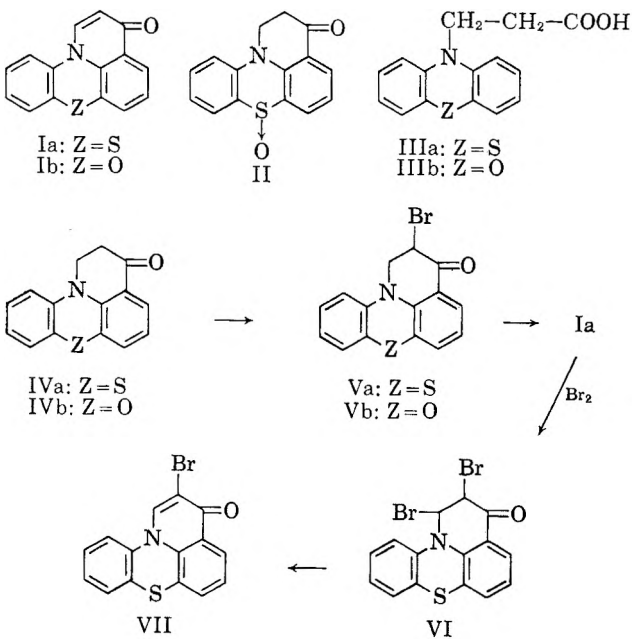
Bromination of 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (IVa) gave the 2-bromo derivative. This dehydrohalogenated essentially quantitatively on attempted reaction with a variety of nucleophiles. The resulting 3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (Ia), which has been considered "aromatic" in some respects, *adds* bromine to its dihydropyridone double bond to give VI. Compound VI dehydrohalogenates readily, *e.g.*, on solution in polar solvents. An improved synthesis of IVa is given.

A recent publication has mentioned the accidental preparation[2] and one, still more recently, the deliberate synthesis[3] of the phenothiazine Ia. The unplanned synthesis of what was presumed to be the analogous phenoxazine derivative Ib has also been reported recently.[4]

The phenothiazine, Ia, was first made by treatment of the sulfoxide, II, with hot aqueous ethanolic hydrochloric acid in an unsuccessful attempt to make a derivative of Ia chlorinated on one or both of the benzene rings. The rational preparation of Ia was by palladium-catalyzed dehydrogenation of IVa. What is probably the phenoxazine analog Ib was formed, together with the anticipated ketone IVb, by the cyclization of the phenoxazine N-propionic acid IIIb under relatively mild conditions.

Discussion of the high melting point and of the ultraviolet and infrared absorption of Ia have been given in terms of the "aromatic nature" of this substance, a point exhaustively debated in the past in connection with both 2- and 4-pyridones. However, little is known about the reactions of 2,3-dihydro-4-(1*H*)-quinolones, of which the compounds IV and V are examples[5] nor about 4-(1*H*)-quinolones such as the compound I.

We have found in the course of work directed at the preparation of amine-substituted derivatives of this ring system, that the compound Ia, whether "aromatic" or not, is the only product obtained in appreciable



amount upon treatment of the monobromo ketone Va with a variety of nucleophilic reagents. These have included sodium thiophenolate (a reagent known generally to give rapid SN2 reactions), dimethylamine (neat, in ether, in isopropyl alcohol, or in other solvents of varying polarities), anhydrous ammonia in absolute ethanol, and sodium acetate in acetic acid (a reagent which frequently gives a ratio of substitution to elimination higher than that of some other nucleophilic reagents, presumably because it leads to a reaction more nearly approximating the SN1 type). Indeed, merely keeping Va in dimethyl sulfoxide solution at room temperature for eighteen hours and subsequent dilution with water or a moderately prolonged attempt to

(1) Previous paper, M. Harfenist, *J. Org. Chem.*, **28**, 538 (1963).

(2) O. Hromatka, M. Knollmüller, and F. Sauter, *Monatsh. Chem.*, **93**, 723 (1962).

(3) J. A. VanAllan, G. A. Reynolds, and R. E. Adel, *J. Org. Chem.*, **27**, 1659 (1962).

(4) P. Müller, N. P. Buu-Hoi, and R. Rips, *ibid.*, **24**, 1699 (1959).

(5) The work of F. G. Mann and his associates, some of which is discussed in connection with our results, is a notable exception. For a leading reference, see P. I. Ittyerah and F. G. Mann, *J. Chem. Soc.*, 467 (1958).

recrystallize Va from boiling methanol–water led to isolation of Ia in good yield.

One diagnostic criterion (of many) advanced to define aromaticity[6] is the substitution of a hydrogen attached to an aromatic system by reagents which, in contrast, react with "ordinary" double bonds by addition. It is, therefore, of interest that Ia, on reaction with bromine in carbon tetrachloride, *adds* bromine to give VI. The crude product of bromination, produced in essentially quantitative yield, was an orange solid which had a fairly wide melting point range. Elemental analysis of this crude material gave a bromine analysis about 1% too high, and a carbon analysis several per cent under the theoretical. This probably is due to contamination of VI by a small amount of the tribromo compound produced from VI by dehydrohalogenation and addition of bromine to the resulting VII. Acceptable analyses of VI were obtained, however, after it was purified.[7]

It would be expected that VI would have its bromines *trans*, and hence that dehydrohalogenation, which should require a hydrogen *trans* to a bromine, might not occur readily. However, it is known that α,β-dibromocyclohexanones often dehydrohalogenate easily.[8] In the case of compound VI it was found that reaction with dimethylamine in toluene, recrystallization from hot nitromethane, or attempted recrystallization from ethanol–water led entirely to dehydrohalogenation to a neutral bromine-containing product, presumably VII.

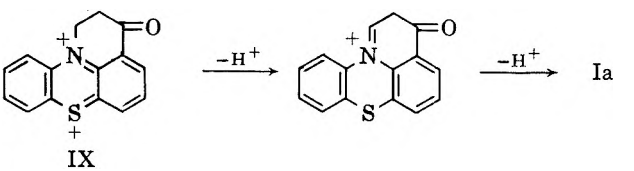
Finally, while VII added bromine in carbon tetrachloride solution with a concomitant change in the appearance of the solution and precipitation of a solid, the product proved difficult to purify sufficiently for adequate characterization. It may well consist of some S-bromo compound and/or the product of addition to the double bond. This product or products reverted to VII on recrystallization from ethanol–water at the boiling point. While this behavior is what one would expect from a substance in the oxidation state of an S-bromo compound, we cannot rule out the possibility of the compound being that produced by addition of bromine to the double bond of VII. For example the dibromo amide VIII has recently been reported[9] to revert to the N,N-diethylcinnamamide from which it was made upon treatment with a representative assortment of nucleophiles.

$C_6H_5CHBrCHBrCON(C_2H_5)_2$
VIII (*erythro*)

Discussion

The compounds IV correspond to structures that would be listed as 1-aryl-1,2,3,4-tetrahydro-4-oxoquinolines, or 1-aryl-2,3-dihydro-4-(1*H*)-quinolones in *Chemical Abstracts*. Although related structural features are found in many natural products, few examples are reported in the literature which are analogous to our experimental results. The simplest analogous compounds, the 1-phenyl- and 1-methyl-4-oxo-1,2,3,4-tetrahydroquinolines, are reported[5] to give a mixture of bromo compounds on direct bromination, from which no 3-bromo compound was obtained. Similarly, use of N-bromosuccinimide was reported to give a mixture of 6-bromo and 6,7-dibromo derivatives of the 4-oxotetrahydroquinoline. It is rather surprising that bromination of the benzene ring, which is deactivated for electrophilic reactions by the carbonyl group, should have occurred in these simple tetrahydro-4-oxoquinolines, rather than bromination α to the carbonyl group, while bromination of our dihydropyridophenothiazine IVa, which contains a benzene ring activated by an arylamino group and feebly activated or feebly deactivated by the arylthio group, nonetheless occurs α to the carbonyl group.[10]

It is recognized that the monobromination product of IVa which we have formulated as Va could be an S-bromo compound. This then might dehydrohalogenate to Ia by way of an intermediate IX as we believe occurs in Hromatka's preparation of Ia from the sulfoxide II. This proposal is an extension of the mechanism suggested[11] for the preparation of 3-chlorophenothiazine and 3,7-dichlorophenothiazine from phenothiazine 5-oxide. We have formulated our monobromo compound as Va rather than as an S-bromo compound, on the grounds of its stability in refluxing ethyl acetate, since other related S-bromo compounds are reported to be decomposed by temperatures above room temperature, and because no evidence of attack of various nucleophiles on the benzene ring was observed (compare ref. 11).



IX

However, dehydrohalogenation reactions similar in many respects to those reported here were found[12] to occur upon treatment of the bromothiochromanone X with a variety of nucleophiles, generally in water or in 95% ethanol solution. It is apparent that the alicyclic ring and one benzene ring are analogous in Xa and Va, but that Xa has a sulfur where Va has a nitrogen. Two reactions are reported to occur with Xa, however, which we have not observed with Va, although their occurrence to a slight degree cannot be completely excluded. Treatment of Xa with dry ammonia in absolute ethanol is reported to give the 3-amino compound, which forms a hydrochloride.

As was mentioned, treatment of Va with the same reagent leads to dehydrohalogenation. No acid-soluble product was found, when the attempted amina-

(6) For a more sophisticated discussion, see for example, A. T. Balaban and Z. Simon, *Tetrahedron*, **18**, 315 (1962).

(7) Crude VI could be recrystallized from much ethyl acetate to a reasonably constant melting point about 153°. Twice, a considerably higher melting point (about 184°) was obtained, presumably due to thermal dehydrohalogenation of VI in the Pyrex capillary melting point tube without macroscopically detectable melting of the solid. Indeed a 24-hr. heating of the solid at 78°, in an attempt to dry an analytical sample, led to extensive loss of bromine. However, it was possible to dry a sample satisfactorily at this temperature for a shorter period.

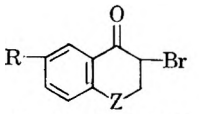
(8) F. G. Bordwell and R. J. Kern, *J. Am. Chem. Soc.*, **77**, 1141 (1955), give examples of other dehydrohalogenations in which a more acidic initially *cis* hydrogen is lost in preference to a less acidic *trans* hydrogen.

(9) A. J. Speziale and C. C. Tung, Abstracts of Papers, 93Q, Division of Organic Chemistry, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

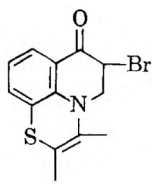
(10) Indeed, it is rather surprising that 1-phenyl-4-oxo-1,2,3,4-tetrahydroquinoline is reported to brominate in the 6-position of the quinoline benzene ring, rather than in the benzene ring attached to N1, which would be activated by the alkylamino group and not deactivated by the carbonyl group, if ionic bromination were being observed.

(11) A. C. Schmalz and A. Burger, *J. Am. Chem. Soc.*, **76**, 5455 (1954).

(12) F. Krollpfeiffer, *et al.*, *Ber.*, **58**, 1654 (1925). This paper was first pointed out to us by J. F. Bunnett, whom we thank.



Xa: Z=S, R=CH_3
b: Z=O, R=H



Va (Partial structure)

tion was run essentially as described by Krollpfeiffer, but using Va rather than Xa. Further, treatment of Xa with sodium acetate in acetic acid gave a coupling product, unlike our results with Va and the same reagents. Simultaneously with Krollpfeiffer's paper on Xa, a paper was published by F. Arndt, *et. al.*,[13] in which the preparation of the bromochromanone Xb is described. However, the yield of Xb is said to be very poor, because it readily undergoes spontaneous dehydrohalogenation in most solvents. The dehydrobromination product then adds bromine, to give the dibromo compound analogous to VI as well as what appears to be a brominated dimer, during the bromination. If the dimeric materials reported in reactions of Xa and of Xb have the structures indicated, they could be formed by displacement of bromine from one molecule of, for example, Xb by the anion of a second molecule of the same Xb. Thus at least the thiochromanone Xa and possibly the chromanone Xb undergo displacement reactions more readily than does our admittedly more complex dihydroquinolone Va. That such comparisons should be made with caution however, is indicated by our bromination of the phenoxazine IVb. In preliminary experiments this could not be brominated to a clean-cut product. Since a really satisfactory method of making IVb in quantity is not available, as it is for IVa (*vide infra*), any report on the chemistry of IVb will have to be deferred, except for a mention of the probability that bromination of the benzene rings, which does not appear to occur to an appreciable extent in the bromination of IVa, is one of the complicating factors in the bromination of IVb.

We have given, as part of the Experimental section, procedures for the preparation of the ketone IVa. The procedure for the cyanoethylation of phenothiazine is essentially that of Smith[14] modified in minor details. The modifications, which were suggested by the late Mr. Everett Lang of our development laboratories, make it a less dangerous and exciting reaction to run. Hydrolysis of the cyanoethyl product was done by methods in the literature without modification.

The cyclization of IIIa to IVa by means of trifluoroacetic anhydride in benzene is modelled on cyclizations of some related compounds given in a patent.[15] We have used proportionately less of the relatively expensive trifluoroacetic anhydride than is used in the examples given. The patent method gave no yield. We have found that the procedure, as given here, results in a nearly quantitative yield of essentially pure IVa, and so is far superior to the cyclization of IIIa using phosphorus pentoxide which we and others had previously used.

(13) F. Arndt, *et al.*, *Ber.*, **58**, 1612 (1925).
(14) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).
(15) P. N. Craig and J. J. Lafferty, U. S. Patent 2,919,271. *Cf.* R. J. Ferrier and J. M. Tedder, *J. Chem. Soc.*, 1435 (1957).

Experimental

10-(2-Cyanoethyl)phenothiazine.—A suspension of 100 g. (0.5 mole) of sublimed phenothiazine in 155 ml. of commercial acrylonitrile in a 4-l. beaker was warmed to 35°. This was stirred with a thermometer as a commercial 38% solution of benzyltrimethylammonium hydroxide was added cautiously, pausing after every few drops. When the thermometer reading started to rise slowly, the addition of base was stopped. With the reagents used by us, this required at different times 3–7 ml. of the basic solution. The solution now spontaneously heated itself to the boiling point in a few seconds, and refluxed on the walls of the beaker. When the initial reaction had subsided, the solution, from which product usually started crystallizing if it were allowed to cool, was heated for an additional hour. The product was then separated by neutralizing the quaternary hydroxide with carbon dioxide immediately after addition of acetone, filtering, and adding water to the hot filtrate. The product crystallized in a first crop of 78 g. of platelets of m.p. 156–158° (lit. m.p. 158–159°) and a second crop of 10 g., m.p. 154–155°, which could be readily recrystallized from acetone–water if necessary.

10-(2-Carboxyethyl)phenothiazine (IIIa).—This was prepared by base-catalyzed hydrolysis of the nitrile, by the method in the literature.

2,3-Dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (IVa).—A mixture of 100 g. (0.37 mole) of 10-(2-carboxyethyl)phenothiazine, 400 ml. of dry benzene and 80 g. (0.38 mole) of trifluoroacetic anhydride was heated under reflux and stirred on a steam bath for 5 min. It was then poured into cracked ice. The benzene solution was washed with aqueous sodium carbonate, acidification of which led to recovery of 2.5 g. of starting acid. The benzene was filtered to free it from suspended water and distilled to dryness. The resulting yellow solid residue was recrystallized from *ca.* 1 l. of absolute ethanol, giving a first crop of 76.3 g. and a second crop of 10.5 g., totaling 93%, m.p. 111–113°.

2-Bromo-3-keto-2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazine (Va).—A solution of 2.53 g. (10 mmoles) of 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (IVa) in 50 ml. of hot carbon tetrachloride was cooled to 50° and 17.5 ml. of a carbon tetrachloride solution containing 1.75 g. (11 mmoles) of bromine was added with stirring during about 30 sec. Hydrogen bromide was evolved copiously, and an oil precipitated. The latter crystallized after the reaction mixture had been heated on the steam bath for 7 min., and weighed 1.86 g. It was recrystallized from 350 ml. of nitromethane for analysis, yielding platelets of essentially the same melting point, approximately 266–270°. As might be anticipated, melting points were not always reproducible, melting point as high as 282° being readily obtained by rapid heating.

Anal. Calcd. for $C_{15}H_{10}BrNOS$ (mol. wt., 332.23): C, 54.08; H, 3.04. Found: C, 54.23; H, 2.98.

3-Keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (Ia).—A suspension of 4.60 g. (13.8 mmoles) of the bromo ketone Va in 200 ml. of glacial acetic acid was stirred at 30° with 4.2 g. (51 mmoles) of reagent grade sodium acetate for 10 min. The resulting homogeneous solution was heated at 60° overnight, filtered from a little black solid, and evaporated to dryness on the steam bath at the water pump. Titration showed that a water extract of the residue had 98% of the theoretical amount of bromide ion. The residue weighed 3.37 g. (97%) and had m.p. 206°, raised to 207° admixed with a known sample of m.p. 207.3–208°. It was recrystallized from ethyl acetate and had the same melting point and infrared absorption as the known sample. The known sample was prepared by treatment of the same bromo ketone Va suspended in ether, with ethereal dimethylamine, and had the correct elemental analysis for C and H. Melting points reported for this ketone have been 207–209°[2] and 204°.[3]

2,3-Dibromo-2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (VI).—Most of 11.32 g. (45 mmoles) of 3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine was dissolved in 1100 ml. of boiling ethyl acetate, and a solution of 10 g. (62.5 mmoles) of bromine in 150 ml. of carbon tetrachloride was added at once. Much orange precipitate formed. The reaction was heated to the boiling point on the steam bath with stirring, cooled slightly, and filtered. The insoluble residue was 17.00 g., and a first crop of orange needles from the filtrate was an additional 2.17 g., totaling 103%. Two-gram portions could be recrystallized from 1-l. of dry ethyl acetate to give orange needle-like prisms,

melting point about 160–163°, which liberated iodine from an aqueous iodide solution acidified with acetic acid. An additional recrystallization dropped the melting point to 146–*ca.* 159°.

Anal. Calcd. for $C_{15}H_9Br_2NOS$ (mol. wt., 411.06): C, 43.61; H, 2.21. Found: C, 43.37; H, 2.72.

2-Bromo-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (VII).—When an attempt was made to recrystallize the preceding 2,3-dibromo-2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (VI) from nitromethane on the steam bath, the initially orange-colored solution lightened almost immediately to yellow, and became strongly acidic. After about 15 min. at 80–100°, the solution was cooled and scratched, giving yellow platelets of m.p. 144–146°, raised to 145–147.3° on recrystallization.

Anal. Calcd. for $C_{15}H_8BrNOS$ (mol. wt., 330.21): C, 54.61; H, 2.44. Found: C, 54.93, 55.00; H, 2.53; 2.48.

Acknowledgment.—The author wishes to thank Professor N. Cromwell for a stimulating discussion. Analyses were done by Dr. S. Blackman and his staff.

Studies on Condensed Systems of Aromatic Nitrogenous Series. XXII. Structural Studies of β-D-Ribofuranosylimidazopyridines[1]

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3-Methyl-3*H*-imidazo[4,5-*b*]pyridine (I), 1-methyl-1*H*-imidazo[4,5-*b*]pyridine (IV), 1-methyl-1*H*-imidazo-[4,5-*c*]pyridine (II), and 3-methyl-3*H*-imidazo[4,5-*c*]pyridine (III) have been prepared. Spectroscopic comparison of a pair of isomers of methyl imidazo[4,5-*b*]pyridines (I and IV) with a nucleoside resulting from condensation of mercuric chloride complex of imidazo[4,5-*b*]pyridine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (followed by debenzoylation) suggests that the supposed 1-β-D-ribofuranosyl-1*H*-imidazo[4,5-*b*]pyridine is 3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine. A nucleoside obtained from 1*H*-imidazo[4,5-*c*]pyridine by an analogous reaction was assigned the 3-β-D-ribofuranosyl-3*H*-imidazo[3,4-*c*]pyridine structure on the basis of spectral comparison with a pair of methylimidazo[4,5-*c*]pyridines.

The synthesis of nucleosides of purines or related heterocyclic bases by condensation reactions is often beset with more than one possibility for the position of attachment of the sugar moiety to the aglycon. In such cases, proof is required for this positional assignment. One technique commonly employed for such proof is to compare the ultraviolet absorption at properly selected pH values of the nucleoside product with appropriate alkyl derivatives of the aglycon.[2,3]

This technique of structural elucidation often makes use of the generally accepted empirical rule: first, in purine ring systems, 7-alkyl substituted purines have the absorption maximum at a longer wave length than corresponding 9-alkyl substituted purines.[4] Secondly, replacement of the alkyl group by a glycosyl moiety would be expected to produce little or no change in the ultraviolet absorption spectrum. Thus, adenosine (9-β-D-ribofuranosyladenine) has an ultraviolet absorption spectrum very similar to that of 9-methyladenine, but not to that of 7-methyladenine,[5] while 7-α-D-ribofuranosyladenine has almost the same absorption maximum as 7-methyladenine.[6] Both of these 7-substituted adenines possess maxima at longer wave lengths than the 9-substituted isomers.[6]

A survey of the literature, however, revealed that the first part of the empirical rule does not always hold, at least in the case of purines possessing no substituents in the pyrimidine moiety. For example, the ultraviolet absorption maximum of 7-methylpurine in cationic form appears at a shorter wave length than that of the cationic form of 9-methylpurine. Yet both have almost identical absorption maxima in their neutral form.[7]

The main purpose of the present investigation is to examine the ultraviolet absorption properties of N-substituted imidazopyridines, with emphasis being laid upon the critical examination of the utility of the aforementioned empirical rule[4] for structural elucidation in the imidazopyridine ring system.

For this purpose, 3-methyl-3*H*-imidazo[4,5-*b*]pyridine (I), 1-methyl-1*H*-imidazo[4,5-*c*]pyridine (II), 3-methyl-3*H*-imidazo[4,5-*c*]pyridine (III), and 1-methyl-1*H*-imidazo[4,5-*b*]pyridine (IV) were required among which I, II, and III have not been described in the literature. Therefore, methods of unambiguous syntheses of these compounds have been devised.

3-Methyl-3*H*-imidazo[4,5-*b*]pyridine (I) was prepared according to two different routes (see Flow Sheet 1). 3-Amino-2-methylaminopyridine (X) was prepared essentially according Schickh, Binz, and Schulz.[8] X was subjected to ring closure with formamidine acetate[9] to I. An improved synthesis of I was obtained when formic acid was employed as condensing agent. For purification, I was converted to its picrate, m.p. 203–203.5°, which, after recrystallization, was converted to I, m.p. 76–78°. I was also prepared by treatment of 1*H*-imidazo[4,5-*b*]pyridine (XIII)[10] with dimethyl sulfate in nitromethane in the presence of acetic acid. After removal of the solvent, conversion of the product to its picrates, followed by fractional recrystallization from aqueous ethanol gave two different picrates, m.p. 203–203.5° and 189–191°. One of them, m.p. 203–203.5°, was found to be identical with that of 3-methyl-3*H*-imidazo[4,5-*b*]pyridine (mixture melting point and infrared absorption spectral comparison). The other picrate was 1-methyl-1*H*-imidazo[4,5-*b*]pyridine (IV). IV was also prepared essentially according to Chatterji,

(1) Part XXI of this series, K. Adachi, *Chem. Pharm. Bull.*, **7**, 479 (1959).

(2) J. Baddiley, "Nucleic Acids," Vol. 1, E. Chargaff and J. Davidson, Ed., Academic Press Inc., New York, N. Y., 1955, pp. 143, 152.

(3) J. M. Gulland, R. E. Holiday, and T. F. Macrae, *J. Chem. Soc.*, 1639 (1934).

(4) J. M. Gulland and L. F. Story, *ibid.*, 692 (1938).

(5) J. M. Gulland and E. R. Holiday, *ibid.*, 765 (1936).

(6) W. Friedrich and K. Bernhauer, *Chem. Ber.*, **89**, 2507 (1956).

(7) A. Bendich, P. J. Russell, and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(8) O. v. Schickh, A. Binz, and A. Schulz, *Ber.*, **69**, 2593 (1936).

(9) E. C. Taylor and W. A. Ehrhart, *J. Am. Chem. Soc.*, **82**, 3138 (1961).

(10) V. Petrov and J. Saper, *J. Chem. Soc.*, 1389 (1948).

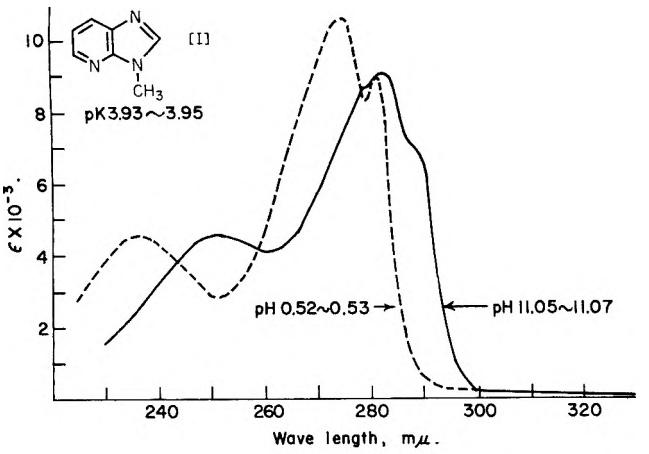


Fig. 1.—3-Methyl-3*H*-imidazo[4,5-*b*]pyridine (I).

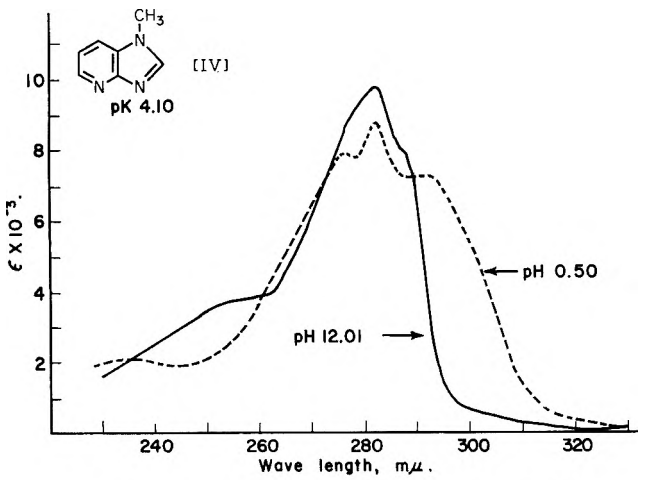


Fig. 2.—1-Methyl-1*H*-imidazo[4,5-*b*]pyridine (IV).

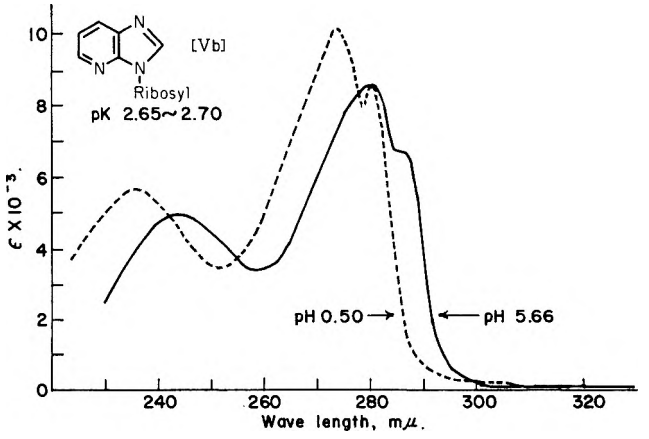


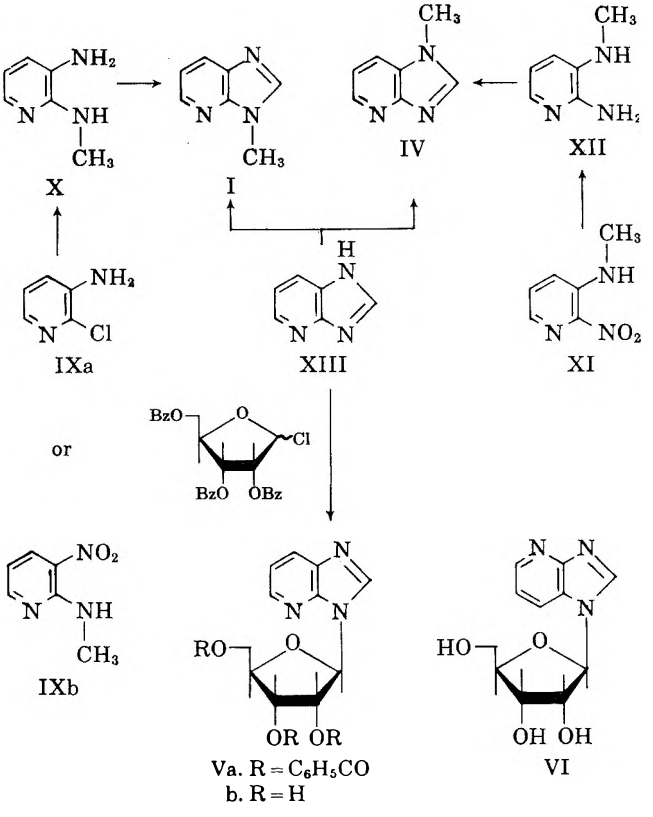
Fig. 3.—3-β-D-Ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine (Vb).

Dhar, Anand, and Dhar,[11] from 3-ethoxycarbonyl-N-methylamino-2-nitropyridine by way of 2-amino-3-methylaminopyridine.[12] Its picrate had m.p. 189–191° which was found to be identical with that of one of two isomers formed from XIII and dimethyl sulfate.

1-Methyl-1*H*-imidazo[4,5-*c*]pyridine (II) was prepared from 4-chloro-3-nitropyridine through 4-methylamino-3-nitropyridine and 3-amino-4-methylaminopyridine (XIV)[13] (see Flow Sheet 2). The yield of II from XIV was 45% using formic acid as the condensing agent. The base was purified by sublimation *in vacuo*. 3-Methyl-3*H*-imidazo[4,5-*c*]pyridine (III) was prepared from 3-chloro-4-nitropyridine 1-oxide (XV) through 4-amino-3-methylaminopyridine (XVII),[14] by ring closure with formic acid.

The ribosylation of 1*H*-imidazo[4,5-*b*]pyridine (XIII) (see Flow Sheet 1) was carried out as follows: the condensation of the mercuric chloride salt with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[15] in boiling xylene gave rise to a crude benzoyl-blocked nucleoside which afforded (after column chromatographic separation) only a single nucleoside (Va) in good yield, which melted at 154–155°. Debenzoylation of Va gave rise to the free nucleoside (Vb) which melted at 220–222°.

1*H*-Imidazo[4,5-*c*]pyridine in the same condensation (see Flow Sheet 2), followed by separation and subsequent debenzoylation gave two different nucleosides, one of which melted at 200–202°.[16]



Flow Sheet 1

The ultraviolet absorption spectra of these compounds are shown in Fig. 1 through 6 along with their apparent p*K* values, determined spectrophotometrically according to Shugar and Fox.[17] As shown in Fig. 1 and 2, the spectra of a pair of isomers (I and IV) of imidazo[4,5-*b*]pyridine series are pH-dependent and have a broad similarity in their neutral form, although

(11) S. K. Chatterji, M. M. Dhar, N. Anand, and M. L. Dhar, *J. Sci. Ind. Res.* (India), **19c**, 35 (1960).

(12) J. W. Clark-Lewis and M. L. Thompson, *J. Chem. Soc.*, 442 (1957).

(13) O. Bremer, *Ann.*, **518**, 274 (1935).

(14) J. W. Clark-Lewis and R. P. Singh, *J. Chem. Soc.*, 2379 (1962).

(15) J. Davoll, B. Lythgoe, and A. Todd, *ibid.*, 967 (1948); H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

(16) Details of this preparation and a structural study of the other nucleoside will appear in a separate communication.[18]

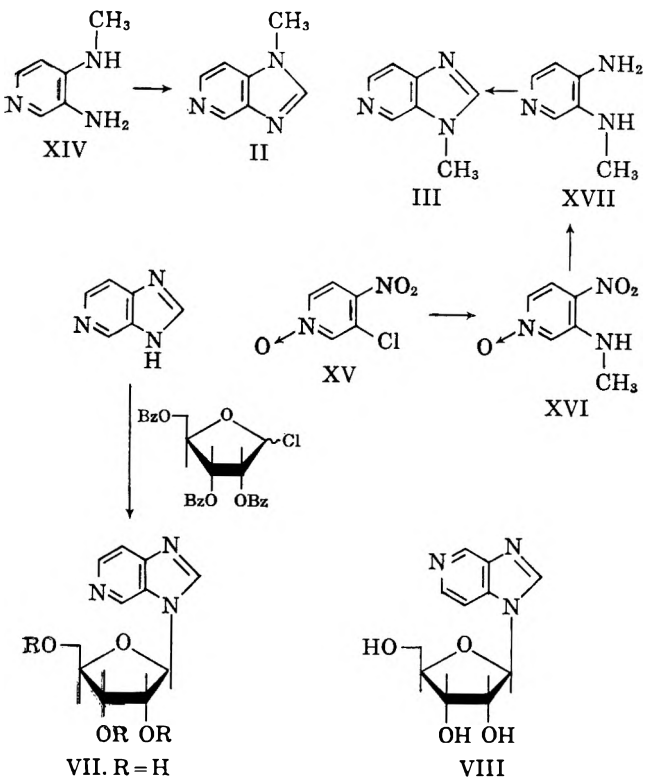
(17) (a) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952); (b) all the p*K* values in this paper were determined by the same method.

(18) Presented at the 15th Hokkaido local meeting of the Japanese Pharmaceutical Society, February, 1963, Sapporo, Hokkaido.

differing considerably in the cationic form where the spectrum of IV shows maxima at 289 mμ (ε 7260), 282 mμ (ε 8700), 277 mμ (ε 7870), and 235 mμ (ε 1960), while that of I shows maxima at 281 mμ (ε 8930), 275 mμ (ε 10,640), and 236 mμ (ε 4470).

In connection with the present investigation, the work of the Indian chemists[11] who also investigated the ribosylation of 1*H*-imidazo[4,5-*b*]pyridine (XIII) is pertinent. They found that only a single nucleoside was formed among two possible isomers V and VI and assigned the 1-β-D-ribofuranosyl-1*H*-imidazo[4,5-*b*]-pyridine structure to their product from a comparison only with 1-methyl-1*H*-imidazo[4,5-*b*]pyridine (IV), neglecting a comparison with 3-methyl-3*H*-imidazo-[4,5-*b*]pyridine (I).

However, our spectral data obtained with the pair of isomers (I and IV) shows that spectral comparison with *both* isomers is essential. Moreover, for the comparison to be valid and useful for unambiguous assignment of structure, curves should be selected at pH values sufficiently removed from the p*K*'s to assure pure species in solution.[19] These requirements for



Flow Sheet 2

comparison are met in all figures (1 through 6). It can be seen that the spectrum of the nucleoside Vb (p*K* of 2.65) for the neutral and cationic species is almost identical with that of I and differs appreciably from that of IV indicating that then ucleoside Vb is 3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine.[20]

(19) For an extensive discussion on this point, see ref. 17a. We are indebted to J. Fox for his participation in the discussion on this point.

(20) The structure was unequivocally established by us[21] on the basis of a series of reactions: the nucleoside (Vb) was converted to 2′,3′-isopropylidene-5′-tosylate. Treatment of the tosylate with boiling acetone gave rise to a water-soluble and intramolecularly quaternized nucleoside. This type of intramolecular quaternization is feasible only with 5′-tosylate of 3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine, excluding absolutely the possibility that the nucleoside might be the 1-derivative.

(21) Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, *Chem. Pharm.*, **11**, 265 ((1963).

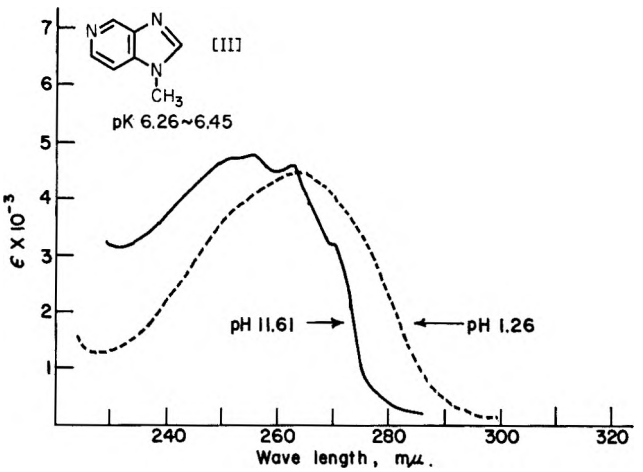


Fig. 4.—1-Methyl-1*H*-imidazo[4,5-*c*]pyridine (II).

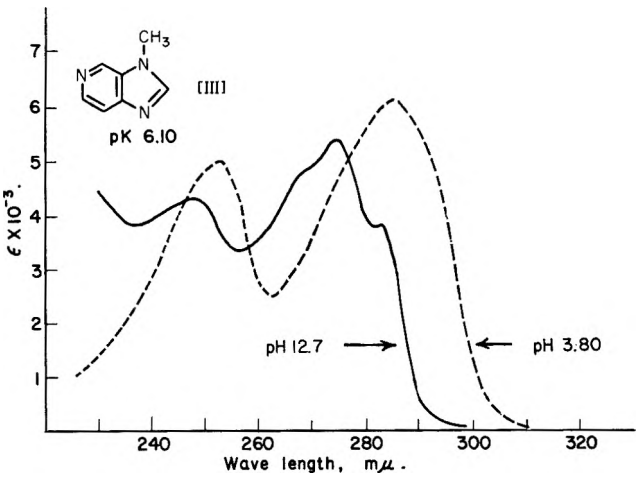


Fig. 5.—3-Methyl-3*H*-imidazo[4,5-*c*]pyridine (III).

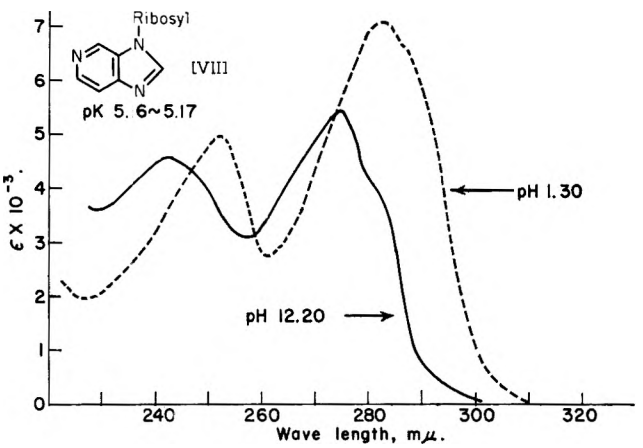


Fig. 6—3-β-D-Ribofuranosyl-3*H*-imidazo[4,5-*c*]pyridine (VII).

As shown in Fig. 4 and 5, 1-methyl-1*H*-imidazo-[4,5-*c*]pyridine (II) and 3-methyl-3*H*-imidazo[4,5-*c*]-pyridine (III), whose p*K*'s are 6.36 and 6.15,[17] respectively, have quite different absorption spectra both in cationic and neutral form. Especially large differences are observed in their absorption maxima in cationic form, III having its maximum at 285 mμ and II at 263 mμ. 3-Methyl-3*H*-imidazo[4,5-*c*]pyridine (III) (7 methyl-3-deazapurine) gives a band at longer wave length than 1-methyl-1*H*-imidazo[4,5-*c*]pyridine (II) (9-methyl-3-deazapurine) showing that the aforementioned empirical rule[4] holds.

The spectral characteristics of the nucleoside (VII) (pK 5.16[17]) derived from 1H-imidazo[4,5-c]pyridine were found to be very similar to that of III in the pH region ranging from 1 to 12, suggesting those the nucleoside (VII) is 3-β-D-ribofuranosyl-3H-imidazo[4,5-c]pyridine.

Experimental[22]

3-Methyl-3H-imidazo[4,5-b]pyridine (I) and Its Picrate. Method A (with Formamidine Acetate).—3-Amino-2-methylaminopyridine[8] (1.10 g.) was treated with formamidine acetate[9] (0.9 g.) in refluxing methoxyethanol (20 ml.) for 1 hr., cooled, and concentrated to dryness. Formamidine acetate was partially removed by sublimation *in vacuo* (90°, 5 mm.) to afford a crude product which was converted to the picrate (500 mg.), needles after two recrystallizations from ethanol, m.p. 203–203.5°.

Anal. Calcd. for $C_{13}H_{10}N_6O_7$: C, 43.10; H, 2.78; N, 23.20. Found: C, 42.97; H, 2.54; N, 22.89.

Method B (with Formic Acid).—2-Methylamino-3-nitropyridine (IXb, 0.9 g.)[23] in ethanol (10 ml.) was reduced over palladium-carbon (5%, 0.1 g.) to afford 0.59 g. of 3-amino-2-methylaminopyridine (81% yield) which was treated with boiling formic acid for 2 hr. Removal of the solvent gave crude product I. On sublimation *in vacuo* (100–120°, 2 mm.) yield was 0.32 g. (41%), m.p. 203–203.5°; R_f, 0.71.[24]

Anal. Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 62.85; H, 5.30; N, 31.26.

Conversion of the Picrate to Free Base. 3-Methyl-3H-imidazo[4,5-b]-pyridine (I).—The picrate of 3-methyl-3H-imidazo[4,5-b]pyridine (450 mg.) in methoxyethanol (10 ml.) was treated with Amberlite IRA 400 (OH^- form, 15 ml.) until the yellow color disappeared. The resin was filtered off and washed twice with water (20 ml.). Concentration of the combined filtrate and washings gave the free base (30 mg.). For further purification the base was sublimed *in vacuo* to give pure product (20 mg.), prisms, m.p. 76–78°. Ultraviolet absorption spectra at pH 0.52–0.53, λ_{max} 236 mμ (ϵ 4470), 275 mμ (ϵ 10,640), 281 mμ (ϵ 8930); λ_{min} 251 mμ (ϵ 2810), 278 mμ (ϵ 8280); at pH 11.05–11.07, λ_{max} 252 mμ (ϵ 4510), 282 mμ (ϵ 9010), 288 mμ (ϵ 6940) (sh); λ_{min} 241 mμ (ϵ 4080).

1-Methyl-1H-imidazo[4,5-b]pyridine (IV).—3-Methylamino-2-nitropyridine (0.89 g.) in methoxyethanol (20 ml.) was hydrogenated over Raney nickel[25] (wet weight, 5 g.) in a hydrogen atomosphere at room temperature. Three hundred and fifty milliliters of hydrogen had been adsorbed at the end of 5 hr. and no further reduction took place after an additional 1 hr. The nickel was filtered, washed twice with methoxyethanol (100 ml.), and filtered. To the combined filtrate was added formamidine acetate (1.9 g.) and the mixture was refluxed for 1.5 hr. The solution was concentrated under reduced pressure to dryness. The solids were purified by distillation *in vacuo* to give the product, m.p. 95–97°, from benzene (lit.[11] m.p. 95–97°). R_f 0.50.[24] Ultraviolet absorption spectra at pH 0.50, λ_{max} 235 mμ (ϵ 1960), 277 mμ (ϵ 7870), 282 mμ (ϵ 8700), 289 mμ (ϵ 7260) (sh); λ_{min} 243 mμ (ϵ 1960), 279 mμ (ϵ 7780); at pH 12.01, λ_{max} 282 mμ (ϵ 9660), 288 mμ (ϵ 7920) (sh). Melting point of the picrate, was 189–191°.

1H-Imidazo[4,5-b]pyridine (XIII).—The procedure used was essentially that reported by Petrow and Saper.[10] Purified base was obtained in 54% yield, m.p. 146–147° (lit.[10] m.p. 153–154°). Sublimation *in vacuo*, followed by recrystallization from acetone, gave product unchanged in melting point, R_f 0.63[24]; melting point of picrate was 188–189°.

Methylation of 1H-imidazo[4,5-b]pyridine. Preparation of 1-Methyl-1H-Imidazo[4,5-b]pyridine (IV) and 3-Methyl-3H-imidazo[4,5-b]pyridine (I).—To a mechanically stirred solution of 1H-Imidazo[4,5-b]pyridine (2.0 g.) in nitromethane (20 ml.) and acetic acid (5 ml.) was added dropwise at 63–65° dimethy sulfate (2.5 g.). The internal temperature rose spontaneously to 75° and then went down to 65° which required 15 min. After the addition was complete, the temperature was raised to 90–93° and the solution was maintained at the same temperature for 30 min. and cooled. The solution was concentrated to dryness. To the residue was added 15 ml. of ethanol which was distilled *in vacuo*. This process was repeated until all trace of acetic acid was removed. The residue was dissolved in water (20 ml.), made alkaline with 4 ml. of 10 N sodium hydroxide pH 11 and then rapidly and repeatedly extracted with ethyl acetate (600 ml.); a yellow fluorescent organic layer was separated, washed with water, dried, and filtered. The filtrate was concentrated to oily solids.[26] For separation and purification, the residue (0.44 g.) was converted to picrates in the following way. One-third (0.252 g., 1.1 mmoles) of the picric acid (0.765 g., 3.3 mmoles), required to convert the entire methyl[4,5 b]pyridine (0.44 g., 3.3 mmoles) to picrates, was dissolved in ethanol (2 ml.) and added to the base (0.44 g.) in ethanol (2 ml.). The reaction mixture was kept standing at room temperature overnight. The precipitate was filtered, and recrystallized from ethanol to give a picrate having m.p. of 203–203.5° which was found to be the picrate of I by comparison with an authentic sample, described earlier. To the filtrate another one-third of the picric acid (0.252 g.) was added to precipitate the second crop which melted after two recrystallizations from ethanol at 203–203.5° and did not depress the melting point of the picrate of I. The combined picrates (m.p. 203–203.5°) weighed 245 mg. By using the second filtrate, the same process was repeated to give a third crop (15 mg.) which melted at 189–191° after two recrystallizations from aqueous methanol and did not depress melting point of picrate of IV.

3-Methyl-3H-imidazo[4,5-b]pyridine Hydrochloride (I·2HCl).—Dry hydrogen chloride gas was passed through a solution of the picrate of I (200 mg.) in absolute ethanol (14 ml.). Ethanol was removed *in vacuo* and the picric acid liberated was extracted repeatedly with ether to give the hydrochloride of I which was dissolved in a minimal amount of absolute methanol and to the solution was added a mixture of dry ether and dioxane to deposit pure hydrochloride.

Anal. Calcd. for $C_7H_7N_3$ 2HCl: C, 40.81; H, 4.41; N, 20.38. Found: C, 41.00; H, 4.28; N, 20.25.

3-Amino-4-methylaminopyridine (XIV).—4-Methylamino-3-nitropyridine was prepared according to Bremer[13] as golden yellow needles, m.p. 157–158° (lit.[13,14] m.p. 162–163°). 4-Methylamino-3-nitropyridine (1.65 g.) was hydrogenated over palladium-carbon prepared by reduction of a mixture of palladium chloride (20 ml. of 1% solution) to give 1.1 g. (83.3%) of product, m.p. 169° (lit.[27] m.p. 169°); the picrate melted at 184° (lit.[24] m.p. 185°).

1-Methyl-1H-imidazo[4,5-c]pyridine (II).—3-Amino-4-methylaminopyridine (0.7 g.) was treated with refluxing formic acid (1 ml.) for 1 hr. and cooled. Excess formic acid was removed under reduced pressure. The residue was dissolved in ethanol and the solution was treated with calcium carbonate (500 mg.), filtered, and concentrated to dryness under reduced pressure. The residue was subjected to sublimation *in vacuo* to give 40% of product, prisms, m.p. 111.5–112.5°. Ultraviolet absorption spectra at pH 1.26, λ_{max} 263 mμ (ϵ 4400); at pH 11.6, λ_{max} 255 mμ (ϵ 4800), 263[1.6] mμ (ϵ 4600); λ_{min} 261 mμ (ϵ 4500). pK_a of II was 6.26–6.46.[17b]

Anal. Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.26; H, 5.43; N, 31.23.

The base was converted to hydrochloride by passing dry hydrogen chloride gas into an ethanol solution of the base.

Anal. Calcd. for $C_7H_7N_3 \cdot 2HCl$: C, 40.79; H, 4.41; N, 20.38. Found: C, 39.92; H, 4.98; N, 19.01. Picrate of II, m.p. 217–218°.

Anal. Calcd. for $C_{13}H_{10}N_6O_7$: C, 43.10; H, 2.78; N, 23.20. Found: C, 39.82; H, 3.22; N, 23.41.

3-Chlorpyridine 1-oxide.—3-Chloropyridine 1-oxide was prepared by a standard procedure.[28] The oxide (11.0 g.) was ob-

(22) All melting points are uncorrected. Ultraviolet absorption spectra were run with the Beckmann Model DK 11 recording spectrophotometer. Molecular extinction coefficients were determined with a Shimadzu manual spectrophotometer. Except where noted sublimation *in vacuo* was done with a "Sublimatometer," devised by E. Shibata (for leading reference, E. Shibata and S. Saito, *Nippon Kagaku Zasshi*, **80**, 604 (1959).

(23) A. E. Chichibabin and A. W. Kirssanow, *Ber.*, **61B**, 1223 (1928).

(24) Paper chromatography was performed using ascending technique; solvent system employed, n-butyl alcohol saturated with water.

(25) D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).

(26) Paper chromatography revealed[24] that the ethyl acetate layer contained two components (R_f 0.73 and 0.53) in addition to starting material (R_f 0.63).

(27) R. Weidenhagen, G. Train, H. Wegner, and L. Nordstrom, *Ber.*, **75**, 1936 (1942).

(28) E. Ochiai, *J. Org. Chem.*, **18**, 535 (1953).

tained from 3-chloropyridine (12.35 g.) in a yield of 78%, m.p. 59–60°, from ether (lit.[29] m.p. 59–60°).

3-Chloro-4-nitropyridine 1-Oxide (XV).—To a solution of 3-chloropyridine 1-oxide (7.2 g.) in concentrated sulfuric acid (sp. gr. 1.80, 16 ml.) was added dropwise with stirring a mixture of fuming nitric acid (sp. gr. 1.54, 24 ml.) and concentrated sulfuric acid (sp. gr. 1.80, 20 ml.). After the addition was complete, the internal temperature was raised to 90° and the mixture was kept at the same temperature for 1.5 hr. after which it was cooled and poured into ice-water, and neutralized with sodium carbonate to deposit a small amount of sodium sulfate which was filtered off. The filtrate was extracted with chloroform. The chloroform layer was separated, washed with water, dried over sodium sulfate, and filtered. The filtrate was concentrated to dryness and recrystallized from acetone to give yellow crystals, m.p. 103–110°; yield was 6.1 g. (64%).

Anal. Calcd. for $C_6H_3N_2O_3Cl$: C, 34.41; H, 1.73; N, 15.96. Found: C, 34.32; H, 1.80; N, 16.10

3-Methylamino-4-nitropyridine 1-Oxide (XVI).—3-Chloro-4-nitropyridine 1-oxide (8.3 g.) was treated for 20 min. with a refluxing methanol solution of methylamine (5%, 50 ml.) on the steam bath. In a few minutes solids separated. Heating was continued for another 20 min. and the solution cooled. After cooling, a precipitate was collected by filtration. Recrystallization from ethanol gave pure product (3.65 g., 45.4%), m.p. 227°, from ethanol (lit.[14] m.p. 227°).

4-Amino-3-methylaminopyridine (XVII).—Methylamino-4-nitropyridine 1-oxide was reduced to 4-amino-3-methylaminopyridine over Raney nickel according to the procedure of Clark-Lewis and Sigh.[14] Reduction of 3-methylamino-4-nitropyridine (3.5 g.) gave 2.4 g. (quantitative yield) of product, needles, m.p. 112° (lit.[14] m.p. 114°). The picrate melted at 225–228°.

3-Methyl-3*H*-imidazo[4,5-*c*]pyridine (III).—4-Amino-3-methylaminopyridine (130 mg.) was refluxed with 10 ml. of freshly distilled formic acid for 4 hr. and cooled. After cooling formic acid was removed *in vacuo* to dryness and to the residue was added to ethanol which was distilled *in vacuo*. The process was repeated until all trace of formic acid was removed, to give 4-formylamino-3-methylaminopyridine. Picrate melted at 177° (from ethanol).

Anal. Calcd. for $C_{13}H_{12}N_6O_8$: C, 41.05; H, 3.15; N, 22.10. Found: C, 40.92; H, 3.34; N, 22.00.

For ring closure the solid residue was sublimed *in vacuo* to give the desired product (65 mg., 46% on the basis of XVII); needles from ethanol, m.p. 101–101.5°. Ultraviolet absorption spectra at pH 3.80, λ_{max} 253 mμ (ε 5000), 285 mμ (ε 6100); λ_{min} 263 mμ (ε 2500); at pH 12.7, λ_{max} 249 mμ (ε 4300), 275 mμ (ε 5400); λ_{min} 257 mμ (ε 3300). pK_a of III was 6.10.[17b]

Anal. Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.26; H, 5.43; N, 31.50.

The base was converted to picrate which melted after recrystallization from ethanol at 199.5–200°.

Anal. Calcd. for $C_{13}H_{10}N_6O_7$: C, 43.10; H, 2.78; N, 23.20. Found: C, 43.08; H, 2.93; N, 23.15.

Mercuric Chloride Salt of 3*H*-Imidazo[4,5-*b*]pyridine.—To a well stirred solution of 3*H*-imidazo[4,5-*b*]pyridine (2.66 g.) in 15 ml. of 1.5 *N* sodium hydroxide was added a solution of mercuric chloride (6.1 g.) in ethanol (20 ml.) to give rise to white precipitates which were collected by centrifugation, washed successively three times with water, four times with ethanol, and finally with dry ether, and dried *in vacuo* at 100° (2 mm.). The mercuric chloride obtained was stable to heat, up to 250°; yield was 7.7 g. (97%).

Anal. Calcd. for $C_6H_4N_3HgCl$: N, 11.84. Found: N, 12.01.

Ribosylation of the Mercuric Chloride Salt of 3*H*-Imidazo[4,5-*b*]pyridine with 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl Chloride.—The procedure used in condensation was essentially that reported by Kissman and Weiss.[30] The mercuric chloride salt (13.9 g.) and 2,3,5-tri-*O*-benzoylribofuranosyl chloride prepared by a standard method[15] from 1-*O*-acetyl-2,3,5-tri-o-benzoyl-β-b-ribofuranose (20 g.) gave a crude benzoyl-blocked nucleoside(s), which was applied to acid-washed alumina (2.5 × 55 cm.). The first seven fractions (200 ml. each) eluted by benzene (1.5 l.) contained only a sugar derivative (total weight, 3.2 g.[31]) and were discarded. Each fraction of the subsequent seven fractions (200 ml. each) eluted by a mixture of ethyl acetate and benzene (1:5 v./v., 1.5 l.) afforded after evaporation of the solvent the same nucleoside,[32] total weight, 8.75 g. The eluting solvent was switched to ethyl acetate (seven 200-ml. portions) which eluted seven fractions, each of which was concentrated to dryness. The residues were found to be identical with each other (total weight, 6.46 g.) and also with preceding nucleoside. On washing the alumina with ethanol (660 ml.) 2.05 g. of 3*H*-imidazo-[4,5-*b*]pyridine was recovered in the form of the free base. The combined benzoyl-blocked nucleoside weighed 15.2 g. (68%), m.p. 154–155°.

Anal. Calcd. for $C_{32}H_{25}N_3O_7$: C, 68.20; H, 4.47; N, 7.46. Found: C, 68.10; H, 4.51; N, 7.42.

3-β-D-Ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine (Vb).—To a solution of the benzoyl-blocked nucleoside (Va, 0.7 g.) in absolute methanol (70 ml.) was added a 1 *N* methanol solution of sodium methoxide (1 ml.); the solution was refluxed for 1 hr. and cooled. After cooling the solvent was removed *in vacuo* at room temperature to furnish a product which was dissolved in water (20 ml.). The aqueous layer was separated and concentrated *in vacuo* to dryness. Recrystallization from water gave colorless needles, 0.22 g., 71%, m.p. 220–222° (lit.[11] m.p. 220°). Ultraviolet absorption spectra at pH 0.50, λ_{max} 236 mμ (ε 5600), 275 mμ (ε 10,120), 281 mμ (ε 8600); λ_{min} 251–252 mμ (ε 3440), 279 mμ (ε 7,900); at pH 5.66, λ_{max} 243 mμ (ε 4940), 281 mμ (ε 8540) 287 mμ (ε 6620) (sh); λ_{min} 259 mμ (ε 3350). pK_a[17] was 2.65–2.70.

Absorption spectra of 3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*c*]-pyridine (VII) at pH 1.30, λ_{max} 252 mμ (ε 5000), 283 mμ (ε 7200); λ_{min} 261 mμ (ε 2800); at pH 12.20, λ_{max} 242 mμ (ε 5600), 275 mμ (ε 5500); λ_{min} 257 mμ (ε 3100). pK_a[17] of VII was 5.16–5.17.

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(29) R. E. Evans and H. C. Brown, *J. Org. Chem.* **27**, 1329 (1962).

(30) H. G. Kissman and M. J. Weiss, *J. Org. Chem.*, **21**, 1053 (1956).

(31) The substance was nitrogen free and infrared spectra were very similar to that of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose which suggested that conversion of this to the corresponding 1-chloride was incomplete.

(32) Identity was based on criteria of infrared and ultraviolet absorption spectral comparisons and on the fact that after recrystallization from ethanol (recovery of the recrystallization was approximately 70%) the mixture melting point with each other were not depressed.

The Formation of 2,7-Anhydro-α-L-*galacto*-heptulofuranose and 2,7-Anhydro-β-L-*galacto*-heptulopyranose by the Action of Acid on L-*galacto*-Heptulose (Perseulose)[1]

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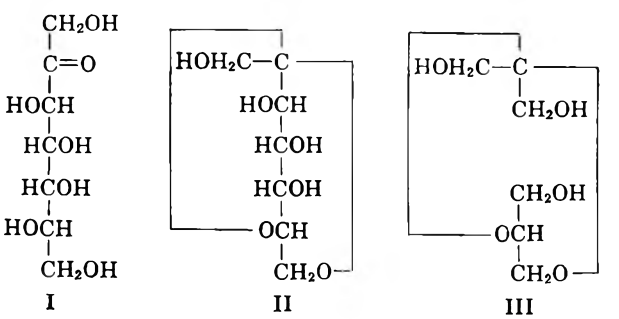
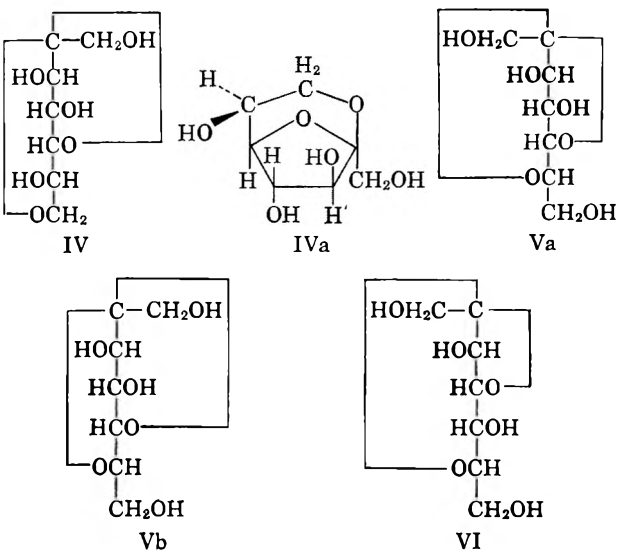
L-*galacto*-Heptulose has been transformed by hot dilute acid to give about a 5% yield of nonreducing anhydro sugars. Separation of the mixture on a Dowex 1 column (borate form) led to the isolation of about equal amounts of 2,7-anhydro-α-L-*galacto*-heptulofuranose and 2,7-anhydro-β-L-*galacto*-heptulopyranose, whose structures were established by the application of methods used earlier for similar compounds.

In the preceding paper on the transformation of reducing sugars to their nonreducing anhydrides in acid solution,[2] one of us showed that D-galactose is converted into 1,6-anhydro-α-D-galactofuranose and 1,6-anhydro-β-D-galactopyranose in yields of 0.95 and 0.71%, respectively. Since a heptulose with the *galacto* configuration was available, we now have studied the behavior of L-*galacto*-heptulose (perseulose, I)[3] and find that it, similarly, yields two crystalline anhydrides. Thus, L-*galacto*-heptulose, heated in 0.2 *N* sulfuric acid for three hours at 80°, gave about a 5% yield of nonreducing material. This was separated readily into two fractions on a column of Dowex 1 (borate form) by elution with sodium tetraborate.[2,4] The compound isolated from the fraction that formed a strong borate complex melted at 133–134° and showed $[\alpha]^{20}D$ +25.5° in water. It was presumed to be the 2,7-anhydro-β-L-*galacto*-heptulopyranose II be-



cause it reacted with sodium metaperiodate with the consumption of two moles of reagent and the slow liberation of one mole of formic acid per mole of compound; this behavior resembled that of sedoheptulosan (2,7-anhydro-β-D-*altro*-heptulopyranose),[5] and the rotation of the expected dialdehyde was about equal in magnitude but opposite in sign to that observed in the periodate oxidation of sedoheptulosan. Final proof of the structure II was obtained by reducing the dialdehyde with sodium borohydride to the trihydric alcohol III, which has only one asymmetric carbon atom; the crystalline tri-*p*-toluenesulfonate of III was shown to be the enantiomorph of the corresponding compound derived similarly from sedoheptulosan. The trihydric alcohol (III) is readily recognized as 1,2-(1,3-dihydroxyisopropylidene)-D-glycerol [and as a 2,2,4-tris(hydroxymethyl)-1,3-dioxolane]; its enantiomorph, derived from sedoheptulosan, was, in fact, hydrolyzed to glycerol as part of its proof of structure.[5]

The fraction from the Dowex 1 column that did not form a borate complex yielded a nonreducing anhydroheptulose that melted at 134–135°, showed $[\alpha]^{20}D$ −20.7° in water, and was not oxidized by periodate. By analogy with 1,6-anhydro-α-D-galactofuranose[6] and 2,7-anhydro-β-D-*altro*-heptulofuranose,[7] we should expect the new compound to be 2,7-anhydro-α-L-*galacto*-heptulofuranose (IV), with a locked pair of *trans* hydroxyl groups[8] at C-3 and C-4 (*cf.* the Haworth formula IVa). There are only two other formulas that might be written for a monomeric, nonreducing, periodate-resistant anhydroperseulose, namely, V and



VI. These differ from IV in that each has a primary hydroxyl group at C-7. When the new anhydride was converted into its tetratosylate and the latter was heated with sodium iodide in 2,5-hexanedione for 75 hours at 100° there was no evidence of any exchange reaction and 63% of the tosylate was recovered. Since it is well known[9] that an ω-sulfonyloxy group of a sugar exchanges readily with sodium iodide to form an ω-deoxy-ω-iodo sugar under relatively mild condi-

(1) Presented in part before the Division of Carbohydrate Chemistry at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) N. K. Richtmyer, *Arch. Biochem. Biophys.*, **78**, 376 (1958).

(3) E. B. Tilden, *J. Bacteriol.*, **37**, 629 (1939); R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **61**, 336 (1939).

(4) J. X. Khym and L. P. Zill, *ibid.*, **74**, 2090 (1952).

(5) J. W. Pratt, N. K. Richtmyer, and C. S. Hudson, *ibid.*, **74**, 2200 (1952).

(6) For a review of the 1,6-anhydrohexofuranoses, see R. J. Dimler, *Advan. Carbohydrate Chem.*, **7**, 37 (1952).

(7) N. K. Richtmyer and J. W. Pratt, *J. Am. Chem. Soc.*, **78**, 4717 (1956).

(8) Other such sterically hindered vicinal glycols include: (a) the two *trans*-camphane-2,3-diols and cholestane-3β,6β,7α-triol [S. J. Angyal and R. J. Young, *ibid.*, **81**, 5467, 5251 (1959)]; (b) methyl 4,6-*O*-benzylidene-α-D-altropyranoside and its anomer [J. Honeyman and C. J. G. Shaw, *J. Chem. Soc.*, 2454 (1959)]; and (c) 2,6-anhydro-β-D-fructofuranose [H. R. Goldschmid and A. S. Perlin, *Can. J. Chem.*, **38**, 2178 (1960)].

(9) See R. S. Tipson, *Advan. Carbohydrate Chem.*, **8**, 181 (1953).

tions (whereas a sulfonyloxy group at C-1 of a ketose is resistant to exchange), we may conclude that neither formula V nor VI can represent our compound. This conclusion was substantiated by the fact that our compound yielded only a monotrityl derivative, just as had been found to occur with the two anhydrides of sedoheptulose,[7] neither of which has a primary hydroxyl group at C-7. Thus, the second anhydroperseulose must have the structure IV. Finally, the new anhydroperseulose was oxidized with lead tetraacetate in pyridine at 0°, a reagent that Goldschmid and Perlin[10] found would cleave even the sterically hindered vicinal diols; one molecular equivalent of reagent was consumed in about two hours, though overoxidation became evident on longer standing. This reaction is in agreement with what would be expected of a compound with the formula IV, and serves as additional evidence to exclude formula VI for the levorotatory anhydro-L-*galacto*-heptulose.

The mother liquor from the anhydride IV was chromatographed further on a cellulose column and a very small amount of a second nonreducing, orcinol-positive, periodate-resistant compound was obtained as a sirup that was not investigated further. It appears possible that perseulose upon acid treatment might yield, besides II and IV, other anhydrides such as V (which can be written either as the 2,5-anhydro-β-L-*galacto*-heptulopyranose Va or as the 2,6-anhydro-α-L-*galacto*-heptulofuranose Vb) or VI. A similar product was obtained from D-galactose and thought possibly to be 1,5-anhydro-α-D-galactofuranose.[2] Three examples of this rare type of nonreducing anhydro sugar, each with a five-membered and a six-membered ring, have been described previously: the 1,5-anhydro-β-D-ribofuranose of Vis and Fletcher,[11] the 2,6-anhydro-β-D-fructofuranose of Goldschmid and Perlin,[8c] and the sirupy 1,4-anhydro-2,3,6-tri-*O*-methyl-α-D-glucopyranose obtained by Pakhomov, Golova, and Nikolaeva[12] through the thermal decomposition of tri-*O*-methylcellulose *in vacuo*.[13]

A comparison of the mobilities on paper chromatograms of the known anhydroheptuloses is given in the Experimental section.

Experimental

The Reaction of L-*galacto*-Heptulose (Perseulose, I) with Dilute Acid and Isolation of the Nonreducing Material.—Preliminary experiments showed that when perseulose hemihydrate[3] in 0.2 *N* sulfuric acid was heated for 3 hr. at 80°; it lost about 9% of its reducing power as determined by the ferricyanide method.[14] At the same time, some further decomposition occurred, and about 1.5% of 5-(1,2-dihydroxyethyl)-2-furaldehyde (DHEF) was estimated to be present as calculated from its ultraviolet absorption spectrum.[7] For isolation of the products formed in this reaction, 120 g. of perseulose monohydrate was dissolved in 4 l. of 0.2 *N* sulfuric acid and the solution was heated quickly to 85° and then placed in an oven at 80° for 3 hr. The solution was cooled in running water, deacidified by passage through a column of Duolite A-4 ion-exchange resin, and concentrated *in vacuo* to a sirup from which most of the unchanged perseulose was crystallized by the addition of ethanol. A total of 392 g. of perseulose monohydrate was subjected to acid treatment in this way and 346 g. of it recovered. The rest of the perseulose in the mother liquor was destroyed by heating with an excess of aqueous barium hydroxide in an open, stainless steel container for several days. The solution was neutralized to phenolphthalein with a stream of carbon dioxide, filtered, and deionized with Amberlite IR-120 and Duolite A-4 ion-exchange resins. Concentration of the effluent *in vacuo* yielded 20 g. (*ca.* 5%) of a colorless sirup. Paper chromatograms, spotted with this sirup and developed in 1-butanol–pyridine–water (6:4:3) by the multiple ascent technique, revealed four spots that could be visualized with an orcinol–hydrochloric acid spray. The slowest, in trace amounts, was identified as perseulose, while the other three ran considerably faster and were nonreducing. Of these three, only the slowest was oxidizable by periodate sprays.

2,7-Anhydro-α-L-*galacto*-heptulofuranose (IV).—A 7-g. portion of the sirup described above was dissolved in 100 ml. of 0.005 *M* aqueous sodium tetraborate and the solution passed through a column (10 cm. × 3.5 cm.) of Dowex 1 strong-base ion-exchange resin in the borate form.[2,4] The resin was eluted with 0.005 *M* borate; five 200-ml. portions were sufficient to remove the two noncomplexing anhydroheptuloses as tested for with Brown's orcinol–ferric chloride reagent.[15] When the next liter of 0.005 *M* borate removed nothing further, a shift was made to 0.1 *M* aqueous sodium tetraborate and the complexing material removed by elution. The remainder of the original sirup was separated into noncomplexing and complexing fractions similarly.

The 0.005 *M* borate fractions were combined, freed from cations by passage through Amberlite IR-120, concentrated *in vacuo* to a mixture of anhydroheptuloses and boric acid, and the latter was removed by several distillations of methanol from the residue. The final sirup weighed 9 g. and was crystallized without difficulty. The 5.7 g. of 2,7-anhydro-α-L-*galacto*-heptulofuranose (IV) thus obtained was recrystallized thrice from methanol to form chunky prisms melting at 134–135° and showing $[\alpha]^{20}D$ −20.7° in water (*c* 1.8). It was not oxidized by sodium metaperiodate in 30 hr. at 20°. Arthur S. Perlin has kindly measured its oxidation with an excess (3 moles/mole) of lead tetraacetate in pyridine at 0° and reports 0.25, 0.40, 0.77, 1.03, and 1.19 moles of oxidant/mole of compound consumed at the end of 10, 20, 60, 120, and 180 min., respectively. He obtained similar values of 0.36, 0.66, and 1.25 for 1,6-anhydro-α-D-galactofuranose and 0.70, 0.99, and 1.34 for 2,7-anhydro-β-D-*altro*-heptulofuranose at the end of 15, 30, and 180 min., respectively. Overoxidation was evident in all three cases.

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.30; mol. wt., 192.2. Found: C, 43.77; H, 6.39; mol. wt. (Mechrolab vapor pressure osmometer), 188.5.

The mother liquor from the 5.7 g. of IV was chromatographed on a cellulose column (36 cm. × 4 cm.) with acetone–water (95:5) as eluent. The principal and fastest-moving component was the same anhydroheptulose IV; it was followed by a slower-moving, nonreducing, periodate-negative heptulose derivative presumed to be the anhydride V; traces of perseulose appeared also in the latter fractions. The third anhydride was very small in amount, did not crystallize, and has not been investigated further.

2,7-Anhydro-1,3,4,6-tetra-*O*-*p*-tolylsulfonyl-α-L-*galacto*-heptulofuranose.—A solution of 0.5 g. of the anhydroheptulose IV and 6 g. of *p*-toluenesulfonyl chloride in 25 ml. of dry pyridine was kept at room temperature for 4 days and then poured onto cracked ice. A granular product (1.8 g.; 85%) was deposited, and became crystalline when a solution of it in 95% ethanol was allowed to evaporate slowly at 5°. It was recrystallized once from hot ethanol and twice from acetone–ethanol, forming fine needles with m.p. 115–118° and $[\alpha]^{20}D$ −5.9° in chloroform (*c* 1).

Anal. Calcd. for $C_{35}H_{36}O_{14}S_4$: C, 51.97; H, 4.49; S, 15.85. Found: C, 52.20; H, 4.79; S, 16.16.

When the tetra-*O*-tosyl compound was heated with sodium iodide in 2-butanone for 6 hr. at 80°, no sodium tosylate separated and 93% of the starting material was recovered. Even after 75 hr. in 2,5-hexanedione at 100° no sodium tosylate was obtained and from the dark-colored reaction mixture 63% of the tetratosylate was recovered unchanged.

2,7-Anhydro-1-*O*-triphenylmethyl-α-L-*galacto*-heptulofuranose.—A solution of 0.5 g. of the anhydroheptulose IV and 2.6 g. (3.6 molecular equivalents) of chlorotriphenylmethane in 25 ml.

(10) H. R. Goldschmid and A. S. Perlin, *Can. J. Chem.*, **38**, 2280 (1960).

(11) E. Vis and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **79**, 1182 (1957).

(12) A. M. Pakhomov, O. P. Golova, and I. I. Nikolaeva, *Izv. Akad. Nauk, SSSR, Otd. Khim. Nauk*, 521 (1957).

(13) Note added February 8, 1963: see also E. Husemann and J. Klar, *Makromol. Chem.*, **53**, 223 (1962), for three additional methods of preparing the anhydride of 2,3,6-tri-*O*-methyl-D-glucose.

(14) C. S. Hanes, *Biochem. J.*, **23**, 99 (1929); H. C. Hagedorn and B. N. Jensen, *Biochem. Z.*, **135**, 46 (1923).

(15) A. H. Brown, *Arch. Biochem.*, **11**, 269 (1946).

of dry pyridine was left at room temperature for 3 days and then poured onto cracked ice. After standing overnight at 5° the precipitated solid was filtered and washed with cold water; wt., 2.9 g., $[\alpha]^{20}D$ −7.5° in chloroform. Trityl derivative was freed from the large amount of contaminating triphenylmethanol by crystallization from chloroform–pentane and ethanol–pentane; after two additional recrystallizations from the latter solvent pair and a final one from acetone–water, the prismatic needles of the trityl derivative of the anhydroheptulose IV melted at 190–192° and showed $[\alpha]^{20}D$ −36.8° in chloroform (*c* 0.4). By a comparison of the two rotations the amount of trityl derivative in the 2.9 g. of crude product could be estimated as 0.6 g. (53%).

Anal. Calcd. for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 72.10; H, 6.30.

2,7-Anhydro-β-L-*galacto*-heptulopyranose (II).—The 0.1 *M* sodium tetraborate eluate from the Dowex 1 column was decationized and freed from boric acid as described for the 0.005 *M* borate eluate. The solution, some of which was spilled accidentally, was concentrated *in vacuo* to a sirup that weighed 6 g. and showed $[\alpha]^{20}D$ +18° in water. It failed to crystallize, even after being run through columns of Amberlite IR-120 and IRA-400 ion-exchange resins (the latter to remove any lactones and traces of perseulose); however, when the new sirup was chromatographed on a column of cellulose powder and eluted with 95% aqueous acetone, a number of the fractions crystallized spontaneously. Combination of the appropriate fractions yielded 2.8 g. of crystalline product from ethanol, and after several recrystallizations from water–acetone the fluffy needles of the 2,7-anhydro-β-L-*galacto*-heptulopyranose (II) melted at 133–134° and showed $[\alpha]^{20}D$ +25.5° in water (*c* 2.1). A small sample of the material, when oxidized with an excess of sodium metaperiodate, consumed 1.94 and 1.95 moles of oxidant per mole of compound after 23 and 48 hr., respectively. The amount of formic acid liberated was 0.33 mole after 23 hr. and 1.2 moles after 19 days; the slow liberation of acid resembles the similar behavior of sedoheptulosan toward periodate.[5] The rotation also changed slowly, becoming constant only after 8 days; the rotation $[\alpha]^{20}D$ +13.3°, calculated as the expected dialdehyde, was of opposite sign and somewhat smaller in magnitude than the −16.9° reported for the oxidation of sedoheptulosan.[5]

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.30; mol. wt., 192.2. Found: C, 43.75; H, 6.33; mol. wt. (Mechrolab vapor pressure osmometer), 184.4.

Periodate Oxidation of 2,7-Anhydro-β-D-*altro*-heptulopyranose (Sedoheptulosan). 1,2-(1,3-Dihydroxyisopropylidene)-L-glycerol Tri-*p*-toluenesulfonate.—To an ice-cold solution of 6.1 g. of sedoheptulosan hydrate in 100 ml. of water was added 180 ml. of 0.5 *M* aqueous sodium metaperiodate and, after 15 min. in the ice bath, the solution was left at room temperature for 10 days. Aqueous barium chloride was added to precipitate the iodate and excess of periodate ions, and the solution was filtered and deionized with Amberlite IR-120 and Duolite A-4 ion-exchange resins. The solution of dialdehyde was concentrated to 50 ml., decolorized with a small amount of carbon, added dropwise to a stirred solution of 3.6 g. of sodium borohydride in 50 ml. of water, and the mixture was stirred for an additional 2 hr. The next morning the excess borohydride was destroyed by the dropwise addition of 45 ml. of acetone; cations were removed by passage of the solution through Amberlite IR-120; and the liberated boric acid was removed by concentrating the solution *in vacuo* and distilling several portions of methanol from the residue. The final sirupy product weighed 2.4 g. (50% over all from sedoheptulosan).

A 0.7-g. portion of this sirup and 13 g. of *p*-toluenesulfonyl chloride were dissolved in 75 ml. of dry pyridine. After 2 days at room temperature the mixture was poured onto cracked ice and the resulting gum and aqueous layer were extracted with chloroform. The chloroform solution was washed in succession with ice-cold sulfuric acid, water, aqueous sodium bicarbonate, and water, dried with sodium sulfate, filtered with a small amount of carbon, and concentrated to 2.2 g. of sirup. A small sample of the sirup in a relatively large volume of 95% ethanol crystallized when kept in the refrigerator over a weekend. Crystallization of the main portion of sirup from chloroform–pentane proceeded slowly to yield 1.7 g. (64%). This product was recrystallized first from 60 ml. of hot 95% ethanol, and then twice from acetone–water. The prismatic needles of the tri-*O*-tosyl compound melted at 91–94° and showed only a small rotation, $[\alpha]^{21}D$ +1.7° in chloroform (*c* 0.9).

Anal. Calcd. for $C_{27}H_{30}O_{11}S_3$: C, 51.74; H, 4.83; S, 15.35. Found: C, 52.02; H, 4.93; S, 15.05.

1,2-(1,3-Dihydroxyisopropylidene)-L-glycerol tri-*p*-nitrobenzoate was prepared by the action of *p*-nitrobenzoyl chloride on another portion of the sirup in dry pyridine in the usual manner. A great deal of difficulty was encountered in obtaining a pure product, but after two recrystallizations from acetone–pentane, two from acetone–water, and one from pyridine–water, the final product (small, grayish, prismatic needles) melted at 175–178° and gave a satisfactory analysis.

Anal. Calcd. for $C_{27}H_{21}N_3O_{14}$: C, 53.03; H, 3.46; N, 6.87. Found: C, 53.13; H, 3.19; N, 6.98.

Periodate Oxidation of 2,7-Anhydro-β-L-*galacto*-heptulopyranose (II). 1,2-(1,3-Dihydroxyisopropylidene)-D-glycerol Tri-*p*-toluenesulfonate.—One gram of the anhydroperseulose II was oxidized in the same manner as sedoheptulosan and the dialdehyde reduced with sodium borohydride to the dioxolane (III); the resulting sirup was tosylated to yield a crystalline product weighing 0.35 g. Recrystallization to constant m.p. from acetone–water gave prismatic needles melting at 92–95°, as compared to 91–94° for the tritosylate from sedoheptulosan. The amount of purified material was so small and the rotation of the compound so small in magnitude that no satisfactory comparison of rotations with the enantiomorph could be made. However, since the infrared spectrum of this tritosylate in chloroform solution was almost identical with that of the tritosylate obtained from sedoheptulosan as described earlier, and the melting point of a mixture of the two substances was depressed to 78–89°, the enantiomorphous nature of the two tosylates was considered to be confirmed thereby.

Anal. Calcd. for $C_{27}H_{30}O_{11}S_3$: C, 51.74; H, 4.83; S, 15.35. Found: C, 51.86; H, 4.58; S, 15.31.

Mobilities of 2,7-Anhydro Heptuloses on Paper Chromatograms.—With sedoheptulosan as a readily available standard, the mobilities of the known 2,7-anhydrides of the heptuloses in 1-butanol–pyridine–water (6:4:3) on Whatman no. 1 paper by the descending method are as follows: anhydro-*galacto*-heptulofuranose, 1.78; anhydro-*manno*-heptulopyranose, 1.53; anhydro-*gluco*-heptulopyranose, 1.50; anhydro-*galacto*-heptulopyranose, 1.46; anhydro-*altro*-heptulofuranose, 1.40; anhydro-*ido*-heptulopyranose, 1.39; anhydro-*gulo*-heptulopyranose, 1.29; and the standard, anhydro-*altro*-heptulopyranose, 1.00. The mobility of the third anhydro-*galacto*-heptulose (V?) is intermediate between the mobilities of the other two forms (II and IV), but a definite value is not available.

Acknowledgment.—The authors wish to thank Dr. William C. Alford, Mr. Harold G. McCann, and their associates of the Analytical Services Unit of this laboratory for obtaining the ultraviolet and infrared spectra and the elemental analysis; also, Dr. Arthur S. Perlin of the Prairie Regional Laboratory, Saskatoon, Saskatchewan, Canada, for his measurements of the oxidation of the three sterically hindered vicinal diols by lead tetraacetate in pyridine.

2,4-Di-*O*-methyl and 3-*O*-Methyl Ethers of 1,6-Anhydro-β-L-idopyranose[1]

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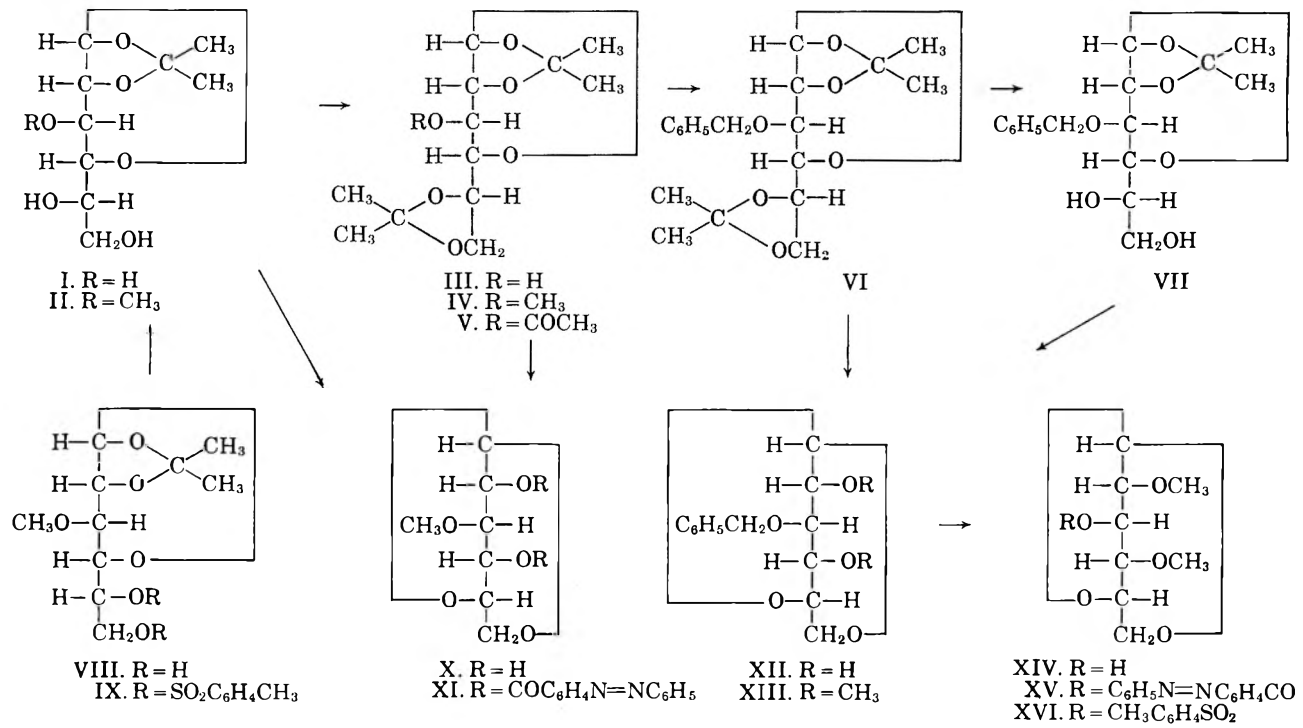
The syntheses of 1,6-anhydro-3-*O*-methyl-β-L-idopyranose and 1,6-anhydro-2,4-di-*O*-methyl-β-L-idopyranose are described.

The methylated derivatives described in this paper are two more members in the series of *O*-methyl-L-idose, of interest as reference substances in the elucidation of the structure of polymers containing L-iduronic acid.

Treatment of 1,2-*O*-isopropylidene-L-idofuranose (I)[3] with acetone gave a di-*O*-isopropylidene-L-idose, previously encountered in the D-series by Iwadare[4] and presumed to have the structure III. Methylation of this compound, followed by acid hydrolysis, gave 1,6-anhydro-3-*O*-methyl-β-L-idopyranose (X), the enantiomorph of which has been described by Reeves.[5] Proof that the methyl group was indeed at position 3 was obtained by synthesis of the same material from 1,2-*O*-isopropylidene-3-*O*-methyl-D-glucofuranose[6] (VIII) by solvolysis, with resultant Walden inversion of the 5,6-di-*O*-*p*-tolylsulfonyl derivative IX. It is quite unlikely that there was any migration of the methyl group under the conditions used.

Analogously, the product obtained by benzylation of III, using the method of Croon and Lindberg,[7] was hydrolyzed, giving 1,6-anhydro-3-*O*-benzyl-β-L-idopyranose (XII), from which 1,6-anhydro-2,4-di-*O*-methyl-β-L-idopyranose (XIV) was readily obtained by complete methylation and reductive debenzylation.

The monomethyl ether X was characterized by a crystalline *p*-phenylazobenzoyl derivative XI, and the dimethyl ether XIV by the crystalline *p*-phenylazobenzoyl derivative XV and the *p*-tolylsulfonyl derivative XVI.



Experimental

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro or micro (for amounts smaller than 3 mg.) tubes with lengths of 100 or 200 mm., using a Rudolph photoelectric polarimeter attachment, Model 200; the chloroform used was A.R. grade and contained approximately 0.75% of ethanol. Infrared spectra were determined on a Perkin-Elmer spectrophotometer Model 237. Chromatograms were made with the flowing method on "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950, 60–200 mesh), used without pretreatment. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (manufacturer's instructions). The sequence of eluents was hexane, benzene or dichloroethane, ether, ethyl acetate, acetone, and methanol individually or in binary mixtures. The proportion of weight of substance to be adsorbed to weight of adsorbent was 1 to 50–100. The proportion of weight of substance in grams to volume of fraction of eluent (ml.) was 1 to 100. The ratio of diameter to length of the column was 1 to 20. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated under a stream of dry nitrogen.

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The microanalyses were done by Dr. M. Manser, Zürich, Switzerland.

1,2:5,6-Di-*O*-isopropylidene-L-idofuranose (III).—To a solution of 960 mg. of 1,2-*O*-isopropylidene-β-L-idofuranose (I)[3] in 25 ml. of dry acetone was added *ca.* 1 g. of anhydrous copper sulfate, and the mixture was stored at room temperature for 1 week. The mixture was filtered, the residue washed with acetone, and the solution evaporated. The residue dissolved in chloroform was chromatographed on 60 g. of silica gel. Elution with ether gave 416 mg. of crystalline solid, which was recrystallized from a mixture of acetone and hexane to give 305 mg. (27%) of stout needles, m.p. 153–154°, $[\alpha]^{22}D$ −22° (in water, *c* 0.60); $[\alpha]^{23}D$ −25° (in acetone, *c* 0.55).[8]

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.33; H, 7.40.

Elution with acetone gave 687 mg. of material which was recrystallized from a mixture of acetone and hexane to give 599 mg. (63%) of unchanged starting material I, m.p. 114–115°.

3-*O*-Acetyl-1,2:5,6-di-*O*-isopropylidene-L-idofuranose (V).—A solution of 102 mg. of 1,2:5,6-di-*O*-isopropylidene-L-idofuranose (III) in 1 ml. of pyridine and 0.5 ml. of acetic anhydride was stored at room temperature for 60 hr. The solution was evaporated by codistillation with toluene, and the residue, dissolved in chloroform, was subjected to chromatography on silica gel. Elution with a mixture of chloroform and ethyl acetate, 4:1, afforded 104 mg. (88%) of crystalline material, which was recrystallized from a mixture of ether and pentane to give 82 mg. (69%) of the desired product, m.p. 77–78°, $[\alpha]^{15}D$ −12° (in chloroform, *c* 0.75).

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 55.62; H, 7.34. Found: C, 55.39; H, 7.32.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-idofuranose (IV).—A suspension of 218 mg. of III in 4 ml. of methyl iodide was heated under reflux, when most of it dissolved, and the compound was methylated with three additions of 270 mg. of silver oxide added over 45 hr. The mixture was filtered, the residue was washed with acetone, and the filtrate was evaporated to dryness. A solution of the residue in chloroform was chromatographed on silica gel. The major part (219 mg.) was eluted with chloroform and a mixture of chloroform and ether, 9:1, as a sirup. Part of this was distilled in a molecular still with a pressure of 0.1 cm. at a bath temperature of 100°, giving a sirup with $[\alpha]^{22}D$ −63° (in chloroform, *c* 2.09).

Anal. Calcd. for $C_{13}H_{22}O_6$: OCH_3, 11.32. Found: OCH_3, 11.05.

1,2-*O*-Isopropylidene-3-*O*-methyl-5,6-di-*O*-*p*-tolylsulfonyl-D-glucofuranose (IX). A solution of 1 g. of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (VIII)[6] and 3.27 g. (4 moles) of *p*-toluenesulfonyl chloride in 2 ml. of pyridine and 20 ml. of dry chloroform was stored overnight at room temperature. A few drops of water were added and the mixture shaken. The mixture was extracted with chloroform and the solution was washed with ice-cold *N* sulfuric acid, cold saturated sodium bicarbonate solution, and water. After evaporation of the solvent, the residue was dissolved in a mixture of benzene and hexane, 1:1, and chromatographed on silica gel. No definite crystalline fraction could be obtained, and, therefore, the total product was recombined, dried, and dissolved in 5 ml. of dry chloroform and 2 ml. of dry pyridine; 2.2 g. of toluene sulfonyl chloride was added, and the mixture stored at room temperature for 24 hr. The solvent was removed by evaporation, water was added to decompose the excess of *p*-toluenesulfonyl chloride, and the product was extracted with chloroform. The solution, after being washed with ice-cold *N* sulfuric acid, and cold saturated sodium bicarbonate solution, was dried and evaporated. The residue was dissolved in a mixture of hexane and benzene, 1:1, and chromatographed on silica gel. Elution with a mixture of benzene and ether, 24:1, gave 1.55 g. of crystalline fractions which were recrystallized from a mixture of methanol and water to give a total of 1.06 g. (46%) of needles, m.p. 90–93°, $[\alpha]^{22}D$ −20° (in chloroform, *c* 0.76).

Anal. Calcd. for $C_{24}H_{30}O_{10}S_2$: C, 53.14; H, 5.58; S, 11.80. Found: C, 53.18; H, 5.56; S, 11.94.

1,6-Anhydro-3-*O*-methyl-β-L-idopyranose (X). From IV.—A solution of 127 mg. of IV in 3 ml. of 1.3 *N* sulfuric acid was heated for 7 hr. at 100°. The acidic solution was extracted with chloroform overnight in a continuous extractor, with lead carbonate added to the chloroform solution. Evaporation of the filtered solution gave 76 mg. (93%), which was recrystallized from a mixture of acetone and ether to give 28 mg. (34%) of rectangular plates, m.p. 110–111°, $[\alpha]^{18}D$ +108° (in acetone, *c* 0.84).[9]

Anal. Calcd. for $C_7H_{12}O_5$: C, 47.72; H, 6.87; OCH_3, 17.62. Found: C, 47.71; H, 6.88; OCH_3, 17.75.

From IX.—A mixture of 575 mg. of freshly fused potassium acetate, 574 mg. of IX, and 10 ml. of acetic anhydride was heated under reflux for 10 hr. The mixture was stored at room temperature overnight, then evaporated under reduced pressure. The mixture was shaken with 100 ml. of chloroform and 100 ml. of water. The chloroform solution was washed with water, dried over anhydrous potassium acetate, and evaporated. The residue was dissolved in benzene and chromatographed on 25 g. of silica gel. Elution with a mixture of benzene and ether, 9:1, gave 373 mg. of sirup which would not be induced to crystallize. The sirup was dried by evaporation with ethanol, dissolved in methanol, and stored overnight at room temperature with 1 ml. of 1.4 *N* barium methylate. Water was added and carbon dioxide passed into the solution. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in 20 ml. of ethanol and the solution was filtered and evaporated. The residue was dissolved in 5 ml. of acetone and the solution was filtered and evaporated. The remaining sirup was dissolved in ethylene dichloride and chromatographed on 10 g. of silica gel. The fractions eluted with a mixture of ether and ethyl acetate, 4:1, were combined and evaporated to give 146 mg. of sirup, probably 1,2-*O*-isopropylidene-3-*O*-methyl-L-idofuranose (II).

A solution of 32 mg. of this sirup in 1 ml. of *N* sulfuric acid was heated at 100° for 4 hr. The cooled solution was passed through a 5-ml. column of Dowex 1 in the acetate form and the column was washed with 25 ml. of a mixture of water and ethanol, 1:1. The solution was evaporated and the residue dissolved in ethylene dichloride and chromatographed on 1 g. of silica gel. Elution with ethyl acetate afforded 20 mg. of material, which was recrystallized to give 12 mg. (50%) of plates, m.p. 110–111°. This product showed no depression of the melting point in admixture with the product described earlier.

1,6-Anhydro-3-*O*-methyl-2,4-di-*O*-*p*-phenylazobenzoyl-β-L-idopyranose (XI).—A solution of 25 mg. of X and 140 mg. of *p*-phenylazobenzoyl chloride in 1 ml. of pyridine was heated in a sealed tube at 100° for 5 hr. After addition of 1 drop of water, the mixture was evaporated to dryness by codistillation with toluene. The residue was dissolved in a mixture of pentane and benzene, 1:2, and chromatographed on neutral alumina, Brockman activity III. The material eluted with a mixture of benzene and pentane, 2:1, was recrystallized from the same solvent to give 44 mg. (52%) of orange platelets, m.p. 198.5–199°, $[\alpha]^{22}D$ +74° (in chloroform, *c* 0.18).

Anal. Calcd. for $C_{33}H_{28}N_4O_7$: C, 66.88; H, 4.76; N, 9.46; OCH_3, 5.24. Found: C, 66.70; H, 4.80; N, 9.37; OCH_3, 5.48.

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose (VI).—A solution of 100 mg. of III in 1 ml. of benzyl bromide and 3 ml. of dimethylformamide was stirred with 1 g. of silver oxide for 24 hr. at room temperature. The mixture was filtered and the residue washed with 3 ml. of dimethylformamide. Then 20 ml. of chloroform and 50 ml. of 1% aqueous potassium cyanide were added to the solution, and the mixture shaken and extracted with chloroform. The dried chloroform solution was evaporated and the residue, dissolved in a mixture of benzene and hexane, 1:1, was chromatographed on silica gel. Two incompletely separated peaks of sirupy material (680 mg.) were eluted with benzene and mixtures of benzene and ether, 4:1 and 2:1. One of the fractions of the latter part of the second peak was dissolved in ether. The solution was filtered through a sintered fritted glass and evaporated, giving a sirup with $[\alpha]^{26}D$ −74° (in chloroform, *c* 0.40).

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.12; H, 7.53.

3-*O*-Benzyl-1,2-*O*-isopropylidene-L-idofuranose (VII).—A mixture of 463 mg. of III and *ca.* 0.5 g. of sodium in 25 ml. of ether was refluxed overnight with exclusion of moisture. The translucent suspension was decanted from the excess sodium, 2 ml. of benzyl bromide was added, and the solution concentrated to half the volume and then refluxed for 5 hr. The mixture was diluted with chloroform and the solution was washed with water, dried, and evaporated. Hexane was added and 110 mg. (24%) of III was obtained by crystallization. The mother liquor was evaporated and the residue dissolved in benzene and chromatographed on silica gel. Elution with ether gave 243 mg. of crystals, which

(8) Iwadare[4] reported m.p. 151–152.5, $[\alpha]^{5}D$ +36° (in acetone) for the D-substance.

(9) Reeves[5] reported m.p. 104–106°, $[\alpha]D$ −107° (in acetone, *c* 0.99).

were recrystallized from ether to give 179 mg. (32%) of fine needles, m.p. 89–90°, $[\alpha]^{15}D$ −48° (in chloroform, *c* 0.59).

The product corresponded to VII and had resulted from hydrolysis, due to the acid developed by the decomposition of benzyl chloride.

Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.65; H, 6.86.

Further elution with acetone gave 124 mg. (27%) of III.

1,6-Anhydro-3-*O*-benzyl-β-L-idopyranose (XII). From VI.—A solution of 282 mg. of partially purified VI in 10 ml. of 2 *N* sulfuric acid and 2 ml. of ethanol was heated for 7 hr. at 150° in a sealed tube. The mixture was partially evaporated and then extracted continuously overnight with chloroform, with lead carbonate added to the organic solvent. After filtration and drying, the solution was evaporated, and the residual product, dissolved in benzene, was chromatographed on silica gel. A mixture of ether and ethyl acetate, 2:1, eluted 48 mg. of crystalline material. It was recrystallized from a mixture of acetone and pentane to give 34 mg. (40%) of platelets, m.p. 157–157.5°, $[\alpha]^{20}D$ +42° (in chloroform, *c* 0.80).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.73; H, 6.27.

From VII.—A solution of 50 mg. of VII in 0.5 ml. of ethanol and 1 ml. of *N* sulfuric acid was heated at 100° for 3 hr. The solution was evaporated to one-half and extracted continuously overnight with chloroform, with lead carbonate added to the organic solvent. The solution was evaporated after filtration. The crystalline residue was recrystallized from a mixture of acetone and pentane, giving 23 mg. (57%) of material identical to the product described previously.

1,6-Anhydro-3-*O*-benzyl-2,4-di-*O*-methyl-β-L-idopyranose (XIII).—A solution of 118 mg. of XII in 11 ml. of methyl iodide and 1 ml. of acetone was heated under reflux and stirred with 1.6 g. of silver oxide added in four portions over 3 days. The mixture was filtered, the residue washed with chloroform, and the solution evaporated. The residual product was dissolved in a mixture of hexane and benzene, 9:1, and chromatographed on silica gel. The major fraction (121 mg., 92%) of sirup was eluted with a mixture of benzene and ether, 4:1, $[\alpha]^{30}D$ +58° (in chloroform, *c* 2.0).

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; OCH_3, 22.15. Found: C, 64.15; H, 7.08; OCH_3, 22.45.

1,6-Anhydro-2,4-di-*O*-methyl-β-L-idopyranose (XIV).—A solution of 115 mg. of XIII in 50 ml. of methanol was stirred with 100 mg. of 2% palladized charcoal under a slight pressure of hydrogen for 8 hr., when the uptake of hydrogen ceased. The solution was filtered and evaporated, and the residual product crystallized from ether, giving 59 mg. (76%) of rectangular prisms, m.p. 82–83°, $[\alpha]^{25}D$ +91° (in chloroform, *c* 1.10).

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42; OCH_3, 32.63. Found: C, 50.64; H, 7.37; OCH_3, 33.29.

1,6-Anhydro-2,4-di-*O*-methyl-3-*O*-*p*-phenylazobenzoyl-β-L-idopyranose (XV).—A solution of 15 mg. of XIV and 40 mg. of *p*-phenylazobenzoyl chloride in 0.5 ml. of pyridine was stored at 50° for 1 hr. then overnight at room temperature. A mixture of water and pyridine was added, and after 10 min. the mixture was extracted with chloroform. The chloroform solution was washed with ice-cold *N* sulfuric acid, with cold saturated sodium bicarbonate solution, and then with water, and dried over sodium sulfate. It was then passed through a column of neutral alumina, Brockman activity III. The material eluted with dry chloroform was recrystallized from a mixture of benzene and hexane to give 15 mg. (48%) of long orange needles, m.p. 172–173.5°, $[\alpha]^{15}D$ +27° (in chloroform, *c* 0.26).

Anal. Calcd. for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03; OCH_3, 15.58. Found: C, 63.38; H, 5.55; N, 6.95; OCH_3, 15.85.

1,6-Anhydro-2,4-di-*O*-methyl-3-*O*-*p*-tolylsulfonyl-β-L-idopyranose (XVI).—A solution of 30 mg. of XIV in 0.2 ml. of dry pyridine was cooled and a solution of 100 mg. of *p*-toluenesulfonyl chloride in 0.05 ml. of dry pyridine and 0.1 ml. of ethylene dichloride was added. The solution was stored at room temperature for 1 week. Water was added to decompose the acid chloride, and the mixture was poured onto ice. It was extracted with chloroform, and the chloroform solution was washed with ice-cold *N* sulfuric acid, then with water, dried over sodium sulfate, and evaporated. The residue, dissolved in benzene, was chromatographed on silica gel. The crystalline fractions, eluted with mixtures of benzene and ether, 4:1 and 2:1, and with pure ether, were combined and recrystallized from ether and pentane to give 40 mg. (74%) of needles, m.p. 106–106.5°, $[\alpha]^{25}D$ +58° (in chloroform, *c* 1.01).

Anal. Calcd. for $C_{16}H_{20}O_7S$: C, 52.31; H, 5.86; OCH_3, 18.02. Found: C, 52.37; H, 5.85; OCH_3, 18.24.

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Monophosphate Esters of D-Erythronic Acid

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The syntheses of D-erythronic acid 2-phosphate and 4-phosphate are described. The synthesis of erythronic acid 3-phosphate from 2-*O*-benzoyl erythronolactone was unsuccessful. Some properties of the phosphate esters and the synthetic intermediates are reported.

In a continuing study of the chemical and biochemical properties of a number of phosphate esters of mono- and polyhydroxy acids,[1] it was of interest to prepare the monophosphates of D-erythronic acid. The starting material for the synthesis was 2,4-*O*-ethylidene-D-erythrose (I).[2]

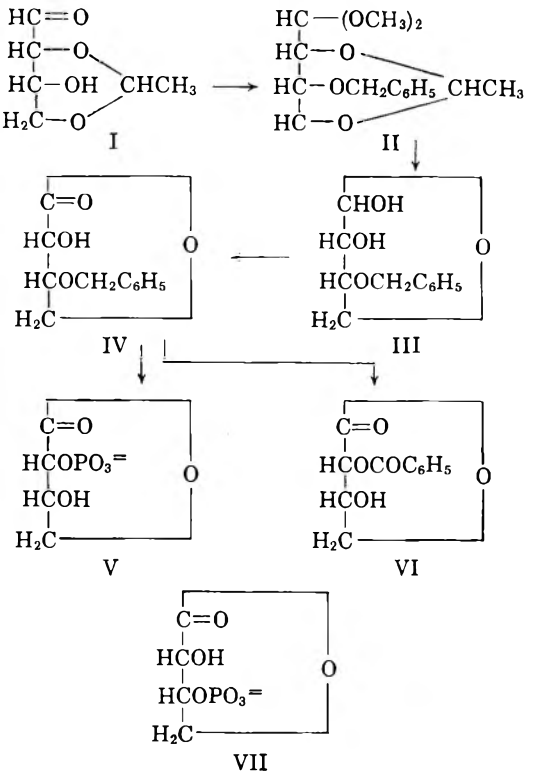
In the preparation of the 2-phosphate the following sequence of reactions was used.

I → 2,4-*O*-ethylidene-D-erythrose dimethyl acetal → 3-*O*-benzyl-2,4-*O*-ethylidene-D-erythrose dimethyl acetal (II) → 3-*O*-benzyl-D-erythrose (III) → 3-*O*-benzyl-D-erythronolactone (IV). This material, IV, was phosphorylated using diphenyl phosphorochloridate, which after hydrogenolysis of the benzyl and phenyl groups, gave D-erythronolactone 2-phosphate (V) which was isolated as the cyclohexylammonium salt.

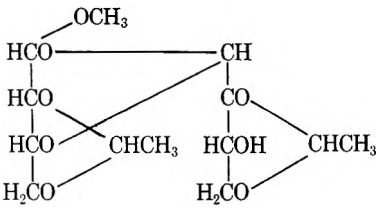
In attempts to prepare D-erythronic acid 3-phosphate (VII), IV was converted to 2-*O*-benzoyl-3-*O*-benzyl-D-erythronolactone which on hydrogenolysis gave 2-*O*-benzoyl-D-erythronolactone (VI). Attempts to phosphorylate this compound, using either diphenyl phosphorochloridate or the more reactive (less hindered) phosphorus oxychloride, gave extremely poor yields of phosphorylated products. Moreover, the properties of the products were not compatible with the expected properties of the desired 3-phosphate ester. Examination of space filling models offers no apparent reason for the low reactivity of the 2-*O*-benzoyl ester (VI) as compared to the 3-*O*-benzyl ether (IV).

(1) F. Wold and C. E. Ballou, *J. Am. Chem. Soc.*, **81**, 2368 (1959); F. Wold, *J. Org. Chem.*, **26**, 197 (1961).

(2) R. Barker and D. L. MacDonald, *J. Am. Chem. Soc.*, **82**, 2301 (1960).



In the synthesis of IV a number of difficulties were encountered. The conversion of I to the dimethyl acetal was carried out by treating a solution of I in methanol–trimethyl orthoformate with ammonium chloride.[3] The yield of the desired product varied from 5 to 70% and appeared to depend upon the degree to which I had undergone dimerization. In all cases the product of the reaction was nonreducing. Treatment of an authentic sample of the dimer of I[4] under the same conditions gave a nonreducing, nondistillable product which had an infrared spectrum essentially identical to that of the residue obtained from the preparation of II. These results are in agreement with the findings of Post[5] who demonstrated that polymerized aldehydes do not react with ortho esters to form monomeric acetals. Based on the structure of dimeric 2,4-*O*-ethylidene-D-erythrose proposed by Schaffer, it is probable that the nondistillable residue is, in part, material with the structure VIII. The presence of a

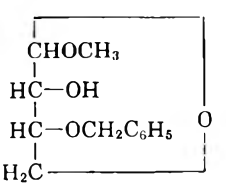


VIII

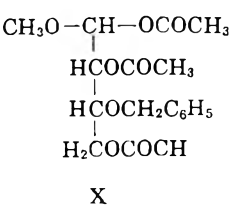
hydroxyl and a carbonyl absorption in the infrared spectrum indicates that in all probability some formylation of the hydroxyl group has occurred as reported by Anderson and Marvell[6] for the analogous β-hydroxylaldehydes. The amount of dimer present in a given preparation of I was not dependent only upon the age of the preparation, since some freshly prepared samples of I gave very poor yields of II; however, storage of I did decrease the yields of II which could be obtained from it.

The hydrolysis of II to give III was difficult to accomplish in good yield. A variety of acids, solvents, and temperatures was used with little effect on the yield of III. The ethylidene group was readily removed by all of the treatments used, provided that the acetaldehyde was allowed to escape from the reaction. The poor yields of III appear to be due to the formation of a methyl glycoside IX which is quite resistant to hydrolysis. Conditions which are sufficiently vigorous to hydrolyze the glycoside also appear to remove the benzyl group. A sample of the glycoside was obtained by chromatography on a Florisil column of the mixture obtained after hydrolysis and oxidation of II. It was found to be quite resistant to acid hydrolysis, being incompletely hydrolyzed by refluxing in 0.1 *N* sulfuric acid for twenty-four hours. Paper chromatography of the products of this hydrolysis indicated that only a very small amount of III was present and that a considerable portion of the material had lost all of its blocking groups and/or undergone polymerization. An attempt was made to obtain III by acetolysis of II followed by deacetylation of the resulting acetate. A crystalline tetra-*O*-acetyl-3-*O*-benzyl-D-erythrose was obtained in low yields, which on catalytic deacetylation gave a product which was reducing, contained vicinal hydroxyl groups, and which had the same R_f as 3-*O*-benzyl-D-erythrose.

Examination of the mother liquors from the crystallization of the tetraacetate indicated that, to some degree, acetolysis had resulted in the complete removal of both the *O*-methyl groups and the *O*-benzyl group, since chromatography of the deacetylated mixture indicated that a small proportion of free erythrose was present. The major component in the deacetylated mother liquors did not react with periodate and was reducing only after hydrolysis with dilute mineral acid. The latter treatment gave a mixture which contained both erythrose and 3-*O*-benzyl-D-erythrose, a behavior which is consistent with this component being a methyl glycoside. The low yield of the desired tetraacetate of 3-*O*-benzylerythrose is probably due to the formation of methyl hemiacetal(s) (X) during the acetolysis. This conclusion is supported by the finding that deacetylation of the sirupy acetates with hot alkali gave a strongly reducing product whereas cold alkali (or catalytic deacetylation) gave the glycoside described previously.



IX



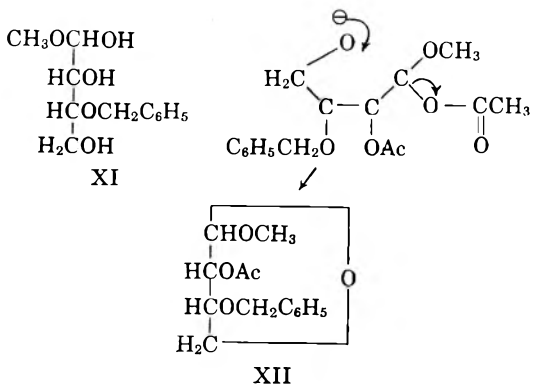
X

Montgomery, Hann, and Hudson[7] obtained such compounds from the acetolysis of methyl tri-*O*-acetyl-β-D-arabinopyranoside using zinc chloride as a catalyst.

(3) C. E. Ballou and H. O. L. Fischer, *J. Am. Chem. Soc.* **78**, 1659 (1956).
(4) R. Schaffer, *ibid.*, **81**, 2838 (1959).
(5) H. W. Post, *J. Org. Chem.*, **5**, 2449 (1940).
(6) E. R. Alexander and E. N. Marvell, *J. Am. Chem. Soc.*, **72**, 3944 (1950).
(7) E. M. Montgomery, R. M. Hann, and C. S. Hudson, *ibid.*, **59**, 1124 (1937).

These authors found that catalysis of acetolysis of furanosides with 4% sulfuric acid gave rise to aldehydo acetates[8] whereas pyranosides gave varying amounts of pyranose, acetates, and aldehydo acetates.

It is not surprising that the deacetylation of X proceeds to give a glycoside. It is probable that the methyl hemiacetal XI is not an intermediate in this deacetylation but that the primary hydroxyl group at C-4 is freed first and that an intramolecular reaction occurs with this hydroxyl group displacing an acetate ion from C-1 with the formation of XII which would undergo further deacetylation in a normal fashion to give IX. The facility with which a C-4 hydroxyl

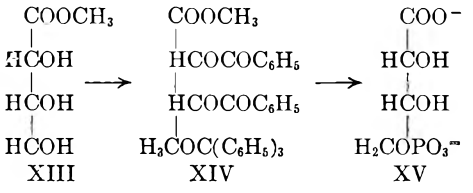


XI XII

group can participate in a displacement at C-1 has been pointed our previously.[9]

The oxidation of the mixtures containing III most easily was carried out using bromine in a slightly acidic medium.[10] No oxidation occurred when perpropionic acid[11] or hydrogen peroxide–ammonium molybdate[12] were used, and alkaline iodine oxidation[13] gave a product which was very difficult to separate from iodine containing contaminants.

In the synthesis of D-erythronic acid 4-phosphate (XV) the following sequence of reactions was used. I → D-erythronolactone → methyl-D-erythronate (XIII) → methyl 2,3-di-*O*-benzoyl-4-*O*-trityl-D-erythronate (XIV) → methyl 2,3-di-*O*-benzoyl-4-*O*-diphenylphosphoryl-D-erythronate → D-erythronic acid 4-phosphate cyclohexylammonium salt (XV).



XIII XIV XV

The conversion of erythronolactone to the ester (XIII) was achieved in 50% yield by treating a methanolic solution of the lactone with barium methylate.[14] The equilibrium favors the lactone since the latter could be recovered in low yield, despite the large molar proportion of methanol present. In all attempts to prepare the methyl esters by this procedure a proportion of the lactone was converted to the barium salt. In an attempt to improve the yield of ester XIII the lactone was hydrolyzed, and the free acid treated with diazomethane. The yield of the desired methyl esters was again 50%. The residue appeared to contain a considerable amount of *O*-methylated material.

The two phosphate esters were chromatographically pure in several solvent systems. The 4-phosphate consumed three equivalents of base (pK_a' <2, 3.6, 6.65) while the 2-phosphate consumed only two equivalents (pK_a' <2 and 6.9), showing that the lactone is still intact. When the free acids (treated with an excess of Dowex 50H+) were heated briefly or left at room temperature for twenty-four hours, both phosphate esters gave identical chromatographic behavior in several solvent systems. The two major components in each of these reaction mixtures cochromatographed with the original 2-phosphate and 4-phosphate, indicating that phosphate migration takes place in spite of the interference from the lactone. The reaction mixture should also contain 3-phosphate, which would not be expected to separate from the 2-phosphate on chromatography.

Experimental[15]

2,4,*O*-Ethylidene-D-erythrose Dimethyl Acetal.—To a solution of 75 g. of freshly prepared 2,4-*O*-ethylidene-D-erythrose in 200 ml. of dry methyl alcohol was added 200 ml. of freshly distilled trimethyl orthoformate and 10 g. of anhydrous ammonium chloride. The mixture was heated at 40 to 50° for 9 hr.; it was then dark brown and gave a negative Benedict's test. To the cooled reaction, 100 ml. of concentrated aqueous ammonia was added and the whole concentrated *in vacuo* to a dark brown sirup which was extracted with three 200-ml. portions of ethyl ether. The extracts were dried over sodium sulfate and concentrated to give 85.2 g. of a mobile, brown sirup which was fractionated by distillation. The fraction, boiling at 55° and 0.2 mm., crystallized spontaneously and weighed 69.7 g. (70.5%). It had $[\alpha]^{23}D$ −26.8° (c 4.7, methanol) and m.p. 40°.

Anal. Calcd. for $C_8H_{16}O_5$ (192.2): C, 50.0; H, 8.39. Found: C, 49.75; H, 8.40.

3-*O*-Benzyl-2,4,*O*-ethylidene-D-erythrose Dimethyl Acetal (II).—To a vigorously stirred solution of 67.5 g. of 2,4-*O*-ethylidene-D-erythrose dimethyl acetal in 500 ml. of benzene was added 170 g. of finely powdered potassium hydroxide[16] and 230 ml. of reagent grade α-chlorotoluene. The reaction mixture was heated to reflux with continued stirring for 14 hr. and then cooled, filtered through Celite, and the filtrate concentrated *in vacuo* at 70°. The residue was fractionated by distillation through a 30-cm. Vigreux column. The fraction (83.5 g.), boiling between 95° and 100° at 0.05 mm., was collected. Examination of this product by vapor phase[17] chromatography demonstrated that it was contaminated with a small amount (*ca.* 10%) of dibenzyl ether. Most, but not all, of this dibenzyl ether was removable by redistillation. A sample which from gas chromatography was estimated to contain *ca.* 5% dibenzyl ether had $[\alpha]^{23}D$ −30.6° (*c* 40.0, tetrahydrofuran), corrected $[\alpha]^{23}D$ −32.2°. The material showed no OH absorption in the infrared.

Anal. Calcd. for 95% $C_{15}H_{22}O_5$ + 5% $C_{14}H_{14}O$: C, 64.84; H, 7.76. Found: C, 64.84; H, 7.63.

1,1,2,4-Tetra-*O*-acetyl-3-*O*-benzyl-D-erythrose.—3-*O*-Benzyl-2,4-*O*-ethylidene-D-erythrose dimethyl acetal (II) (5.0 g.) was dissolved in an ice-cold mixture of 35 ml. of glacial acetic acid, 70 ml. of acetic anhydride, and 4 ml. of concentrated sulfuric acid. After 24 hr. at 4° the reaction mixture was poured over a slurry of ice in sodium bicarbonate solution and the mixture stirred for 30 min. with the addition of sufficient solid sodium bicarbonate to neutralize the acid. The mixture was extracted three times with 100-ml. portions of methylene chloride, the

(8) E. M. Montgomery and C. S. Hudson, *J. Am. Chem. Soc.* **56**, 2643 (1934).
(9) F. C. Hartman and R. Barker, *J. Org. Chem.*, **28**, 1004 (1963).
(10) C. S. Hudson and H. S. Isbell, *J. Am. Chem. Soc.*, **51**, 2225 (1929).
(11) J. d'Ans and W. Frey, *Ber.*, **45**, 1845 (1912).
(12) H. Zinner and K. H. Falk, *Chem. Ber.*, **88**, 566 (1955).
(13) E. E. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 293 (1940).
(14) O. Touster and V. H. Reynolds, *ibid.*, **197**, 863 (1952).
(15) Melting points are corrected.
(16) Hooker Chemical Corp., Niagara Falls, N. Y.
(17) Column packing, 20% Dow-Corning high-vacuum grease on Chromosorb W (Johns Manville and Co.). Helium carrier gas with the column at 250°.

extracts were washed with water, dried over sodium sulfate, filtered, and concentrated to a sirup. Crystals were obtained by dissolution of the sirup in methylene chloride and addition of cyclohexane; yield 560 mg., m.p. 114–116°. After two recrystallizations from the same solvent the material had m.p. 116°, $[\alpha]^{23}D$ +5.4° (*c* 2.0 ethylacetate).

Anal. Calcd. for $C_{19}H_{24}O_9$ (396.4) C, 57.6; H, 6.05. Found: C, 57.50; H, 6.04.

The compound contained no methoxy groups and reduced Benedict's reagent. Treatment with ethanolic base at room temperature over night gave consistently a high base consumption (5 equiv. instead of 4). This is consistent with the known effect of alkali on reducing sugars.

3-*O*-Benzyl-D-erythronolactone (IV).—A solution of 3-*O*-benzyl-2,4-*O*-ethylidene-D-erythrose dimethyl acetal (II) (15.4 g.) in 670 ml. of 75% aqueous acetic acid was heated in an open flask on a steam cone for 5 hr. At this time the reducing sugar value had been constant for 1 hr. and no acetaldehyde could be detected. The solvents were removed at 50° *in vacuo* and the residue (11.8 g.) dissolved in 100 ml. of freshly distilled tetrahydrofuran. To this solution was added 100 ml. of water containing 10 g. of barium acetate and 3.0 ml. of bromine. After 18 hr. at 23° in the dark the reaction mixture gave a negative Benedict's test.

Bromine and tetrahydrofuran were removed by aerating the reaction mixture at 50°. The aqueous residue was extracted with five 50-ml. portions of methylene chloride. The extracts were combined, dried over sodium sulfate, and taken to dryness to give 12 g. of semicrystalline material. From this residue 1.5 g. of crystalline material (m.p. 70–73°) was obtained from ethyl acetate by the addition of hexane. More of the same material was obtained by chromatography of the mother liquors from the first crop on a column containing Florisil (60–100 mesh). The first fraction (3.0 g.), eluted with benzene, appeared to be a mixture of dibenzyl ether and starting material. The second fraction (1.75 g.) was eluted with ether and was essentially pure 3-*O*-benzylerythronolactone. Elution with methanol gave 3.7 g. of material which was neutral, contained a benzyl residue, was nonreducing, but which gave a reducing substance after treatment with hot aqueous acid. On the basis of these observations it is proposed that this substance is methyl (α or β) 3-*O*-benzyl-D-erythroside (IX).

The combined crops of 3-*O*-benzyl-D-erythronolactone after recrystallization from ethyl acetate–cyclohexane had m.p. 89°, $[\alpha]^{22}D$ −44.2° (*c* 1.13, ethyl alcohol); R_f in *n*-butyl alcohol–ethyl alcohol–water (10:1:2), 0.65.

Anal. Calcd. for $C_{11}H_{12}O_4$ (208.2); C, 63.5; H, 5.82. Found: C, 63.46; H, 6.13.

3-*O*-Benzyl-D-erythronic Acid.—3-*O*-Benzyl-D-erythronolactone (0.25 g.) was saponified with 2 meq. of aqueous potassium hydroxide. This reaction mixture was then acidified with 2 meq. of aqueous hydrochloric acid and the acidic aqueous solution extracted with ether several times. The extracts were dried and concentrated to give 0.25 g. of a sirup which deposited crystals (200 mg.) from ethyl acetate–petroleum ether. Recrystallization from the same solvent gave a material with m.p. 105° $[\alpha]^{25}D$ −4.5° (*c* 1.0, ethyl alcohol). R_f in *n*-butyl alcohol–ethyl alcohol–water (10:1:2), 0.43.

Anal. Calcd. for $C_{11}H_{14}O_6$ (226): C, 58.4; H, 6.25. Found: C, 58.25; H, 6.36.

D-Erythronolactone 2-Phosphate Dicyclohexylammonium Salt (V).—Diphenyl phosphorochloridate (2.3 ml., 10.8 mmoles) was added dropwise to an ice-cold solution of 1.91 g of 3-*O*-benzyl-D-erythronolactone in 5 ml. of dry pyridine. The reaction was kept at 4° for 20 hr., chipped ice was added, and after a further 2 hr. at 4° the mixture was partitioned between methylene chloride and water. The methylene chloride layer was washed successively with 1 *N* sulfuric acid, saturated sodium bicarbonate, and water, dried over sodium sulfate, and concentrated to give the calculated weight of a colorless sirup. An ethyl acetate solution of the sirup was subjected to hydrogenolysis, first with palladium-on-carbon, and then with platinum catalysts. When the uptake of hydrogen was completed, the catalyst was removed by filtration and 1 ml. of cyclohexylamine was added to the filtrate. The resultant precipitate, which weighed 1.9 g., was purified by crystallization from water–acetone. A chromatographically pure sample (665 mg.) [R_f (*n*-butyl alcohol–acetic acid–water, 3:1:2), 0.26; R_f (methanol–ammonia–water, 6:1:3), 0.87; R_f (Methyl Cellosolve–pyridine–acetic acid–water, 8:4:1:1), 0.59; R_f (isobutyric acid–ammonia–water–66:10:20), 0.57] was obtained with $[\alpha]^{22}D$ −55.0 (*c* 0.43, 1 *N* HCl). Titration showed that the lactone was intact. In subsequent crops of crystals 10–20% of the free carboxylic acid was found to be present.

Anal. Calcd. for $C_{16}H_{33}N_2O_7P$ (396.4): C, 48.5; H, 8.4; N, 7.06; P, 7.81: Found: C, 47.23; H, 8.54; N, 7.14; P, 7.56.

2-*O*-Benzoyl-3-*O*-benzyl-D-erythronolactone was obtained in quantitative yield from 3-*O*-benzyl-D-erythronolactone. The esterification was carried out in pyridine at 24° using a 10% excess of benzoyl chloride. The product after three recrystallizations from ether–petroleum ether had m.p. 64–65°, $[\alpha]^{23}D$ −60.8° (*c* 1.4, ethyl acetate).

Anal. Calcd. for $C_{18}H_{16}O_5$ (312.2): C, 69.3; H, 5.16. Found: C, 68.80; H, 5.15.

2-*O*-Benzoyl-D-erythronolactone (VI).—Hydrogenolysis of an ethyl acetate solution of 2-*O*-benzoyl-3-*O*-benzyl-D-erythronolactone in the presence of freshly prepared palladium on carbon at 25° gave a quantitative yield of 2-*O*-benzoyl-D-erythronolactone, m.p. 124–126°. Two recrystallizations from ethyl acetate–petroleum ether gave material with m.p. 126–127°, $[\alpha]^{23}D$ −62.8° (*c* 2.0 ethyl acetate).

Anal. Calcd. for $C_{11}H_{10}O_5$ (222.2); C, 59.5; H, 4.54. Found: C, 59.60; H, 4.63. This compound could not be phosphorylated to any significant extent even at 70° for several hours.

Methyl D-Erythronate (XIII). A. From D-Erythronolactone.—To a solution of 6.7 g. of D-erythronolactone in 200 ml. of dry methyl alcohol was added sufficient barium methylate to make the solution basic to indicator paper. The continued addition of barium methylate was necessary. After 8 hr. the reaction was neutralized with carbon dioxide and filtered. The filtrate was concentrated to dryness at 40° *in vacuo* and the residue taken up in ethyl acetate from which solution 2.45 g. of crystals (m.p. 60–62°) were deposited. Further crystallizations from ethyl acetate gave a product which had m.p. 77°, $[\alpha]_D^{23}$ −20.2° (*c* 1.4, water).

Anal. Calcd. for $C_5H_{10}O_5$ (150.1); C, 40.0; H, 6.71. Found: C, 40.03; H, 6.78.

The mother liquors from the first crop of ester were shown by chromatography on Whatman no. 1 paper in *n*-butyl alcohol–ethyl alcohol–water (10:1:2) to contain a mixture of D-erythronolactone (R_f 0.36) and the methyl ester (R_f 0.46). The precipitate which formed during the reaction was probably barium D-erythronate, since chromatography of a sample after treatment with Dowex 50 (H^+) showed the presence of erythronic acid (R_f 0.08) and a small proportion of the lactone (R_f 0.36).

B. From D-Erythronic Acid.—To a solution of 5 g. of D-erythronolactone in 150 ml. of methyl alcohol was added 55 ml. of aqueous 0.88 *N* potassium hydroxide. The reaction mixture was left at 25° for 4 hr. and then 20 g. of dry Dowex 50 (H^+) was added. After shaking for 10 min., the resin was filtered off and the filtrate treated with an ethereal solution of diazomethane. A rapid gas evolution occurred and diazomethane addition was continued until a slight yellow color persisted in the reaction mixture. Removal of the solvents followed by crystallization from ether gave 2.4 g. of the methyl ester (m.p. 60–65°).

Examination of the mother liquors by chromatography on Whatman no. 1 using *n*-butyl alcohol–ethyl alcohol–water (10:1:2) showed that they contained some of each of the methyl ester, the lactone, and the free acid (or salt), and some fast moving spots. When examined by vapor phase chromatography on a column packed with Dow-Corning high vacuum silicone grease (20%) on firebrick at 210° it was apparent that small quantities of a number of other components were present, presumably produced by *O*-methylation of the acid, lactone, or ester. These components were not investigated further.

Methyl 2,3,*O*-Benzoyl-4-*O*-trityl-D-erythronate (XIV).—To a solution of 1.3 g. of methyl erythronate (XIII) in 7 ml. of dry pyridine at 25° was added 2.65 g. of trityl chloride. After 17 hr. the mixture was cooled to 0° and 2.2 ml. of benzoyl chloride was added. Chips of ice were added to the reaction mixture after 20 hr. and the product extracted into chloroform and washed in the usual fashion. After two recrystallizations from ether–petroleum ether and one from *n*-propyl alcohol, the product had m.p. 151–152°, $[\alpha]^{26}D$ −15.8° (*c* 1.0, chloroform).

Anal. Calcd. for $C_{38}H_{32}O_7$ (600.6); C, 75.88; H, 5.36; OCH_3, 5.12; Found: C, 75.81; H, 5.47; OCH_3, 5.46.

D-Erythronate 4-Phosphate Tricyclohexylammonium Salt (XV).—Methyl 2,3-di-*O*-benzoyl-4-*O*-trityl-D-erythronate (XIV) (2.5 g.) was dissolved with heating in 250 ml. of absolute ethyl alcohol. To the cooled solution was added 2.5 g. of freshly pre-

pared 10% palladium-on-carbon catalyst. Hydrogen uptake was complete in 10 hr. The catalyst was removed by filtration and the solvent removed *in vacuo* leaving a semicrystalline residue (2.5 g.).

A solution of 2.3 g. of the residue in 5 ml. of dry pyridine was treated with 1.28 g. of diphenyl phosphorochloridate. The reaction was kept 25° for 10 hr. and then worked up in the usual fashion to give 3.5 g. of a colorless sirup. The phenyl groups were removed by hydrogenation of the sirup in absolute ethanol solution over 0.7 g. of platinum oxide. When the uptake of hydrogen ceased (2.5 hr.) the catalyst was removed by filtration and 20 ml. of 1.02 *N* sodium hydroxide was added to the filtrate. The saponification was complete in 4 hr.; the ethyl alcohol was removed *in vacuo* at 40°; and the aqueous residue was extracted with ether to remove the triphenylmethane. Sodium ions were removed on Dowex 50 (H+) and the majority of the benzoic acid by filtration. The clear aqueous solution was adjusted to pH 9.0 with cyclohexylamine and then concentrated to a small volume. Upon addition of acetone crystallization occurred and after 8 hr. a small crop of crystals was collected and identified as cyclohexylammonium benzoate. Addition of more acetone gave 1.15 g. of a crude crystalline product which on being fractionally crystallized from water–acetone gave 0.7 g. of material which gave a positive periodate test and a negative test for inorganic phosphate. The chromatographically pure material [R_f (*n*-butyl alcohol–acetic acid–water, 3:1:2), 0.23; R_f (methanol–ammonia–water, 6:1:3), 0.87; R_f (Methyl Cellosolve–pyridine–acetic acid–water, 8:4:1:1), 0.3; R_f (isobutyric acid–ammonia–water, 66:10:20), 041] had $[\alpha]^{25}D$ −20.0° (*c* 1.0, water) and analyzed as a dihydrate.

Anal. Calcd. for $C_{22}H_{48}N_3O_8 2H_2O$ (549) C, 48.1; H, 9.49; N, 7.65; P, 5.66. Found: C, 48.5; H, 9.70 N, 7.17; P, 5.65.

The Reactions of 4-Phenyl-2-butanone and 5-Phenyl-2-pentanone with Phosphorus Pentachloride[1]

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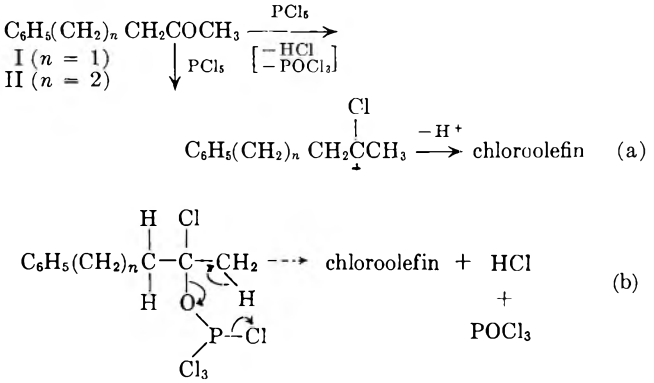
Received December 20, 1962

On treatment with phosphorus pentachloride at 25° in methylene chloride, 4-phenyl-2-butanone gave mixtures of 2-chloro-4-phenyl-1-butene (53%), *cis*-2-chloro-4-phenyl-2-butene (12%), and *trans*-2-chloro-4-phenyl-2-butene (35%). Similarly 5-phenyl-2-pentanone gave mixtures of 2-chloro-5-phenyl-1-pentene (43%), *cis*-2-chloro-5-phenyl-2-pentene (14%), and *trans*-2-chloro-5-phenyl-2-pentene (43%). These results indicate that chlorocarbonium ions are not involved in these reactions.

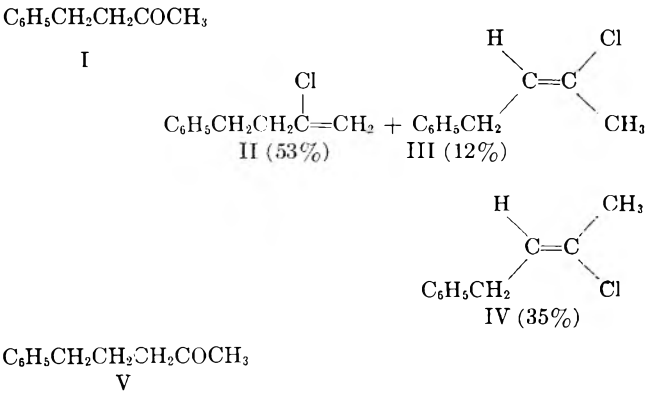
In a previous discussion of the mechanism of the reaction of ketones with phosphorus pentachloride two paths for the formation of chloroolefin were outlined: (a) loss of a proton from a chlorocarbonium ion; and (b) direct elimination of hydrogen chloride and phosphorus oxychloride from the addition product of the ketone and phosphorus pentachloride.[3] The work herein presented was done in order to shed light on the processes involved.



The two ketones chosen for study were 4-phenyl-2-butanone, I, and 5-phenyl-2-pentanone, V, since, if chlorocarbonium ions were involved in the reaction with phosphorus pentachloride (scheme a above), cyclization to 1-chloro-1-methylindane and 1-chloro-1-methyl-1,2,3,4-tetrahydronaphthalene would be expected.[4] Since no trace of either of these cyclic products (or of their dehydrochlorination products) was found, we believe that chlorocarbonium ions are not involved in these reactions with phosphorus pentachloride.

The main products, formed in well over 90% yield in each case, consisted of mixtures of chloroolefins (see Tables II and II). The large amounts of terminal olefins, 2-chloro-4-phenyl-1-butene, II (*ca.* 53% of total), and 2-chloro-5-phenyl-1-pentene, VI (*ca.* 43% of total), obtained provide another argument against the involvement of chlorocarbonium ions. If the latter were involved, much smaller amounts of terminal olefins would be expected in analogy with elimination of protons from ordinary carbonium ions.[5]

The remaining olefins consisted of *cis*-2-chloro-4-phenyl-2-butene, III (*ca.* 12%), and *trans*-2-chloro-4-phenyl-2-butene, IV (*ca.* 35%), in the case of I and of *cis*-2-chloro-5-phenyl-2-pentene, VIII (*ca.* 44%), and *trans*-2-chloro-5-phenyl-2-pentene, VIII (*ca.* 14%), in the case of V. These olefins were separated as described in Experimental.



(1) This work was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research.

(2) This work formed part of the M.S. thesis of W. N. K. presented to the Ohio State University in June, 1962.

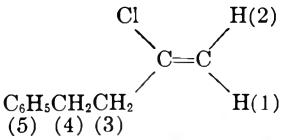
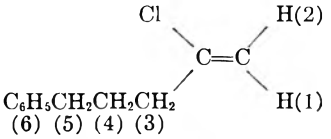
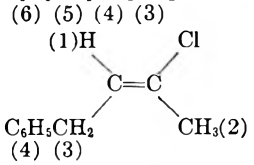
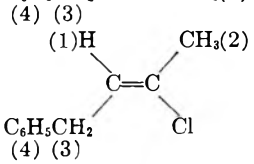
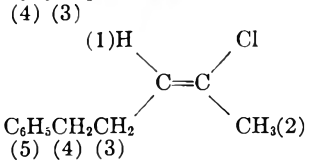
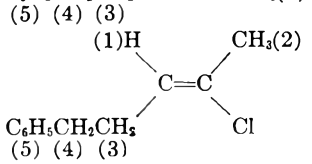
(3) M. S. Newman and L. L. Wood, Jr., *J. Am. Chem. Soc.*, **81**, 4300 (1959).

(4) Cyclization of ordinary carbonium ions to form five- and six-membered rings are known to occur readily, *e.g.*, D. Perlman, D. Davidson, and M. T. Bogart, *J. Org. Chem.*, **1**, 288 (1936).

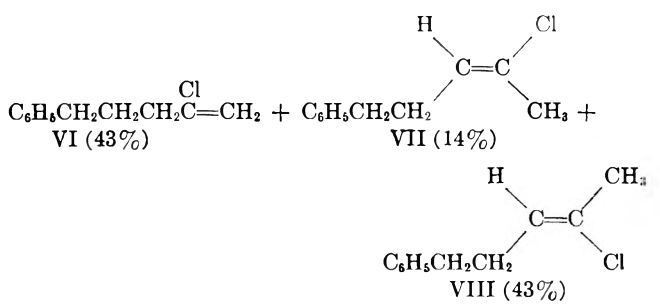
(5) See discussion in E. S. Gould, "Mechanism and Structure in Organic Chemistry," H. Holt and Co., New York, N. Y., 1959, pp. 475–577.

TABLE I

N.M.R. DATA FOR CHLOROOLEFINS

Compound	Chemical shifts, τ scale						Coupling constants, c.p.s.		
	δ_1	δ_2	δ_3	δ_4	δ_5	δ_6	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$
	4.95	5.03	7.3[a]	7.3[a]	2.89			−1.06	−1.20
	4.73	4.91	8.00[a]	8.00	8.00[a]	2.91		−1.41	−0.94
	4.41	7.91	6.54	2.88			−1.37	+7.20	+1.53
	4.27	7.92	6.71	2.90			−1.46	+7.95	+0.70
	4.44	7.99	7.4[a]	7.4[a]	2.90		−1.07	6.40	
	4.46	8.10	7.5[a]	7.5[a]	2.89		−1.50	7.20	

[a] Approximate region for δ.



The structures of these olefins were established by the methods of n.m.r. spectroscopy.[6] The types and relative numbers of hydrogens in each compound were obtained from the positions and relative integrated intensities of the different bands in each spectrum. Chemical shift and coupling parameters are listed in Table I.

The chemical shift for terminal olefinic hydrogens occurs in the region of 4.9 ± 0.2 p.p.m. Thus compounds II and IV are identified as terminal olefins. For the other compounds the vinyl hydrogen resonance pattern consisted in each case of a triplet of quartets. The large triplet splitting yields the value for $J_{CH_2,\,CH}$ and the smaller quartet structure arises form $J_{CH_3,\,CH}$. Bothnerby[7] has reported that for propene $J_{CH,\,CH_2\,cis} = -1.75$ c.p.s. while $J_{CH,\,CH_2\,trans} = -1.33$ c.p.s. By analogy to this result we assign the structure in which the vinyl hydrogen and methyl group are oriented *cis* to the isomer with the *larger negative coupling constant* in each pair of *cis, trans* isomers, see Table I.

Interestingly, we were unable to find any of the dichlorides which would result from replacement of the carbonyl oxygen with two chlorine atoms. This result may be contrasted with that for pinacolone in which case considerable dichloride is produced.[8]

Results described previously were those obtained when the ketones were treated with a small excess of phosphorus pentachloride in methylene chloride at about 25°. In a brief study of solvent effects it was found that in methylene chloride, V, reacted completely in three hours whereas, in nitroethane, after twenty-five hours only 43% had reacted and, in acetonitrile, only 32% had reacted after forty-eight hours. Similar results were obtained with I. In the reactions in methylene chloride the effect of added anhydrous aluminum chloride was studied briefly. When one equivalent of the 1:1 complex of phosphorus pentachloride–aluminum chloride[9] was used in methylene chloride solution, the ketones, I and V, were recovered essentially unchanged. The dark color of the reaction mixtures suggested that the $PCl_4^+AlCl_4^-$ complex dissociated and that the ketones then complexed with aluminum chloride. The latter complex is evidently stable toward phosphorus pentachloride.

(6) All spectra were determined with the Varian HR 60 n.m.r. spectrometer at 33°. The solvent was carbon tetrachloride and the internal standard was tetramethylsilane. Calibrations were accomplished by the methods of audio-side-band modulation.

(7) A. A. Bothnerby and C. Naar-Colin, *J. Am. Chem. Soc.*, **83**, 231 (1961).

(8) M. P. Ivitsky, *Bull. soc. chim.*, [4] **35**, 357 (1924). We have confirmed this in our laboratory.

(9) See footnote 6 in ref. 3. We are indebted to S. Shore and V. Petro for a gift of this complex, $PCl_4^+AlCl_4^-$.

Experimental[10]

Phenylbutyric Acid.—This acid was obtained in 95% yield by the modified Wolff–Kishner reduction.[11]

5-Phenyl-2-pentanone, V.—This compound was prepared by adding a solution of 0.98 mole of methyllithium in 400 ml. of ether to a solution of 72 g. of δ-phenylbutyric acid in 150 ml. of dry ether at gentle reflux. After an additional 1 hr. at reflux, V was isolated by a conventional procedure and distilled to give pure V, b.p. 89–91° at 2 mm.,[12] in 67% yield. The semicarbazone melted at 128–129°. In addition 23% of starting acid was recovered. The ketone was pure by v.p.c. analysis over Carbowax 4000 on firebrick.

4-Phenyl-2-butanone was purchased from the Aldrich Chemical Co., and found pure by similar v.p.c. analysis.

Reactions of Ketones with Phosphorus Pentachloride.—In a typical run a solution of 29.6 g. (0.2 mole) of 4-phenyl-2-butanone, I, in 100 ml. of methylene chloride was added to a suspension of 45.7 g. (0.22 mole) of phosphorus pentachloride in 200 ml. of dry methylene chloride in a three-necked 500-ml. flask fitted with a reflux condenser and stirrer. The reaction mixture was held at reflux for 30 hr., cooled, and treated with ice. The organic products were taken into benzene–ether and washed well with water, 10% sodium carbonate solution, water, and saturated sodium chloride solution. The organic layer was then filtered through a magnesium sulfate layer and the solvent removed by distillation. On vacuum distillation the residue yielded a mixture of II, III, and IV, boiling in the range 84–94° at 7 mm., in 93–98% yield. The entire distillate in the above run was analyzed.

Anal. Calcd. for $C_{10}H_{11}Cl$: C, 72.0; H, 6.7; Cl, 21.3. Found[13]: C, 72.1; H, 6.6; Cl, 21.3.

In a similar run using 5-phenyl-2-pentanone, V, chloroolefins were obtained in about 95% yield and boiled in the range 105–115° at 11 mm.

Anal. Calcd. for $C_{11}H_{13}Cl$: C, 73.1; H, 7.2; Cl, 19.8. Found[13]: C, 73.0; H, 7.3; Cl, 19.6.

TABLE II

(All runs were at 25° in methylene chloride unless otherwise indicated)

	Reactants (moles × 10)				Products,[a] %			
Expt.	Ketone	PCl_5	$AlCl_3$	Time, hr.	I	II	III	IV
1[a]	0.14	0.15	0	96	0	52	12	36
2[b]	2.0	2.2	0	40	0	54	12	34
3[c]	2.0	2.2	0	30	0	53	12	35
4	1.0	1.0	1.0	80	87	7	1	5
5	0.8	0.8	0.008	5	16	41	10	33
6	0.8	0.8	0.008	20	14	40	12	34
7[d]	0.2	0.2	0	48	69	15	1	15
8[e]	0.8	0.9	0	4	39	20	8	33
9[e]	0.8	0.9	0	20	32	23	6	39
10[f]	0.19	0.19	0.19	44	80	10	2	8

[a] The per cents listed are those determined by v.p.c. analysis of a representative sample of the reaction mixture. [b] Run at 0°. [c] Run at 40°. [d] Solvent was acetonitrile. [e] Solvent was nitroethane. [f] The complex, $PCl_4^+AlCl_4^-$, was used as supplied by S. Shore and Victor Petro.

(10) All melting points uncorrected.

(11) Compare Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(12) J. Levy and M. Sfiras, *Compt. rend.*, **184**, 1337 (1927), give b.p. 132–135° at 17 mm., m.p. of semicarbazone, 127–128°.

(13) Microanalyses by J. Galbraith Co., Knoxville, Tenn.

A number of other runs were carried out and the results are listed in Tables I and II. The analyses of the reaction mixtures were carried out as described.

Gas Chromatographic Analyses.—The chloroolefins obtained as described earlier were analyzed on a 6 ft. × 1/4 in. copper column packed with Carbowax 4000[14] on 42–60-mesh firebrick using a Model 500 unit manufactured by the F. and M. Scientific Corp. equipped with an integrating unit manufactured by Minneapolis-Honeywell Corp. Quantitative determination of the composition of runs was done by integration of the area under each peak. Addition of synthetic 1-methylindene,[15] b.p. 70–72° at 10 mm., prepared in 90% yield from 1-indanone and methyllithium, to the reaction mixture of phosphorus pentachloride and 4-phenyl-2-butanone proved that no methylindene was present. Similarly, addition of 1-methyl-3,4-dihydronaphthalene,[16] b.p. 90–93° at 8 mm., prepared in 80% yield from 1-tetralone and methylmagnesium bromide in ether, proved that none of this material was formed in the reactions of 5-phenyl-2-pentanone.

In the case of results reported in Table II three separate peaks were obtained in addition to a peak corresponding to starting ketone in certain runs. A representative sample was put through the column on a preparative scale and the fractions were identified by n.m.r. and infrared analyses.

In the case of the results reported in Table III only two peaks were obtained other than starting ketone. The larger of these peaks was analyzed by n.m.r. and found to consist of about equal amounts of VI and VIII. This result was confirmed by analysis on a 100-ft. squalene capillary column.[17]

TABLE III

(All runs were at 25° in methylene chloride unless otherwise noted)

	Reactants (moles × 10)				Products,[a] %		
Expt.	Ketone	PCl_5	$AlCl_3$	Time, hr.	V	VI and VIII	VII
1[b]	1.2	1.2	0	96	6	77	17
2	3.7	1.2	0	3	6	77	17
3	3.7	4.3	0	3	2	84	14
4	3.7	4.3	0	18	2	85	13
5[c]	1.6	1.7	0	34	0	85	15
6	1.2	1.2	1.2	15	100	0	0
7	6.0	6.0	6.0	80	100	0	0
8[d]	1.8	1.9	1.9	44	76	19	5
9[e]	1.2	1.3	0	48	68	25	7
10[f]	1.2	1.3	0	25	57	36	7

[a] The per cents listed are those determined by v.p.c. analysis of a representative sample of the reaction mixture. The column headed by VI and VIII represents the total per cent of VI and VIII. These were not separated on the v.p.c. column used. N.m.r. and infrared[15] studies on the mixture showed that this fraction was very nearly a 1:1 mixture of VI and VIII in each of the cases examined. It is assumed that all of these are 1:1 mixtures of VI and VIII. [b] Run at 0°. [c] Run at 40°. [d] The complex, $PCl_4^+AlCl_4^-$, was used as supplied by S. Shore and Victor Petro. [e] Solvent was acetonitrile. [f] Solvent was nitroethane.

(14) Carbowax 4000 is a polyethylene glycol of molecular weight about 4000, having a melting range of 50–55° and made by the Union Carbide Co.

(15) Our material agreed well with that reported by W. E. Parham, H. E. Reiff, and P. Swartzen, *J. Am. Chem. Soc.*, **78**, 1437 (1956).

(16) K. von Auwers, *Ber.*, **58**, 154 (1925) gives b.p. 238–239° at 760 mm.

(17) We thank J. Wiley for this analysis.

The Retropinacol Rearrangement of 17β-Hydroxyandrostanes

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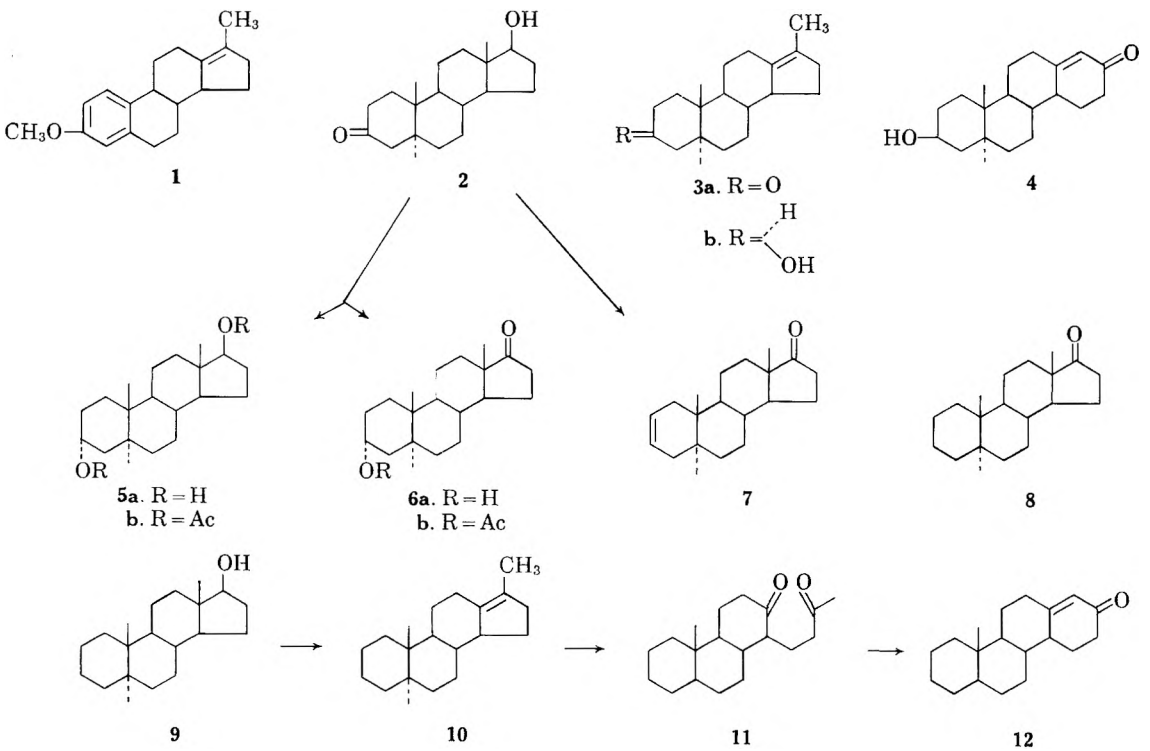
The reaction of 17β-hydroxyandrostan-3-one with boric acid at 380° leads to the formation of androst-2-en-17-one (**7**). Similar treatment of androstan-17β-ol produces 17-methyl-18-norandrost-13(17)-ene (**10**).

The successful conversion of estradiol 3-methyl ether to 17 - methyl - 3 - methoxy - 18 - norestra - 1,3,5(10),-13(17)-tetraene (**1**) by use of boric acid at elevated temperatures[1] prompted application of this reaction to the androstanes. The anticipated product, an analogous 17-methylandrost-13(17)-ene (such as **3**), could be used readily in the preparation of a variety of 18-nor steroids in direct analogy to the synthesis of 18,19-dinor steroids.[2] The sequence of reactions would proceed from olefin **3** through the derivative unsaturated ketone **4**. Although both compounds **3b** and **4** had been described previously by Miescher and Kagi,[3] the use of their synthesis was made unattractive by the relative difficulty in obtaining the starting material, androstane-3β,17α-diol. Since the inception of this project, preparation of 18-nor steroids has been accomplished by several methods.[4]

was 17β-hydroxyandrostan-3-one. When heated with boric acid to 380°, then distilled, and chromatographed, this steroid yielded a crystalline unsaturated ketone having the expected empirical formula, $C_{19}H_{28}O$. An alcohol, obtained by hydride reduction of this ketone, was treated with ozone or osmium tetroxide–periodic acid to oxidize the double bond. The resulting dicarbonyl compound failed to yield any of the desired unsaturated ketone **4** on treatment with base.

The results of these two experiments showed clearly that the parent olefin was not **3a**. It then became important to know whether the product had the rearranged skeleton and was simply a double bond isomer of the expected material **3a**, or whether the dehydration had proceeded without effecting rearrangement, perhaps to yield an androst-16-ene. That both hypotheses were incorrect was determined by



Ideally the starting androstane chosen for the boric acid rearrangement would contain a C-3 grouping that would be stable under the acidic dehydrating conditions employed. Such stability is lacking in ordinary derivatives of the alcohol or ketone functions (such as esters or ketals). The compound thus selected for the reaction

hydrogenation of the unknown keto olefin. The dihydro derivative was clearly different from androstan-3-one but proved to be identical to androstan-17-one (**8**) by spectral comparison with an authentic sample. Identification of the parent olefin was then assisted by inspection of its n.m.r. spectrum, which showed both angular methyl groups undisturbed and the existence of two vinyl hydrogens. The unknown unsaturated ketone was then proved to be androst-2-en-17-one (**7**) by virtue of the identity of its infrared spectrum with that of an authentic sample.[5]

(1) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961).

(2) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958).

(3) K. Miescher and H. Kagi, *Helv. Chim. Acta*, **32**, 761 (1949); **22**, 683 (1939).

(4) R. Anliker, M. Muller, M. Perelman, J. Wohlfahrt, and H. Heusser, *ibid.* **42**, 1071 (1959); L. Velluz, G. Amiand, R. Heymes, and B. Goffinet, *Compt. rend.*, **250**, 371 (1960); W. S. Johnson and K. V. Yorka, *Tetrahedron Letters*, **8**, 11 (1960); R. Pappo, U. S. Patent 3,080,360; D. K. Fukushima and H. L. Bradlow, *Abstr. Endocrine Soc.*, 7 (June, 1962).

(5) R. E. Marker, O. Kamm, D. M. Jones, and L. W. Mixon, *J. Am. Chem Soc.*, **59**, 1363 (1937).

Formation of olefin **7** is reasonably explained by postulating first the formation of a borate ester at C-17.[6] Internal oxidation–reduction might follow, the borate ester acting as the reducing agent. This type of reduction of carbonyl groups by alkyl borates at elevated temperatures[7] employs a mechanism analogous to that found in Meerwein–Ponndorf reduction and Oppenauer oxidation.[8] The equilibrium in the present case could be driven to the formation of a C-17 carbonyl not only by the inherently greater stability of a cyclopentanone carbonyl over a cyclohexanone carbonyl,[9] but also by virtue of a much more facile elimination of the C-3 hydroxyl group as compared to the C-17β hydroxyl. This is particularly true since the Meerwein–Ponndorf reduction is expected to give more of the axial isomer than is obtained by other methods of reduction, especially as the size of the reducing agent is increased.[10] The axial hydroxyl would then be removed readily by a facile *trans* diaxial elimination.[11]

Experimental validation of the proposed mechanism of the oxidation–reduction step was initiated by running the boric acid reaction at a lower temperature, conditions which would avoid the final elimination step. The product, acetylated to facilitate separation of components, was carefully chromatographed, allowing isolation of two crystalline compounds, androstane-3α,-17β-diol diacetate (**5b**) and androsterone acetate (**6b**). Although several other constituents could be detected by paper chromatography, none could be isolated and crystallized. This multiplicity of products under preparative conditions would be expected to simplify itself as the reactants approached 380°; the products would undergo transformation to the more stable keto ester and elimination of ester or hydroxyl groups would occur.

To show the absence of an inherent barrier to the retropinacol rearrangement of androstan-17β-ols generally, the reaction sequence was performed on androstan-17β-ol (**9**). Lacking the alternate course of reaction described for the 3-keto analog, this steroid provided the expected olefin **10** as the major product. Its identity was suggested by the n.m.r. spectrum which shows a methyl group attached to a double bond. Ozonolysis of the olefin led to a diketone (**11**) (no spectral indication of aldehyde) which cyclized readily to the unsaturated ketone **12**. The n.m.r. spectrum of the diketone showed an acetyl methyl group and the ultraviolet spectrum of the unsaturated ketone showed the expected cyclohexenone absorption. These data preclude the possibility of the double bond in **10** being in any position besides $C_{13(17)}$ and thus established concretely the structure of compounds **10**–**12**.

Experimental[12,13]

Boric Acid Treatment of 17β-Hydroxyandrostan-3-one (2). A. At 310–380°.—The hydroxy ketone **2** (40 g.) and boric acid (10 g.) were ground together and heated at 320° for 1 hr. under nitrogen. The temperature was lowered to 220° and the pressure carefully reduced to 22 mm. at a slow rate to control foaming. The product was then distilled between 310° and 380° at 20 mm. The distillate, dissolved in ether, was washed with aqueous sodium bicarbonate and dried. Removal of solvent and distillation of the products afforded 14.77 g. of an oil of which 5.1 g. was chromatographed on 150 g. of silica. Elution of the column with 5% ethyl acetate in benzene yielded 2.31 g. of crystalline material which was recrystallized from aqueous ethanol to yield 1.75 g. of product, m.p. 80–86°. An infrared comparison of this material to authentic androst-2-en-17-one (**7**)[5] showed a very close similarity. The n.m.r. spectrum, $\Delta\nu$ 334 (C_2–C_3) and 319 (C_3–C_4) c.p.s., indicated a minor impurity to be androst-3-en-17-one.

Another sample was chromatographed and recrystallized twice from methanol, yielding plates, m.p. 100–108°, identical by mixture melting point and infrared absorption to an authentic sample of androst-2-en-17-one (**7**).

Hydrogenation[14] of 0.18 g. of the olefin **7**, m.p. 80–86°, in 30 ml. of ethanol containing 30 mg. of 5% palladium on charcoal, was complete in 1 hr. The product was purified by crystallization from methanol; 0.090 g., m.p. 121–123°, and 0.070 g., m.p. 117–121°, both crops being identical in infrared characteristics to an authentic sample of androstan-17-one (**8**).

B. At 250°.—17β-Hydroxyandrostan-3-one, 20 g., was ground with 5 g. of boric acid and heated under nitrogen in a short-necked distilling apparatus. Application of a metal bath, preheated to 185°, caused the mixture to melt and bubble vigorously as water was evolved. In 20 min. the bath was at 250°; bubbling was very slow; and the mixture had become a clear, heavy glass. Heating was discontinued. The main bulk of the glass, excepting samples removed at time intervals, was treated with repeated changes of water and benzene on the steam bath until the glassy residue had dissolved. The total benzene solution, 250 ml., was filtered and distilled to dryness, leaving 12 g. of clear glass as residue.

In order to assist fractionation, 11.5 g. of the residue was acetylated during 20 hr. in 50 ml. of pyridine and 50 ml. of acetic anhydride. The residue from the usual work-up with water, ether, dilute acid, and sodium bicarbonate was also a glass, 11.65 g.

The acetylated mixture, 2.71 g., was chromatographed on silica. Three poorly resolved bands were eluted in very close succession by 2% ethyl acetate in benzene. A fraction from the first peak, recrystallized three times from dilute acetone, melted at 157–165°, and was shown to be androstane-3α,17β-diol diacetate (**5b**), m.p. 163–166° (sweating at 160°), through similar R_f values in paper chromatography, identical infrared absorption spectra, and undepressed mixture melting point.

Repetition of the chromatogram on silica using a slower elution scheme gave crystalline fractions with 0.5% and 1% ethyl acetate in benzene, as well as an oily material upon elution with 5% ethyl acetate in benzene. The first peak consisted mainly of androstane-3α,17β-diol diacetate. The second peak was mainly androstanolone acetate (acetate of **2**) although the leading edge of the band contained a keto acetate, m.p. 161–166°, shown by infrared to be androsterone acetate (**6b**). A sample on a mixture with authentic androsterone acetate, m.p. 167.5–169.0°, melted at 163–168°. Paper chromatography showed the third band to be a mixture of about six compounds, a main component being perhaps a diketone. This band was not examined further.

Androst-2-en-17β-ol.—The olefin mixture (5.7 g.), obtained directly from the 380° boric acid treatment, in 100 ml. of ether was added to a stirred solution of 2.1 g. of lithium aluminum hydride in 180 ml. of ether. After the mixture was heated at reflux for 1 hr., the excess hydride was decomposed by addition of ethyl acetate followed by addition of dilute hydrochloric acid. The ether layer was separated, washed with water and with aqueous sodium bicarbonate, was dried, and concentrated. The resulting residue, 5.4 g. of semicrystalline material, was chromatographed on 300 g. of silica. Elution with benzene afforded 2.02 g. of crystalline material, which on sublimation yielded pure androst-2-en-17β-ol, m.p. 167–168°, having the same infrared spectrum as an authentic sample.[5]

(6) G. L. O'Connor and H. R. Nace, *J. Am. Chem. Soc.* **77**, 1578 (1955).

(7) H. G. Kuivila, S. C. Slack, and P. K. Siiteri, *ibid.*, **73**, 123 (1951).

(8) A. L. Wilds, *Org. Reactions*, **2**, 178 (1944); C. Djerassi, *ibid.*, **6**, 207 (1951).

(9) H. C. Brown, *J. Chem. Soc.*, 1248 (1956); *J. Org. Chem.*, **22**, 439 (1957). See also R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, **80**, 1428 (1958).

(10) H. R. Nace and G. L. O'Connor, *ibid.*, **73**, 5824 (1951).

(11) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(12) The authors wish to acknowledge the assistance of E. G. Daskalakis and his staff with chromatography and R. T. Dillon and his staff in providing the analyses and spectra reported.

(13) Infrared spectra were determined in chloroform. Rotations were recorded at 1% in chloroform. The n.m.r. spectra were determined in deuteriochloroform by use of an A-60 spectrometer, Varian Associates, Inc., at 60 Mc., using tetramethylsilane as an internal standard ($\Delta\nu$ 0 c.p.s.). The petroleum ether used boils at 63–68°.

(14) We wish to thank W. Selby for conducting the hydrogenation.

This material was cleaved with ozone in methylene chloride at −70° (same procedure as given later) or with osmium tetroxide-catalyzed hydroxylation followed by periodate cleavage (see ref. 1 for procedure), yielding in each instance the same noncrystalline product. Treatment of this material with refluxing methanolic potassium hydroxide failed to produce a pure material. None of the fractions from chromatographic analysis showed appreciable absorption at 240 mμ, indicating the absence of a conjugated cyclohexenone system.

18-Nor-17-methylandrost-13(17)-ene (10).—Androstan-17β-ol (9) was prepared by heating a stirred solution of 40 g. of 17β-hydroxyandrostan-3-one (2) in 0.4 l. of diethylene glycol containing 40 g. of potassium hydroxide and 50 ml. of 85% aqueous hydrazine in a slow stream of nitrogen at 140° for 30 min. and then at 190° for an additional hour. Dilution of the cooled solution with water, followed by filtration of the resulting crystalline mass and recrystallization of the product from methylene chloride–methanol, yielded 38.7 g. of material, m.p. 171–172°, identical in infrared absorption to an authentic sample.

Androstan-17β-ol (38 g.) and boric acid (20 g.) were mixed thoroughly and heated at 200° for 30 min. The mixture was then distilled at 400° and 10 mm. The distillate (18 g.) was dissolved in benzene and washed with aqueous potassium bicarbonate. A portion (3.1 g.) was purified from polar contaminants by chromatography over 150 g. of silica. Elution with petroleum ether gave 2.85 g. of a mobile oil, 18-nor-17-methyl-androst-13-(17)-ene (10); $[\alpha]_D$ −15°; $\Delta\nu$ 42 (C_{19}–CH_3), 95 (C=CCH_3) c.p.s.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.08; H, 11.72.

The distillation residue was dissolved in hot benzene and dilute aqueous potassium hydroxide. The washed and dried benzene solution was concentrated, affording 13 g. of semicrystalline material. Chromatography of 4.0 g. of this material on 50 g. of silica yielded 1.72 g. of the desired olefin **10**. Later eluates produced 1.95 g. of crystalline starting material (**9**), identified by melting point and infrared spectrum.

13,17-Secoandrostane-13,17-dione (11).—A solution of 10 g. of the olefin **10** in 100 ml. of methylene chloride and 2 ml. of pyridine were treated at −70° with a stream of oxygen containing ozone until the solution turned blue. Zinc dust, 10 g., and 10 ml. of acetic acid in 10 ml. of methylene chloride were added and the mixture was stirred in an ice bath for 30 min. The mixture was filtered and the filtrate was washed with water and aqueous potassium bicarbonate. Concentration of the dried extract afforded 12.5 g. of mobile oil, 4.0 g. of which was chromatographed on 150 g. of silica. The major portion was eluted with 2% ethyl acetate in benzene, yielding 1.98 g. of 13,17-secoandrostane-13,17-dione (11); $[\alpha]_D$ +3°; λ_{max} 5.82 μ; $\Delta\nu$ 44 (C_{10}–CH_3), 127 (–$COCH_3$) c.p.s. Despite a repeated chromatographic fractionation of this material and the use of a variety of solvents on the components, no crystalline material was obtained.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.73; H, 10.29.

18-Nor-D-homoandrost-13(17a)-en-17-one (12).—A solution of 0.80 g. of the diketone 11 (purified by chromatography) in 30 ml. of methanol containing 5 ml. of 15% aqueous potassium hydroxide was heated at reflux for 1 hr. The cooled solution was diluted with water, and the resulting precipitate was separated by filtration. The product was washed with water, air-dried, and dissolved in petroleum ether. The solution, after treatment with charcoal, was concentrated, yielding 0.30 g. of the pure unsaturated ketone **12**, m.p. 158–160°; $[\alpha]_D$ −39°; λ_{max} 5.98, 6.15 μ; λ_{max} 240 (16,800) mμ.

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.62; H, 10.44.

Synthesis of 3-Methoxy-17-acetyl-18-norestra-1,3,5(10),16-tetraene

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Conversion of the D-homo unsaturated ketone **5** to the title compound has been accomplished by a sequence of five reactions: reduction (to **2b**), Grignard addition (**11**), dehydration (**13**), ozonolysis (**18**), and cyclization (**20**). Formation of the dienedione **10**, a by-product of the reduction step, is also discussed.

The facile production of the unsaturated ketone **5** from estradiol 3-methyl ether in three steps[1] allowed continuation of a projected synthesis of 18-norestrone and 18,19-dinor steroids.[2] The potential physiological interest of such materials was clear from the enhanced activities of several 19-nor steroids as compared to their methylated analogs.[3]

Proper introduction of a single asymmetric center into the D-homo ketone **5** is necessary to produce a molecule having the desired, naturally occurring *trans–anti–trans* ring junctures of rings B, C, and D. None of the remaining reactions in the planned sequence would labilize these bridgehead carbon atoms; thus the stereochemistry of these centers would remain unchanged. Ample literature precedent exists for the reduction of systems such as $\Delta^{1(9)}$-decalone-2 to *trans*-2-decalone by means of metal–ammonia systems.[4] Application of this reaction to the planar molecule **5** was complicated only by the possible concommitant reduction of the A-ring. In practice this problem was circumvented by use of lithium–ammonia in the absence of alcohol[5] which allowed conversion in good yield of the unsaturated ketone **5** to the saturated ketone **2b**.

An alternate method was to use a metal–ammonia reaction in the presence of alcohol, effecting reduction of both the A-ring and the unsaturated ketone moieties to produce the enol ether **4a**. With this method of preparation the C-17 hydroxyl is expected to be in the more stable α-configuration.[4] Whereas Oppenauer oxidation of this compound afforded the corresponding C-17 ketone **4b**, pyridine–chromium trioxide caused oxidation of both the A-ring and the alcohol producing the ketone **2b**.

The enol ether **4a** was readily transformed into the unsaturated ketone **1a** and, in turn, into the diketone **1b**. If purification of the enol ether **4a** was omitted and instead the entire metal–ammonia reduction product was hydrolyzed, a new component was isolable. In addition to the major product, the unsaturated ketone **1a**, there was obtained 7% of a compound having an ultraviolet maximum at 242 mμ (ε 35,600) with twice the intensity of a steroidal cyclohexenone. All additional information about this material confirmed the fact that it had two unsaturated ketone groups. Only

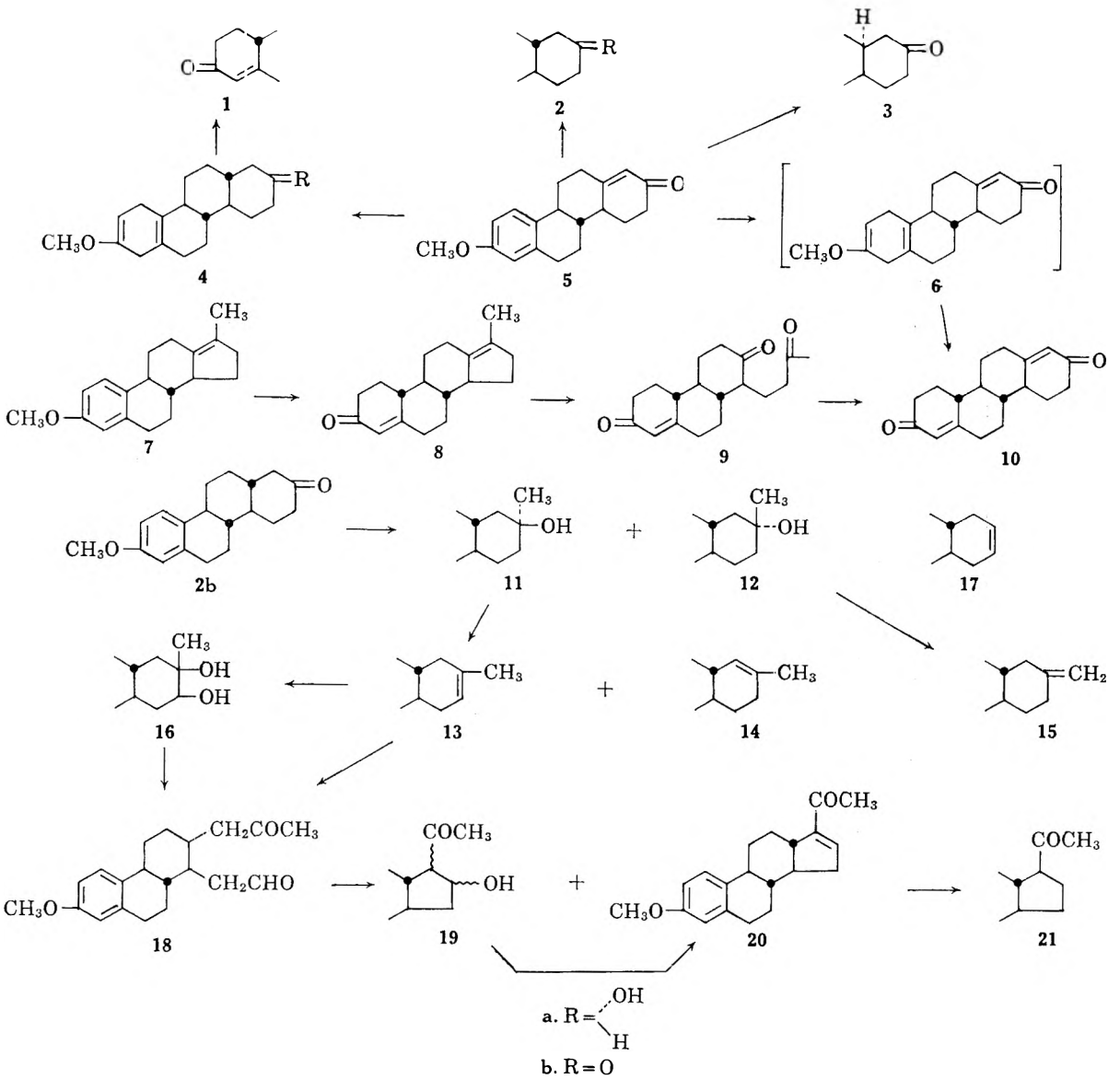
(1) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961).

(2) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958).

(3) See, *e.g.*, H. P. Schedl, C. Delea, and F. C. Bartter, *J. Clin. Endocrinol. Metab.*, **19**, 921 (1959).

(4) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954); E. E. van Tamelen and W. C. Proost, Jr., *J. Am. Chem. Soc.*, **76**, 3632 (1954).

(5) F. Sondheimer, R. Yashin, G. Rosenkranz, and C. Djerassi, *ibid.*, **74**, 2696 (1952); A. Bowers, H. J. Ringold, and E. Denot, *ibid.*, **80**, 6115 (1958).



one logical placement of these groups is possible, that shown in structure **10**.[6] An alternate synthesis of this material was accomplished from the readily available estratetraene **7** by reduction with lithium–ammonia, acid hydrolysis to the unsaturated ketone **8**, ozonolysis to the triketone **9**, and base-catalyzed cyclization to the same dienedione **10** previously obtained. The triketone **9** could also be produced by periodate cleavage of the corresponding 13,17 glycol.

Unsaturated ketones are known to be reduced readily with metal–ammonia systems, as is, for example, shown in the production of **2b** in this synthesis. Therefore, the formation of the dienedione **10** must be rationalized by hypothesizing removal of an intermediate such as **6** during the reaction, presumably by precipitation of an enolate salt.

Hydrogenation of the unsaturated ketone **5** over palladium catalyst gave a new saturated ketone (**3**) having a 13α-hydrogen. This compound was clearly different from **2b**. Optical rotatory dispersion measurements confirmed the assigned configurations at C-13 for both **2b** and **3**.[7]

Transformation of the cyclohexanone **2b** to an acetylcyclopentene derivative (such as **20**) followed the general methods outlined by Woodward[8] and by Stork.[9] Methylmagnesium bromide when added to the ketone **2b** produced a mixture of two methyl hydroxy compounds, **11** and **12**, partially separable by chromatography. The preponderant isomer (**11**) was eluted first, and on this basis its hydroxyl group could be assigned the axial configuration.[10] The dehydration products from each isomer provided more conclusive evidence to this point. Treatment of **11** with thionyl chloride in pyridine provided a mixture of two endocyclic olefins. The first olefin (**14**), $[\alpha]D$ +80°, showed a single peak in its n.m.r. spectrum at 313 c.p.s. ($\Delta\nu$ from the tetramethylsilane signal at 60 Mc.), reasonably ascribed only to the 17a-proton on a 17(17a) double bond. The second compound, $[\alpha]D$ −30°, exhibited a doublet at 321 and 326 c.p.s., clearly the C-16 isomer **13**. The proportion of these two olefins formed by this reaction could be estimated by integration of the n.m.r. spectrum of the mixture in the 300–330-c.p.s. region or from the rotation ($[\alpha]D$ +15°), showing approximately 40% of the olefin **14** and 60% of the olefin **13** had been formed.

(6) This compound has been prepared by total synthesis: A. J. Birch and H. Smith, *J. Chem. Soc.*, 1882 (1951).

(7) We wish to thank C. Djerassi for these measurements.

(8) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(9) G. Stork, H. J. E. Loewenthal, and P. C. Mukharji, *ibid.*, **78**, 501 (1956).

(10) S. Winstein and N. J. Holness, *ibid.*, **77**, 5564 (1955).

The second Grignard adduct (12) on dehydration gave preponderantly the exocyclic olefin **15**, easily identified from the n.m.r. signal at 278 c.p.s. (two protons). This is consistent with an equatorial hydroxyl group in the starting material, the favored *trans*-diaxial elimination being impossible except to the exocyclic position.[11]

In the direct reaction path, the mixture of Grignard adducts was dehydrated directly and the desired olefin **13** separated by crystallization. Additional olefin **13** was obtained by acid-catalyzed equilibration of the mixture to one ($[\alpha]_D$ −14°) containing approximately 70% of the desired olefin **13**.

Obtained as a by-product in the dehydration was a sulfite, transformed with perchloric–acetic acid to an acetate, and by pyrolysis to a new olefin. Both the sulfite and the acetate could be produced directly from the alcohol **2a**, showing the initial source of the sulfite to be from the alcohol **2a**, presumably a contaminant in ketone **2b** prior to the reaction with methyl magnesium bromide. The n.m.r. spectra of the crude olefin, besides showing the absence of the D-ring methyl group, also indicated that two isomers were present in a 2:1 ratio. The major component (**17**) was separable on recrystallization. The relative proportion of dehydration products of the secondary alcohol **2a** corresponds to that observed in the dehydration of C-3 hydroxyl groups of A/B *trans* steroids.[12]

Conversion of the olefin **13** to the ketoaldehyde **18** was effected either by ozonolysis or by hydroxylation with osmium tetroxide and subsequent cleavage with periodic acid. Cyclization of the ketoaldehyde **18** with aqueous potassium hydroxide[13] provided a mixture of unsaturated ketone **20** and the hydroxy ketone **19**. Further treatment of the latter with base afforded additional unsaturated ketone **20**.

In order to correlate the final products of this synthetic sequence to racemic compounds prepared by Nelson and Garland,[14] ketone **20** was hydrogenated to yield the saturated derivative **21**. Comparison of the infrared spectra showed the *d*- and *dl*-compounds to have identical structures.[15] Final proof of the stereochemistry of this series of compounds was arrived at through their eventual conversion to 18-norestrone methyl ether.[2]

Experimental[16,17]

3-Methoxy-18-nor-D-homoestra-1,3,5(10)-trien-17-one (2b). A. By Direct Lithium–Ammonia Reduction of the Unsaturated Ketone 5.—A solution of 10.0 g. of the unsaturated ketone **5** in 50 ml. of dioxane and 50 ml. of ether was added over a 3-min. period to a solution of 0.5 l. of ammonia containing 1 g. of lithium wire. The solution was stirred for an additional 2 min. and 30 g. of ammonium chloride was added. The ammonia was distilled, and the remaining mixture was diluted with benzene and then with water. The organic layer was washed three times with water, dried, and concentrated *in vacuo*. The residue was recrystallized from acetone–petroleum ether yielding 4.0 g. of the pure saturated ketone **2b**, m.p. 190–192°; $[\alpha]_D$ +31°; λ_{max} 5.82 μ.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.99; H, 8.65.

A second crop amounted to 3.8 g., m.p. 185–190°. The mother liquors showed in the infrared weak absorption at 5.99 μ indicating the reduction was not complete. That no significant reduction of the aromatic A-ring had occurred was seen by acid hydrolysis of the product; no increase was seen in the ultraviolet absorption in the 230–240-mμ region.

B. By Oxidation of the Dihydro Alcohol 4a.—A solution of 5.0 g. of the dihydro alcohol **4a** in 50 ml. of pyridine was added to 8.0 g. of chromium trioxide slurried in 80 ml. of pyridine. The solution was allowed to stand at room temperature overnight and was then diluted with water and extracted with ether. The extract was washed with water, dried, and concentrated to dryness. The residue was recrystallized from acetone–cyclohexane, yielding 3.65 g. of the crystalline ketone **2b**, m.p. 190–192°, identical in the infrared to an authentic sample.

C. By Oxidation of the Dihydro Ketone 4b.—The dihydro alcohol **4a** (1.8 g.) in 20 ml. of pyridine was added to a slurry of 2 g. of chromium trioxide in 20 ml. of pyridine. After 18 hr. the solution was diluted with water and extracted with ether. The ether extract was washed with water, dried, and concentrated to dryness. Chromatography of the residue on 35 g. of silica afforded the pure ketone **2b**, 0.65 g., m.p. 188–190°, identical with the previous product.

3-Methoxy-18-nor-D-homoestra-2,5(10)-dien-17-α-ol (4a). A. Vigorous Birch Reduction of the Unsaturated Ketone 5.—A solution of 46.7 g. of the unsaturated ketone **5** in 700 ml. of tetrahydrofuran was added over a 60-min. period to 1.6 l. of ammonia and 700 ml. of *t*-butyl alcohol in a round-bottomed flask equipped with a Dry Ice condenser. Lithium wire was added in six 5-g. portions over this same period. Stirring was continued for 4 hr. at which time the solution had decolorized. The ammonia was distilled, water was cautiously added, and the solution was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated to dryness. The product, obtained from a chilled acetone solution, amounted to 28.6 g., m.p. 180–182°, and 9.9 g., m.p. 174–178°. Recrystallization of a portion of the first crop from acetone gave the analytically pure alcohol **4a**, m.p. 180–182°; λ_{max} 2.88, 5.83, 5.98 μ; no maxima in the ultraviolet.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.18; H, 9.64.

The corresponding 17-ketone (**4b**) was isolable in small amounts from a few runs by virtue of its lesser solubility in pyridine.

B. Birch Reduction of the Saturated Alcohol 2a.—The alcohol **2a** (1.3 g.) in 50 ml. of tetrahydrofuran was added to 200 ml. of ammonia and 50 ml. of *t*-butyl alcohol. To this solution was added 2.0 g. of lithium wire in four portions over a 30-min. period. The stirring was continued for 4 hr. at which time the color had discharged, the ammonia was distilled, and water was carefully added. A benzene extract was washed with water, dried, and concentrated to dryness, giving 0.52 g. of the alcohol **4a**, identical to that obtained previously.

18,19-Dinor-D-homo-17α-hydroxyandrost-4-en-3-one (1a).—The dihydroaromatic derivative **4a**, 0.40 g., was stirred in 25 ml. of methanol containing 5 ml. of water and 1.5 ml. of concentrated hydrochloric acid for 18 hr. The solution was diluted with water and filtered, yielding 0.34 g. of crystals. Recrystallization from acetone–petroleum ether gave the analytical sample, m.p. 189–191°; λ_{max} 2.92, 6.05, 6.21 μ; λ_{max} 240 mμ (ε 17,100).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.67; H, 9.35.

18,19-Dinor-D-homoandrost-4-ene-3,17-dione (1b).—Oxidation of the alcohol **1a** was effected by dissolving 1.0 g. in 40 ml. of pyridine containing 1.0 g. of chromium trioxide. After 90 min. the solution was diluted with water and extracted with ether. The extract was washed, dried, and concentrated to dryness. The residue was recrystallized twice from acetone–petroleum ether, yielding 0.30 g. of the pure diketone **1b**, m.p. 179–182°; $[\alpha]_D$ −6°; λ_{max} 5.82, 5.99, 6.15 μ; λ_{max} 240 mμ (ε 16,600).

(11) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(12) J. Fajkos and F. Sorm, *Collection Czech. Chem. Commun.*, **24**, 3115 (1959).

(13) G. I. Poos, W. F. Johns, and L. H. Sarett, *J. Am. Chem. Soc.*, **77**, 1026 (1955).

(14) N. A. Nelson and R. B. Garland, *ibid.*, **79**, 6313 (1957).

(15) We wish to thank Dr. Nelson for affording us this comparison.

(16) We wish to thank E. G. Daskalakis and staff for the chromatography and R. T. Dillon for the analyses and spectra described here. We wish also to thank W. M. Selby and staff for the hydrogenations reported.

(17) Infrared spectra were determined in chloroform, ultraviolet spectra in methanol, and rotations in chloroform (1%). Petroleum ether refers to the fraction with b.p. 63–68°. Melting points are uncorrected. N.m.r. spectra were determined in deuteriochloroform on a Model A-60 spectrometer, Varian Associates, Inc., at 60 Mc., using tetramethylsilane as an internal standard.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.06; H, 8.93.

1β-(3-Ketobutyl)-1,2,3,4,4a,4aα,4bβ,5,6,7,9,10,10aβ-dodecahydrophenanthren-2,7-dione (9). A. From the 13,17-Glycol of the Tetraene 7.—The 13,17-glycol of the tetraene 7[1] (1.00 g.) in 50 ml. of tetrahydrofuran was added to a solution of 200 ml. of ammonia and 50 ml. of *t*-butyl alcohol. Lithium wire (2 g.) was added in six portions over a 30-min. period. After 3 hr. the solution was decolorized by addition of methanol, the ammonia was distilled, water, was added, and a benzene extraction was made. The washed and dried extract was concentrated, and the semicrystalline residue, 1.15 g., was dissolved in 40 ml. of methanol, 8 ml. of water, and 4 ml. of concentrated hydrochloric acid. After 1 hr. at room temperature the solution was treated with excess potassium bicarbonate, diluted with water, and extracted with 1:1 benzene–ethyl acetate. The extract was concentrated to dryness, and the resulting product (1.1 g.) was chromatographed on 30 g. of Florisil. Elution with 30% ethyl acetate in benzene afforded 0.86 g. of material, recrystallized from acetone–petroleum ether to yield 0.53 g. of the pure 13ξ,17ξ-dihydroxy-17-methyl-18,19-dinorandrost-4-en-3-one, m.p. 158–159°; $[\alpha]_D$ +58°; λ_{max}^{KBr} 2.87, 2.99, 5.97, 6.18 μ; λ_{max} 240 mμ (ε 17,800).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.49; H, 9.03. Found: C, 74.24; H, 8.70.

The previous glycol (0.15 g.) in 10 ml. of methanol and 0.4 ml. of pyridine was treated with a solution of 0.15 g. of periodic acid dihydrate in 1.5 ml. of water at room temperature for 1 hr. The solution was diluted with water and the product was isolated by benzene extraction. The residue was recrystallized from acetone–petroleum ether to yield 0.11 g. of the triketone 9, m.p. 104–105°; λ_{max} 5.83, 6.00 μ; λ_{max} 238 mμ (ε 18,000).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.48.

B. From the Unsaturated Ketone 8.—A solution of 30 g. of the tetraene 7 in 300 ml. of tetrahydrofuran, 250 ml. of *t*-butyl alcohol, and 600 ml. of ammonia was treated with 12 g. of lithium wire in six portions over a 30-min. period. After 4 hr. the solution was decolorized with methanol, the ammonia was distilled, water was added, and a benzene extraction was made. The extract was washed with water, dried, and concentrated yielding 32 g. of a mobile oil. This oil was dissolved in 600 ml. of ethanol containing 30 ml. of hydrochloric acid. The solution was heated at reflux for 10 min. and then allowed to stand overnight at room temperature. After 18 hr. the solution was diluted with water and a poorly crystalline mixture was separated by filtration. This precipitate was dissolved in methylene chloride, and the resulting solution was washed with aqueous potassium bicarbonate, dried, and concentrated to dryness. Chromatography of the product (31 g.) on 1.7 kg. of silica gel yielded 24.2 g. of the crude unsaturated ketone by elution with 10% ethyl acetate in benzene. Recrystallization from petroleum ether gave 6.8 g. of pure **17-methyl-18,19-dinorandrost-4,13(17)-dien-3-one (8)**, m.p. 115–118°; $[\alpha]_D$ +51.5°; λ_{max} 5.97, 6.14 μ; λ_{max} 238 mμ (ε 17,000).

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.37; H, 9.31.

Ozonolysis of 2.9 g. of the olefin 8 in 250 ml. of methylene chloride and 1 ml. of pyridine was effected by passing a stream of oxygen containing 1.1 equivalents of ozone through the solution cooled to −70°. Zinc dust (5 g.) and 5 ml. of acetic acid in 5 ml. of methylene chloride were added and the mixture was stirred in an ice bath for 40 min. The solution was filtered and the filtrate was washed with aqueous potassium bicarbonate. The organic solvent was then removed and the resulting product crystallized from ether, yielding 0.70 g. of the triketone 9, m.p. 104–105°. Chromatography of the mother liquors on 110 g. of silica gel yielded an additional 0.50 g. of the pure triketone 9 and 0.30 g. of starting material 8.

1,2,3,5,6,6aα,6bβ,7,8,9,11,12,12aβ,12bα-Tetradecahydrochrysen-3,9-dione (10). A. From the Triketone 9.—A solution of 0.20 g. of the triketone 9 in 20 ml. of methanol and 2 ml. of 10% aqueous potassium hydroxide was heated at reflux. A precipitate formed quickly; after 10 min. the solution was cooled and filtered. The crystalline product was washed with water and air dried, yielding 0.17 g. of the dienedione 10, m.p. 235–240°; λ_{max} 6.00, 6.17 μ; λ_{max} 242 mμ (ε 35,600).[6]

B. From the Hydrolysis of the Total Reduction Product of Ketone 5.[18]—A total of 42 g. of the crude alcohol 4a, as obtained directly from the lithium–ammonia reduction described for the preparation of pure 4a, was hydrolyzed with hydrochloric acid in methanol as described before. The product consisted mainly of the unsaturated ketone 1a. Fractional crystallization of the mother liquors from acetone–petroleum ether yielded 3.9 g. of dienedione 10, m.p. 238–240°, identical to the product preceding by comparison of the infrared spectra.

3-Methoxy-18-nor-D-homoestra-2,5(10)-dien-17-one (4b).—A solution of 1.22 g. of the alcohol 4a in 7 ml. of redistilled cyclohexanone and 60 ml. of toluene was dried by distillation of 10 ml. of solvent. To this solution was added 1.6 g. of aluminum isopropoxide dissolved in 10 ml. of toluene over a 10-min. period. The reaction mixture was heated at reflux with stirring in a nitrogen atmosphere for a total of 35 min. The solution was cooled to 60° and 110 ml. of a saturated aqueous solution of Rochelle salts was added over a 10-min. period. The solution was then steam distilled rapidly for 90 min. A chloroform extract was made, washed with water, dried, and concentrated to dryness. Recrystallization of the residue from acetone–petroleum ether yielded 0.61 g. of product, m.p. 170–176°. Further recrystallization from acetone provided the pure ketone 4b, m.p. 193–195°; $[\alpha]_D$ +83°; λ_{max} 5.81, 5.97 μ; no selective ultraviolet absorption.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.51; H, 8.96.

3-Methoxy-18-nor-D-homoestra-1,3,5(10)-trien-17α-ol (2a).—The saturated ketone 2b (1.8 g.) in 30 ml. of tetrahydrofuran was added to a stirred slurry of 0.5 g. of lithium aluminum hydride in 40 ml. of ether. After 30 min. at room temperature the solution was carefully treated with water followed by aqueous hydrochloric acid. A benzene extract was made and washed twice with water. The dried solution was concentrated, yielding 1.8 g. of crystalline residue. Recrystallization from acetone–petroleum ether afforded 1.35 g. of material, m.p. 159–162°. The pure alcohol 2a was obtained from acetone, m.p. 162–163°; $[\alpha]_D$ +65°; λ_{max} 2.79 μ.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.79; H, 9.12.

Acetylation with acetic anhydride in pyridine at 100° for 2 min. followed by dilution with water, filtration, and recrystallization from acetone gave in quantitative yield **3-methoxy-18-nor-D-homoestra-1,3,5(10)-trien-17α-ol acetate**, m.p. 153–154°; $[\alpha]_D$ +62°; λ_{max} 5.79 μ.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.80; H, 8.64.

3-Methoxy-18-nor-D-homo-13α-estra-1,3,5(10)-trien-17-one (3).—To 400 ml. of ethanol was added 5.65 g. of the ketone 5, 1.0 g. of 5% palladium on charcoal, and 2 ml. of 10% aqueous potassium hydroxide. The mixture was shaken in an atmosphere of hydrogen. After 8 hr. the uptake of hydrogen ceased, the solution was filtered, acidified with a little acetic acid, and concentrated to dryness. The residue was chromatographed on 530 g. of silica. The eluates obtained with 2% ethyl acetate in benzene were combined and the resulting crystalline material (3.1 g., m.p. 134–138°) was recrystallized from petroleum ether (Darco) to yield the analytically pure ketone 3, m.p. 140–141°; $[\alpha]_D$ +40°; λ_{max} 5.81 μ. The rotatory dispersion curve showed a positive Cotton effect with a maximum at 305 mμ ($[\alpha]_D$ +765°) at 0.101 g./100 ml. of methanol.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.99; H, 8.65.

This material was homogeneous by paper chromatography, running slightly ahead of its C-13 epimer.

Semicrystalline material, 0.65 g., was obtained by elution with 20% ethyl acetate in benzene and was recrystallized from petroleum ether–ether to give 0.30 g., m.p. 144–148°. The analytical sample was obtained from ether; λ_{max} 2.89, 5.86 μ; Δν 137 c.p.s. (–$COCH_3$).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.57; H, 8.12.

This material, stable to base-catalyzed dehydration, was not investigated further.

3-Methoxy-17α-methyl-18-nor-D-homoestra-1,3,5(10)-trien-17-ol (11).—The saturated ketone 2b, 4.6 g., in 100 ml. of benzene was added over a 30-min. period to a solution of 250 ml. of ether containing 40 ml. of 3 *M* methylmagnesium bromide in *n*-butyl ether (Arapahoe Chemicals, Inc.). The solution was then boiled for 18 hr., cooled, and treated carefully with water

(18) We wish to thank R. Dahm for his assistance with these experiments.

and sufficient dilute hydrochloric acid to dissolve the precipitated salts. The solution was extracted with benzene and the extract was washed with aqueous potassium bicarbonate solution. The dried and concentrated extract yielded 4.4 g. of semicrystalline material which was chromatographed on 300 g. of silica. Elution with 1% ethyl acetate in benzene yielded fractions weighing 2.9 g. which were crystallized from acetone to yield 1.80 g. of the pure alcohol 11, m.p. 169–170°; $[\alpha]_D$ +53°; λ_{max} 2.75 μ; $\Delta\nu$ 73 c.p.s. (17α-CH_3).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.67; H, 9.32.

Further elution of the column with 1% ethyl acetate in benzene afforded first a mixture of compound 11 and then fractions weighing 0.61 g., recrystallized from acetone to afford 0.20 g., of **3-methoxy-17β-methyl-18-nor-D-homoestra-1,3,5(10)-trien-17-ol** (12), m.p. 160–162°; $[\alpha]_D$ +59°; λ_{max} 2.74 μ; $\Delta\nu$ 74 c.p.s. (17β-CH_3).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.93; H, 9.21.

This material was clearly different in its infrared spectrum from its epimer.

3-Methoxy-17-methyl-18-nor-D-homoestra-1,3,5(10),16-tetraene (13) and 3-Methoxy-17-methyl-18-nor-D-homoestra-1,3,5-(10),17(17a)-tetraene (14).—A solution of 15 ml. of thionyl chloride in 40 ml. of pyridine at 5° was added to 38 g. of the total Grignard adduct (11,12) in 200 ml. of pyridine over a 20-min. period. After a total of 1 hr. the solution was diluted with water and then with aqueous potassium bicarbonate. The mixture was extracted with chloroform and the extract was washed with water and with aqueous bicarbonate solution. A portion (5 g.) of the residue (34 g.), obtained by concentration of the extract, was chromatographed on 150 g. of silica. The first component, 0.7 g., was obtained by elution with 5% benzene in petroleum ether and was recrystallized from methanol and then from petroleum ether to yield 0.26 g. of the pure 17(17a)-olefin **14**, m.p. 112–113°; $[\alpha]_D$ +80°; $\Delta\nu$ 313 c.p.s. (C_{17a}–H).

Anal. Calcd. for $C_{19}H_{26}O$: C, 85.05; H, 9.28. Found: C, 85.07; H, 9.19.

The rotation of subsequent fractions decreased indicating an increase in the proportion of the second isomer (**13**). Later fractions, 0.90 g., were recrystallized from petroleum ether, methanol, and ethanol, yielding 0.36 g. of the pure Δ^{16}-olefin **13**, m.p. 126–128°; $[\alpha]_D$ −30°; $\Delta\nu$ 321, 326 c.p.s. (C_{16}–H).

Anal. Found: C, 84.84; H, 9.27.

In another run starting with the pure isomer 11, m.p. 169–170°, essentially the same procedure as before afforded 0.93 g. of product from 1.0 g. of starting material. This material was chromatographed over 70 g. of silica to effect separation of the olefins. Elution with 10% benzene in petroleum ether gave 0.80 g. of the olefin (**13** and **14**) mixture, $[\alpha]_D$ +15°; integration of the expanded n.m.r. peaks and rotational data indicated the presence of approximately 40% of isomer **14** and 60% of isomer **13**.

3-Methoxy-17-methylene-18-nor-D-homoestra-1,3,5(10)-triene (15).—A stirred solution of 0.30 g. of the equatorial isomer **12** in 20 ml. of pyridine at −5° was treated with 0.50 ml. of thionyl chloride. After 1 hr. the solution was poured into aqueous potassium bicarbonate solution and extracted with benzene. The extract yielded 0.27 g. of crystalline material which was purified on 25 g. of silica. The olefin, 0.18 g., obtained by elution with benzene, was recrystallized from aqueous methanol to yield 0.12 g. of the tetraene **15**, m.p. 112–114°; $\Delta\nu$ 278 c.p.s. (C_{17}=CH_2).

Anal. Calcd. for $C_{20}H_{28}O\cdot 1/4\ H_2O$: C, 83.72; H, 9.31. Found: C, 83.52, 83.37, 83.52; H, 8.99, 8.92, 10.01.

This compound, homogeneous by paper chromatography, sublimed to an oil on drying.

The mother liquors contained olefins **13** and **14**, as indicated by n.m.r.

Acid-Catalyzed Isomerization of the Olefin Mixture (13 and 14).—The olefin mixture (0.65 g., $[\alpha]_D$ +26°) was dissolved in 50 ml. of benzene containing 0.10 g. of *p*-toluenesulfonic acid. The stirred solution was distilled slowly, portions being withdrawn at intervals. The rotation was seen to drop rapidly to −14° within 1 hr. and then remained unchanged. The product was isolated by washing the benzene solution with aqueous potassium bicarbonate, drying over anhydrous magnesium sulfate, and concentrating to dryness under reduced pressure. One portion, 0.36 g., on recrystallization from ether–methanol gave 0.20 g. of the olefin **13**, m.p. 126–128°; $[\alpha]_D$ −26°; n.m.r. showed a small amount of the isomer **14** as contaminant.

3-Methoxy-18-nor-D-homoestra-1,3,5(10)-trien-17α-ol Sulfite (2a Sulfite).—The alcohol **2a** (1.5 g.) dissolved in 20 ml. of pyridine was cooled to −15° and to this stirred solution was added 1.0 ml. of thionyl chloride in 10 ml. of pyridine over a 2-min. period. After 30 min. the solution was poured onto an iced aqueous potassium bicarbonate solution. The resulting precipitate, 0.75 g., m.p. 215–218°, on recrystallization from methylene chloride–methanol showed no change in melting point; λ_{max} 7.39, 8.32 μ (sulfite bands).

Anal. Calcd. for $C_{38}H_{50}O_6S$: C, 73.75; H, 8.14; S, 5.18. Found: C, 73.92; H, 8.43; S, 5.31.

An additional 0.30 g. of sulfite, m.p. 213–216°, was obtained from the mother liquors. Incompleteness of reaction was evidenced by appearance of a hydroxyl band (starting material) in the infrared spectrum of the mother liquors.

The sulfite was stable to boiling pyridine for 20 hr. and to boiling in 1% potassium hydroxide in aqueous dioxane for 24 hr.

Treatment of 0.30 g. of the sulfite in 3 ml. of acetic acid and 0.1 ml. of 70% perchloric acid at 100° for 25 min., yielded, after dilution with water and ether extraction, 0.25 g. of a crystalline solid. Recrystallization from methanol gave 0.12 g. of the C-17 acetate of alcohol **2a**, m.p. 152–153°, identical in the infrared to an authentic sample.

3-Methoxy-18-nor-D-homoestra-1,3,5(10),16-tetraene (17).—The sulfite (0.7 g.) was distilled at 1 mm., 230–260°, yielding 0.60 g. of a crystalline product which was chromatographed on 20 g. of silica. Elution with 50% benzene–petroleum ether gave 0.32 g. of a mixture of two olefins; the n.m.r. spectra of this material showed it to consist of one-third of the 17(17a)-olefin (333 c.p.s.) and two-thirds of the C-16 olefin **17** (340, 343 c.p.s.). Recrystallization from methanol afforded 0.18 g. of the tetraene **17**, m.p. 114–117°; $[\alpha]_D$ −10°; $\Delta\nu$ 340, 343 c.p.s.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 85.26; H, 9.13.

Eluted after 100% benzene was a second crystalline material (0.30 g.), recrystallized from acetone–petroleum ether to provide 0.20 g. of the alcohol **2a**, m.p. 157–159° (identical by infrared).

3-Methoxy-17-methyl-18-nor-D-homoestra-1,3,5(10)-trien-16ξ,17ξ-diol (16).—To a solution of 0.30 g. of the olefin **13**, ($[\alpha]_D$ −30°) in 20 ml. of ether was added 0.27 g. of osmium tetroxide. After 2 hr. at room temperature the solution was diluted with 30 ml. of ethanol and a solution of 2 g. of sodium sulfite in 4 ml. of water. The mixture was then heated at reflux for 1 hr. The mixture was filtered, washing the filter cake generously with hot ethanol. The combined filtrates were concentrated to a small volume, diluted with water, and extracted with chloroform. The extract, washed with water and dried over anhydrous magnesium sulfate, was concentrated to dryness yielding 0.30 g. of a crystalline mixture. Recrystallization from acetone–petroleum ether yielded the pure glycol **16**, solvated with a half mole of acetone, m.p. 170–173°; λ_{max}^{KBr} 2.90 μ.

Anal. Calcd. for $C_{20}H_{28}O_3\cdot 1/2C_3H_6O$: C, 74.74; H, 9.04. Found: C, 74.99; H, 8.90.

1β-Formylmethyl-2α-acetonyl-1,2,3,4,4aα,9,10,10aβ-octahydrophenanthren-7-ol 7-methyl Ether (18). A. By Cleavage of the Diol 16.—A solution of 8.30 g. of periodic acid dihydrate in 40 ml. of water and 9.85 g. of glycol **16** in 300 ml. of methanol and 40 ml. of pyridine were mixed at 5°. The mixture was then removed from the cooling bath and allowed to stand at room temperature for 1 hr. The solution was diluted with 100 ml. of water and the resulting product filtered, yielding 5.10 g. of ketoaldehyde **18**, m.p. 136–139°, and 3.25 g., m.p. 127–133°. Recrystallization from benzene–petroleum ether gave the analytically pure ketoaldehyde **18**, m.p. 143–143.5°; λ_{max} 3.67, 5.83 μ.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.61; H, 8.27.

B. By Ozonolysis of the Olefin 13.—A solution of 0.56 g. of the olefin **13** in 50 ml. of methylene chloride and 50 ml. of methanol at −70° was treated with a stream of oxygen containing ozone. When the effluent gases showed a sharp increase in ozone concentration (after absorption of roughly 1 equivalent), the solution was removed from the stream of ozone, and treated with 5 g. of zinc dust and 5 ml. of acetic acid in 5 ml. of methylene chloride. The mixture was stirred at 0° for 20 min., was filtered, and was diluted with water. The layers were separated, the organic layer being washed again with water and with aqueous sodium bicarbonate. The dried extract was concentrated to

dryness leaving a crystalline residue. Recrystallization from benzene–petroleum ether afforded 0.36 g. of the ketoaldehyde 18, m.p. 135–139°, identical to the compound obtained previously by comparison of infrared spectra.

3-Methoxy-17-acetyl-18-norestra-1,3,5(10),16-tetraene (20).

A. From the Ketoaldehyde 18.—Potassium hydroxide (15.6 g.) and the ketoaldehyde 18 (26.0 g.) were added to 780 ml. of water. The flask was then evacuated and about 30 ml. of water was distilled. The mixture was then heated at reflux in a nitrogen atmosphere with stirring for a total of 5 hr. The material in the flask quickly changed to an oil and then slowly began to crystallize. The solution was cooled, was treated with excess acetic acid, and was filtered with a generous water wash. The air-dried material, 24.0 g., was chromatographed on 450 g. of acid-washed alumina. A total of 13.4 g. of material, eluted with 50% benzene–petroleum ether, was recrystallized from methanol to yield 7.6 g. of product, m.p. 166–169°, and 4.55 g., m.p. 163–168°. Recrystallization of a portion of this material led to a pure sample of **20**, m.p. 168–169°; $[\alpha]_D$ +112°; λ_{max} 5.99 μ; λ_{max} 231 mμ (ϵ 13,900).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 81.04; H, 8.16. Found: C, 81.08; H, 8.31.

Following elution of 5.8 g. of semicrystalline mixture with 10% ethyl acetate in benzene there was obtained 3.7 g. of crystalline material by washing the column with ethyl acetate. Recrystallization from acetone–petroleum ether provided 1.45 g. of material, m.p. 169–173°. Pure **3-methoxy-17ξ-acetyl-18-norestra-1,3,5(10)-trien-16ξ-ol** (19) was obtained by recrystallization from acetone–ether, m.p. 172–174°; $[\alpha]_D$ +64°; λ_{max}^{KBr} 2.90, 5.98 μ.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.39; H, 8.11.

B. From the Hydroxy Ketone 19.—A solution of 0.10 g. of the hydroxy ketone 19 and 30 ml. of dioxane containing 5 ml. of 10% aqueous potassium hydroxide was heated at reflux under nitrogen for 20 hr. The solution was cooled and diluted with water yielding 90 mg. of crystals. These were dissolved in benzene and chromatographed on 10 g. of silica. Crystalline material (80 mg.), eluted at 5% ethyl acetate in benzene, was recrystallized from methanol to give 40 mg. of the unsaturated ketone **20**, m.p. 161–164°, identical in the infrared to the previously obtained material.

This dehydration was also effected by heating at reflux for 7 hr. a solution of 0.31 g. of the hydroxy ketone 19, 1 g. of benzoic acid, and 0.875 ml. of triethylamine. Isolation of the product by ether extraction and chromatography yielded 0.11 g. of the unsaturated ketone **20** and 0.15 g. of starting material 19. Partial dehydration could also be effected by sublimation.

3-Methoxy-17-acetyl-18-norestra-1,3,5(10)-trien-20-one (21). A solution of 0.175 g. of the unsaturated ketone **20** in 30 ml. of ethanol containing 0.40 g. of 5% palladium on charcoal was stirred in an atmosphere of hydrogen. One equivalent of hydrogen was taken up in 15 min. The catalyst was filtered and the solution was concentrated to dryness. The product was recrystallized from petroleum ether, yielding 55 mg. of pure saturated ketone 21, m.p. 125–126°; λ_{max} 5.86 μ.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.47; H, 8.81.

This material was identical in the infrared to a sample of the *dl*-material.[14,15]

Condensed Cyclobutane Aromatic Compounds. XXV. The Thermal Decomposition of 1,2,5,6-Tetrabromo-3,4,7,8-dibenzotricyclo[4.2.0.0^{2,5}]octadiene

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The thermal decomposition of 1,2,5,6-tetrabromo-3,4,7,8-dibenzotricyclo[4.2.0.0^{2,5}]octadiene (I) yields not 5,10-dibromobenzo[*b*]biphenylene (II), as previously believed, but rather 5,10-dibromo-7*H*-indeno[2,1-*a*]indene (VI). The proof of structure of VI is described, and the mechanism of its formation from I is discussed. Spectral evidence confirming the structure of I is presented.

The reaction of excess potassium *t*-butoxide with $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene has been reported to give a mixture of the colorless 1,2,5,6-tetrabromo-3,4,7,8-dibenzotricyclo[4.2.0.0^{2,5}]octadiene (I, m.p. 214°) and the yellow 5,10-dibromobenzo[*b*]biphenylene (II, m.p. 222–223°). Structure I was assigned to the colorless tetrabromide on the basis of two reactions: (1) catalytic reduction of I gave 1,2,5,6-dibenzocyclooctadiene (III) in high yield, and (2) dibromide II was formed in 35.8% yield when tetrabromide I was refluxed in ethanolic sodium iodide solution for two weeks.[1] More recently, the direct thermal conversion of I into II by refluxing a solution of I in *o*-dichlorobenzene for four hours has been claimed.[2] The product from this reaction was described as orange-brown needles, m.p. 222–223°.

Since it has been found that the hydrocarbon 3,4,7,8-dibenzotricyclo[4.2.0.0^{2,5}]octadiene (IV) forms an adduct (V) with *N*-phenylmaleimide at moderate temperatures,[3,4] we investigated the reaction of this dienophile with tetrabromide I in nitrobenzene at 200°. No Diels–Alder adduct was obtained, but a brown crystalline substance, $C_{16}H_8Br_2$, m.p. 222–225°, was isolated in 64% yield. This compound was not identical with yellow dibromide II by the criteria of mixture melting point and infrared comparison; we have assigned to it the structure of 5,10-dibromo-7*H*-indeno[2,1-*a*]indene (VI). The same brown dibromide VI, in impure form, was the only product isolable by us from attempts to reproduce the reported conversions of I into biphenylene II[1,2]; however, when a little phenol was added to scavenge the elemental bromine which was otherwise present, the pyrolysis of I in *o*-dichlorobenzene proceeded very cleanly, giving pure VI in 92% yield.

As expected on the basis of the assigned structure, dibromide VI shows a marked similarity to the known dichloro analog (VII)[5,6] in both its infrared and ultraviolet absorbtion spectra (see Experimental section). Furthermore, like VII, VI was reduced catalytically by palladium on charcoal in the presence of triethylamine to give 4*b*,5,9*b*,10-tetrahydro-7*H*-indeno[2,1-*a*]indene (VIII)[7] in high yield. Finally, dibromide VI

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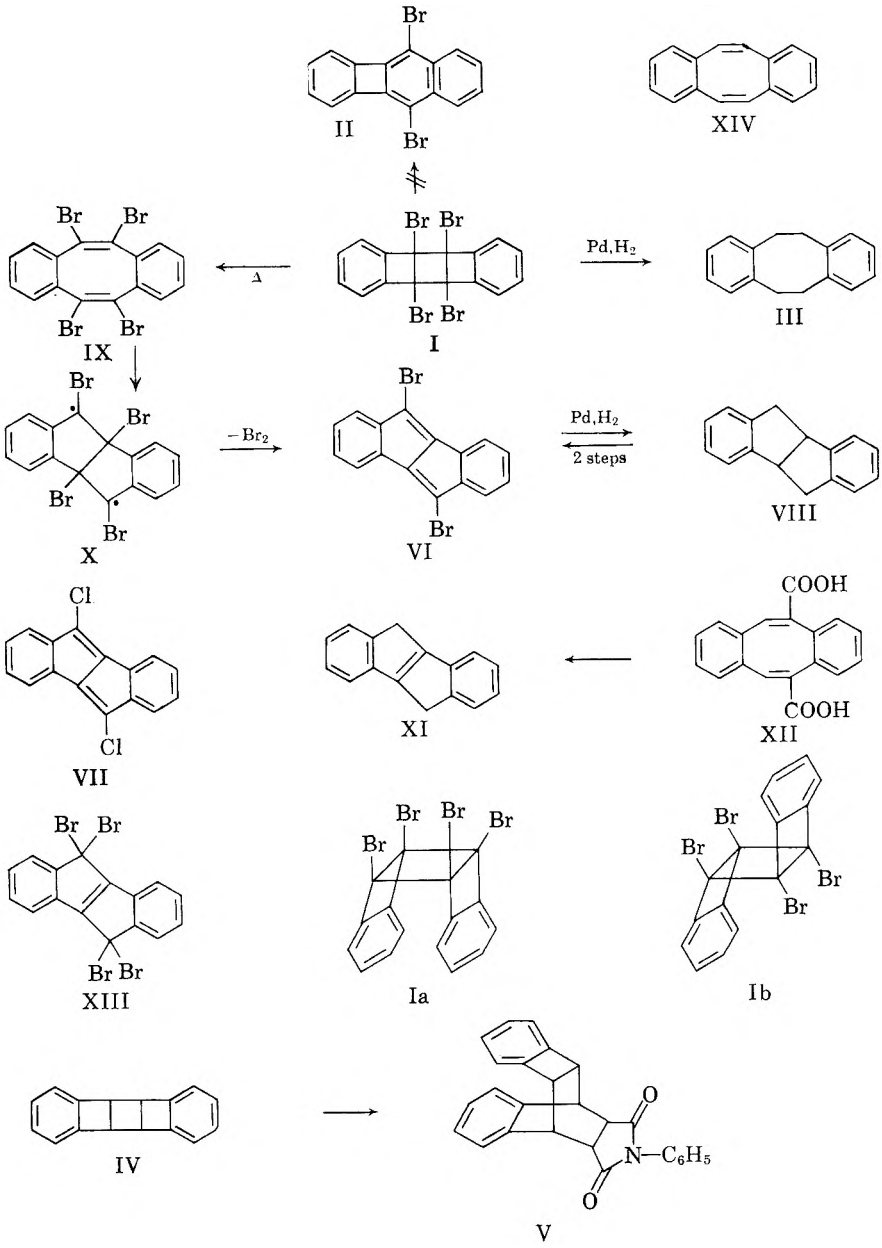

was synthesized from hydrocarbon VIII (15% over-all yield) by reaction of VIII with *N*-bromosuccinimide, followed by treatment of the crude bromination product with sodium acetate.

The mechanism of the pyrolytic formation of VI from I deserves some comment. It seems likely that, by analogy with the behavior of the parent hydrocarbon (IV),[8,9] tetrabromide I may decompose thermally to a cyclooctatetraene derivative (IX). In the case of the open tetrabromide (IX), all four bromines are forced into very close proximity with each other due to the tub structure of the central ring; indeed, it is impossible to construct a molecular model (Leybold type) of IX because of this proximity effect. Steric factors may, therefore, favor a decoupling of the π-electrons of the central bonds of IX and rearrangement to the diradical X. The diradical would then afford the observed product VI and elemental bromine. The formation of free bromine during the pyrolysis of I in *o*-dichlorobenzene may be observed visually. The formation of a central pentalane nucleus in the pyrolysis of a dibenzocyclooctatetraene is not without analogy: hydrocarbon XI has been found to be one of the thermal decarboxylation products of diacid XII.[10]

The finding that the alledged conversion of tetrabromide I into biphenylene II does not occur considerably weakens the structure proof of I. However, the catalytic reduction of I to octadiene III,[1] which we have confirmed, eliminates the pentalane structure XIII and leaves only the octatetraene IX and the *syn* and *anti* isomers Ia and Ib for possible consideration. In both structures Ia and IX the aromatic rings lie over each other, and the protons of each ring should be shielded by π-electrons of the overlying ring. This effect is clearly discernible in the n.m.r. spectrum (deuteriochloroform solution) of the model compound, dibenzocyclooctatetraene (XIV), which shows aromatic protons shifted upfield to 2.92 τ. In contrast, the unshielded aromatic protons of dibenzotricyclooctadiene (IV), which is known to possess the *anti* configura-

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tion,[11] appear at 2.72 τ. This value is almost identical with that (2.75 τ) found for the protons of tetrabromide I, which, therefore, most likely has the *anti* configuration Ib. Final confirmation of this structure must await the results of an X-ray crystallographic analysis of I which is now in progress.

In conclusion, the reported conversions of tetrabromide I into biphenylene II appear to be in error, the actual transformation product of I being pentalene derivative VI. It must be emphasized, however, that the results reported here cast no doubt on the constitution of authentic biphenylene II as obtained by the potassium *t*-butoxide transformation of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene.

Experimental[12]

Attempted Preparation of a Diels–Alder Adduct from Tetrabromide I. — 1,2,5,6 - Tetrabromo - 3,4,7,8 - dibenzotricyclo-[4.2.0.0^{2,5}]octa-3,7-diene (I, 520 mg., 1 mmole) was heated with 800 mg. (4.6 mmoles) of *N*-phenylmaleimide in 20 ml. of nitrobenzene at 200° for 2–3 min. The reaction mixture was allowed to cool slowly to room temperature and was then passed through a short column of grade III neutral alumina. Vacuum evaporation of the resulting solution gave a brown residue which was recrystallized from ethanol to give 230 mg. (64%) of 5,10-dibromo-7*H*-indeno[2,1-*a*]indene (VI), brown crystals, m.p. 222–225° dec.; the infrared and ultraviolet spectra of the product were identical with those of a sample prepared from 4*b*,5,9*b*,10-tetrahydro-7*H*-indeno[2,1-*a*]indene (VIII → VI).

Dehalogenation of Tetrabromide I with Sodium Iodide.—A solution of 520 mg. (1 mmole) of tetrabromide I and 500 mg. (3.33 mmoles) of sodium iodide in 25 ml. of ethanol was refluxed for 17 days. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was extracted with 1:5 benzene–cyclohexane. The residue was worked up to give 348 mg. of starting material. The benzene–cyclohexane extract was washed with 5% aqueous sodium bisulfite, dried over magnesium sulfate, and subjected to chromatography on a column (2 × 30 cm.) of grade I neutral alumina (Woelm) with 1:5 benzene–cyclohexane to give two fractions: (A) 750 ml., containing 78 mg. of starting material; and (B) 900 ml., containing 25.2 mg. (38.4% based on unrecovered starting material) of virtually pure 5,10-dibromo-7*H*-indeno[2,1-*a*]indene (VI), which was crystallized once from absolute ethanol to give the pure product, m.p. 222–223°; the infrared spectrum of the pure material was identical with that of the sample isolated from the attempted Diels–Alder reaction (see preceding) and also with that of the sample prepared from 4*b*,5,9*b*,10-tetrahydro-7*H*-indeno[2,1-*a*]indene (VIII → VI, see following).

Preparation of 5,10-Dibromo-7*H*-indeno[2,1-*a*]indene (VI). A. By Thermolysis of Tetrabromide I.—A solution of 0.5 g. tetrabromide I in 50 ml. of *o*-dichlorobenzene was refluxed for 4 hr., cooled, and mixed with *ca.* 50 ml. of ether. The resulting solution was washed with water, 5% aqueous sodium bicarbonate, and 5% aqueous sodium bisulfite; it was dried over magnesium sulfate and evaporated to dryness *in vacuo*. The residue was taken up in 50 ml. of 1:5 benzene–cyclohexane and chromatographed with the same solvent on a column (4 × 20 cm.) of grade I neutral alumina (Woelm) to give fractions: (A) 450 ml., containing 35 mg. of crude starting material; (B) 500 ml., 24 mg. of VI, m.p. 205–206° (from ethanol); (C) 900 ml., 51 mg. of VI, m.p. 210–213°; (D) 400 ml., 55 mg. of VI, m.p. 180–185°; (E) 500 ml.; and (F) 350 ml. which were combined to give 70 mg. of VI, m.p. 176–18°. The yield of VI was 200 mg. (48%). Infrared analysis of samples A through F showed the presence of a small amount of impurity (*not* 5,10-dibromobenzo[*b*]biphenylene).

The thermolysis of tetrabromide I under the same conditions described earlier, but in the presence of 200 mg. of phenol (bromine scavenger), gave 333 mg. (92%) of virtually pure 5,10-dibromo-7*H*-indeno[2,1-*a*]indene (VI), m.p. 218–221° (from benzene–methanol).

B. From 4*b*,5,9*b*,10-Tetrahydro-7*H*-indeno[2,1-*a*]indene.—A solution of 103 mg. (0.5 mmole) of 4*b*,5,9*b*,10-tetrahydro-7*H*-indeno[2,1-*a*]indene (VIII)[7] in 10 ml. of carbon tetrachloride was refluxed with 356 mg. (2 mmoles) of *N*-bromosuccinimide while a solution of 50 mg. of benzoyl peroxide in 10 ml. of 1:4 chloroform–carbon tetrachloride was added slowly from a Hershberg dropping funnel. When all of the peroxide solution had been added (3 hr.), the reaction mixture was cooled, filtered, and the filtrate was evaporated to an oil. The oil was mixed with 1.0 g. of sodium acetate and *ca.* 25 ml. of absolute ethanol and the resulting suspension was refluxed for 3 hr. The reaction mixture was evaporated to dryness *in vacuo*, the residue was extracted with 1:5 benzene–cyclohexane, and the extract was chromatographed on a column (40 mm. × 20 cm.) of grade I neutral alumina (Woelm). The eluate containing the first brown zone to leave the column was collected and evaporated to dryness; the residue was recrystallized from absolute ethanol to give 26 mg. (15%, based on VIII) of 5,10-dibromo-7*H*-indeno[2,1-*a*]-indene (VI), m.p. 215–218°.

Anal. Calcd. for $C_{16}H_{18}Br_2$: C, 53.57; H, 2.24; Br, 44.39. Found: C, 53.29; H, 2.38; Br, 44.55.

The spectral properties of dibromide VI, *i.e.*, its absorption in the ultraviolet [$\lambda_{max}^{dioxane}$ 278 mμ, log ϵ 4.70; 379 (3.84); 402 (4.16); 428 (4.47)] and its infrared absorption [ν_{max}^{KBr} 6.19, 6.26, 6.34 (w); 7.03 (s); 7.49 (w); 8.32, 10.5, 13.5 μ (s)], compare favorably with those of the known dichloro analog (VII),[5,6] *i.e.*, in the ultraviolet [$\lambda_{max}^{dioxane}$ 273 mμ, log ϵ 4.74; 382 (3.83); 397 (4.22); 423 (4.33)] and in the infrared [ν_{max}^{KBr} 6.19, 6.27, 6.35 (w); 7.04 (m); 8.26, 10.3, 13.5 μ (s)].

Hydrogenolysis of 5,10-Dibromo-7*H*-indeno[2,1-*a*]indene (VI).—A suspension of 280 mg. (0.778 mmole) of dibromide VI in 5.0 ml. of triethylamine was hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal. The reaction mixture consumed 54.3 ml. (STP) of hydrogen, out of an expected 66.4 ml. (STP). The reaction was filtered, the filtrate was poured into water, and the resulting suspension was extracted with benzene. Chromatography of the benzene extract on grade I neutral alumina (Woelm) gave 151 mg. (94%) of 4*b*,5,9*b*,10-tetrahydro-7*H*-indene[2,1-*a*]indene, m.p. 104–105°, identical in its melting point and infrared spectrum with an authentic sample.[7]

Hydrogenolysis of Tetrabromide I.—A suspension of 200 mg. (0.384 mmole) of 1,2,5,6-tetrabromo-3,4,7,8-dibenzotricyclo-[4.2.0.0^{2,5}]octa-3,7-diene (I) in 30 ml. of 2% ethanolic triethylamine was hydrogenated at atmospheric pressure in the presence of 100 mg. of 10% palladium on charcoal for 1.5 hr. The reaction mixture absorbed 51.4 ml. (STP) of hydrogen which is 99% of the theoretical volume (6 moles of hydrogen per mole of tetrabromide). The reaction mixture was filtered, the filtrate was poured into water, and the resulting suspension was extracted with petroleum ether (b.p. 30–60°). The extract was passed through a short column of grade I neutral alumina and the eluate was evaporated to dryness *in vacuo* to give 78 mg. (97%) of dibenzo[*a*,*e*]cyclooctadiene (III), identical in its melting point and infrared spectrum with an authentic sample.[13]

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Polymerization of Benzene to *p*-Polyphenyl by Ferric Chloride[1]

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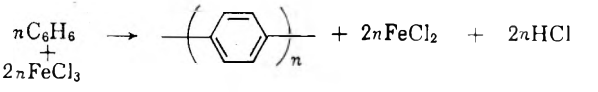
p-Polyphenyl containing a small amount of chlorine was prepared from benzene under mild conditions by treatment with ferric chloride. The polymer was identified by elemental analyses, infrared spectrum, X-ray diffraction pattern, pyrolysis products, and oxidative degradation. A minor amount of structural irregularity was indicated by the pyrolysis studies. The benzene–ferric chloride reaction also yielded a very small quantity of low molecular weight product composed mainly of chlorobenzene and 4,4′-dichlorobiphenyl. The oxidative cationic mechanism for the polymerization is supported by the finding that ferric chloride easily converts 1,4-cyclohexadiene to benzene. The initially formed *p*-polyphenyl is readily transformed during reaction to a polymer possessing a darker color and a higher C/(H + Cl) atomic ratio.

Recently it was shown that the aromatic nucleus can function as a monomer in polymerizations leading to homopolymers.[2] For example, benzene was transformed in a simple, one-step procedure to *p*-polyphenyl by treatment with either aluminum chloride–cupric chloride[2,3] or molybdenum pentachloride.[4] Except for the synthesis of impure *p*-polyphenyl from poly-1,3-cyclohexadiene,[5] previous attempts to prepare a highly homogeneous polyphenyl by classical methods have been unsuccessful. The pertinent literature has been summarized recently.[3,4]

We have found that when benzene is allowed to react with a 1:1 molar ratio of ferric chloride–water for very short periods at about 70°, *p*-polyphenyl which contains a small amount of chlorine is formed (Table I). Since hydrogen chloride and ferrous chloride are also generated, the reaction apparently proceeds as indicated.



The structure of the rust-colored product was derived primarily from elemental analyses, infrared spectrum, X-ray diffraction pattern, pyrolysis products, and oxidative degradation. The polymer possessed a C/(H + Cl) atomic ratio of 1.51, in good agreement with the limiting theoretical value of 1.5 for polyphenyl.

TABLE I

POLYMERS FROM BENZENE–FERRIC CHLORIDE–WATER

H_2O/$FeCl_3$, molar ratio	Time, min.	Temp., °C.	Polymer: Yield, g.	Polymer: % C	Polymer: % H	Polymer: % Cl	C/(H + Cl), atomic ratio
1.0	0.5	70 ± 2	3.9	88.38	4.69	6.00	1.51
1.0[a]	120	70 ± 8	8.1	84.23	3.43	11.35	1.87
0.2[b]	120	80 ± 2	4.2	82.74	2.42	13.50	2.46

[a] See the standard procedure. [b] Ref. 11.

In the infrared spectrum, a strong band occurred at 807 cm.$^{-1}$ characteristic of *para*-substitution. Other absorption maxima were situated at 1001 cm.$^{-1}$ (*para*) and 1481 cm.$^{-1}$ (C=C skeletel in-plane vibrations). In addition, diffuse bands were detected at 767, 1095, and 1400 cm.$^{-1}$.

The X-ray diffraction pattern, which established the crystallinity of the polymer, gave *d*-spacings of 4.48, 3.82, 3.16, 7.96, and 2.07 Å., in decreasing order of intensity. These *d*-spacings correspond closely to the values reported for *p*-quaterphenyl: 4.49, 3.83, 2.04, 3.14, and 1.76 Å., in decreasing order of intensity.[4] The most intense *d*-spacing of 4.48 Å. corresponds to the distance of 4.5 Å. reported to be the length of a phenyl unit.[5,6] The X-ray data provide support for the thesis that the rings are essentially co-planar (as in the lower *p*-polyphenyls[6]) and that the structure is predominantly *para*.[5]

Pyrolysis of the polymer *in vacuo* at 750–800° gave a sublimate in addition to residual material resembling carbon black. The sublimed product contained biphenyl, low molecular weight *p*-polyphenyls including terphenyl, quaterphenyl, and quinquephenyl, in addition to uncharacterized higher molecular weight substances. Identification was accomplished by comparison of the melting points and the infrared and ultraviolet spectra with those of the authentic materials. Gas chromatographic analysis of the unpurified terphenyl revealed the presence of 10–15% of *m*-terphenyl. The *meta* isomer might arise from rearrangement[7,8] during pyrolysis, or from a small amount of irregular structure in the polymer, such as *meta*-linkages, polyphenyl branches or cross links. The occurrence of a minor amount of *p*-chlorobiphenyl in the sublimate provides information concerning the terminal structure of the chains.

Chromic acid oxidation of the polymer yielded terephthalic acid, 4,4′-biphenyldicarboxylic acid, *p*-chlorobenzoic acid, and unidentified acidic products. The dicarboxylic acids were characterized in the form of their dimethyl esters. It is reasonable to conclude that the terephthalic acid is derived from *p*-terphenyl units in the polymer chain, the 4,4′-biphenyldicarboxylic acid from *p*-quaterphenyl units, and the *p*-chlorobenzoic acid from end-group structures. The absence of isomeric benzenedicarboxylic acids was established by gas chromatographic and infrared analysis of the unpurified dimethyl terephthalate.

Attention was also given to the low molecular weight products formed in the reaction. The benzene

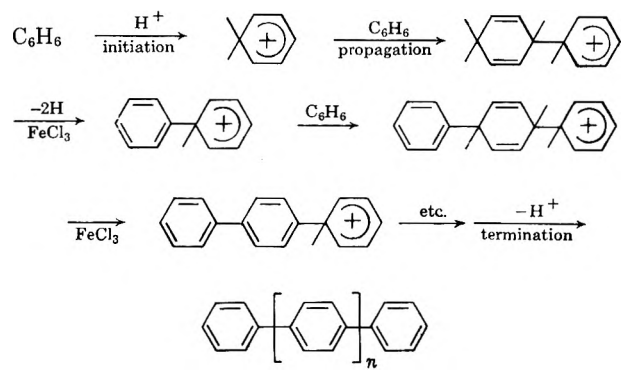
(1) Paper IV in the series, Polymerization of Aromatic Nuclei; from the forthcoming Ph.D. thesis of F. W. Koch.
(2) P. Kovacic and A. Kyriakis, *Tetrahedron Letters*, 467 (1962).
(3) P. Kovacic and A. Kyriakis, *J. Am. Chem. Soc.*, **85**, 454 (1963).
(4) P. Kovacic and R. M. Lange, *J. Org. Chem.*, **28**, 968 (1963).
(5) C. S. Marvel and G. E. Hartzell, *J. Am. Chem. Soc.*, **81**, 448 (1959).
(6) L. W. Pickett, *Proc. Royal Soc.* (London), **142A**, 333 (1933); *J. Am. Chem. Soc.*, **58**, 2299 (1936).
(7) E. H. Smith, Polyphenyls: Literature Search, U. S. Atomic Energy Commission, ER-8098, 1956.
(8) L. Silverman, *et al.*, NAA-SR-1203, North American Aviation, Inc., 1955.

filtrate from the reaction mixture contained very small amounts of a gross mixture. In addition to chlorobenzene which was the major component, 4,4′-dichlorobiphenyl was isolated by gas chromatography, and its identity revealed by comparison with authentic material. The biphenyl derivative can be considered to represent the dimer stage of the polymerization. Since ferric chloride readily chlorinates aromatic compounds, the presence of the chlorine substituents is understandable.[9] Solvent extraction studies demonstrated the essential absence of low molecular weight extractable material in the polymer. Unfortunately, the high insolubility of the product prevents molecular weight determination by colligative or light scattering techniques. However, the position of the principal *para*-band and the absence of fine structure in the infrared spectrum indicate that the molecular weight is higher than that of the *p*-polyphenyl synthesized from poly-1,3-cyclohexadiene.[3,5]

The extreme insolubility and good thermal stability of the polymer are characteristic of *p*-polyphenyl.[3,5] After one-half hour in air at 450°, there was a weight loss of only 16%. In summary of the data relevant to the polymer configuration, the infrared and X-ray diffraction studies, pyrolysis products, and oxidative degradation point to a predominantly *para*-structure. However, thermal degradation also indicates a minor amount of irregularity, presumably branching or cross-linking. On the basis of the experimental evidence, one may conclude that the polymer obtained with ferric chloride is very similar to the *p*-polyphenyl synthesized by the cupric chloride–aluminum chloride[2,3] or the molybdenum pentachloride method.[4]

The concept of oxidative cationic polymerization provides a plausible interpretation of the reaction.

$$FeCl_3 + H_2O \rightleftharpoons H_2O \cdots > FeCl_3 \rightleftharpoons H^+FeCl_3(OH)^-$$



Except for the oxidative aspect, the scheme closely resembles the generally accepted interpretation for olefin polymerization catalyzed by Lewis acids.[10] The necessity of a Brönsted acid cocatalyst in order for polymerization to occur has been demonstrated previously.[11] Presumably, ferric chloride functions both as the catalyst and oxidant. In order to test the hypothesis that cyclohexadiene units are converted to aromatic structures during the reaction, the dehydrogenation of 1,4-cyclohexadiene by ferric chloride was investigated. Reaction was found to occur readily with formation of benzene. The chlorine content of the polymer might arise from nuclear chlorination by ferric chloride or from chain termination by chloride.

Alternative hypotheses should also be considered. For example, one-electron reduction of ferric chloride could conceivably provide a radical–carbonium ion[12] (I) as the initiating species.

I

Unless the polymerization conditions are carefully controlled, a product is obtained possessing a darker color and a C/(H + Cl) atomic ratio greater than 1.5. Higher temperatures and increased reaction times favor the subsequent transformation which presumably involves the conversion of *p*-polyphenyl to a polymer containing polynuclear structures (Table I). The increase in the atomic ratio is accompanied by a corresponding rise in chlorine content. The close similarity of the infrared spectra for the polymers of varying C/(H + Cl) atomic ratio supports the contention that chlorinated polynuclear structures are present in the high ratio polymers. It is significant that the brown-black product is more susceptible to oxidative thermal degradation than is *p*-polyphenyl (Table II). The presence of polynuclear structures would be expected to darken the color and make the polymer more susceptible to oxidative and substitutive attack. Since the *p*-polyphenyl obtained with ferric chloride is darker in color and undergoes oxidative thermal degradation more readily than the product from aluminum chloride–cupric chloride,[3] it very likely contains a minor amount of polynuclear structure. The possible presence of trace amounts of metal catalyst complicates rationalization of the data on oxidative thermal stability.

TABLE II

THERMAL AND OXIDATIVE STABILITY OF BENZENE POLYMERS

Temp., °C.	Wt. loss, % Polyphenyl[a]	Chlorinated *p*-polyphenyl[b]	Polynuclear polymer[c]
350	0.49	0.35	2.08
400	0.99	0.94	4.88
450	16.15	2.70	56.89
500	55.50	15.55	95.59
550	97.0	73.0	...
600	100	99.9	...

[a] C, 88.38%; H, 4.69%; Cl, 6.00%; C/(H + Cl), atomic ratio 1.51. [b] C, 72.40%; H, 3.54%; Cl, 23.60%; C/(H + Cl), atomic ratio 1.47. [c] C, 75.05%; H, 1.96%; Cl, 20.15%; C/(H + Cl), atomic ratio 2.45; from C_6H_6 (2 moles)–$FeCl_3$ (1 mole) at reflux for 28 hr.

Several interpretations come to mind relative to the subsequent transformation: (1) the direct linking of individual *p*-polyphenyl chains, and (2) a reaction of the polymer with benzene–ferric chloride leading to polynuclear structures. Item 1 appears unlikely since attempts to cross link *p*-polyphenyl by treatment with ferric chloride in liquid media were unsuccessful. Although there was a drastic rise in chlorine content due to chlorination by ferric chloride, the C/(H + Cl) ratio did not increase (Table III).

(9) P. Kovacic, C. Wu, and R. W. Stewart, *J. Am. Chem. Soc.*, **82**, 1917 (1960); P. Kovacic and N. O. Brace, *ibid.*, **76**, 5491 (1954).

(10) See ref. 3 for leading references.

(11) P. Kovacic and C. Wu, *J. Polymer Sci.*, **47**, 45 (1960).

(12) W. Aalbersberg, J. Gaaf, and E. L. Mackor, *J. Chem. Soc.*, 905 (1961).

TABLE III

p-POLYPHENYL–FERRIC CHLORIDE

Solvent	G.	*p*-Polyphenyl, C/H atomic ratio	$H_2O/FeCl_3$, molar	Time, hr.	Polymer product: Yield, g.	Polymer product: % C	% H	% Cl	Polymer product: C/(H + Cl), atomic ratio
n-C_8H_{18}	114	1.42	0	9	6.3	79.31	4.88	9.86	1.28
n-C_8H_{18}	114	1.42	0.5	9	4.8	73.29	3.74	18.55	1.43
o-$C_6H_4Cl_2$	147	1.50	0.5	6	4.8	72.40	3.54	23.60	1.45
o-$C_6H_4Cl_2$	147	1.50	0	9	4.8	79.19	4.00	15.59	1.48
H_3PO_4 (85%) + P_2O_5	115 + 27.4	1.53	...	9	4.9	85.02	4.89	7.60	1.40
$SnCl_4$	260	1.53	0	14	5.4	75.10	4.00	18.69	1.38

Furthermore, there is positive evidence in support of the second interpretation. *p*-Polyphenyl was allowed to react with benzene and ferric chloride under conditions whereby benzene undergoes only a minute amount of polymerization (Tables IV and V). A significant increase both in weight and C/(H + Cl) ratio resulted.

TABLE IV

p-POLYPHENYL–BENZENE–FERRIC CHLORIDE REACTION

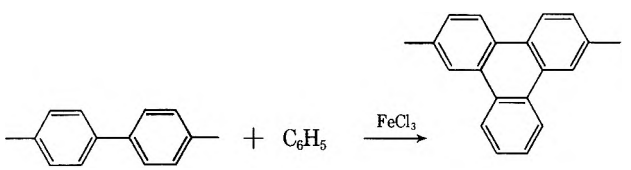
Time, hr.	Product: Yield, g.	Product: % C	% H	% Cl	C/(H + Cl), atomic ratio
2	5.9	84.05	3.58	11.58	1.79
4	6.1	84.30	3.92	10.62	1.66

TABLE V

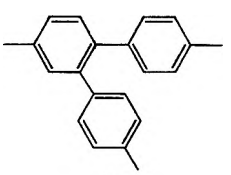
BENZENE–FERRIC CHLORIDE REACTION

Time, hr.	Product: Yield, g.	Product: % C	% H	% Cl	C/(H + Cl), atomic ratio
2	0.14	85.08	3.89	8.78	1.72
4	0.20	78.74	2.92	11.74	2.02

The polynuclear synthesis may take place as illustrated.



Alternatively, protonation of the polymer could well produce sites capable of initiating polymerization.



II

The *o*-terphenyl units might then be converted subsequently to polynuclear regions by intramolecular dehydrogenation. The initially formed fused ring system could conceivably facilitate further reaction. The problem of polynuclear formation is undergoing further investigation.

Experimental[13]

Materials.—The following reagent grade chemicals were used: benzene, thiophene free, Mallinckrodt Chemical Works, dried over sodium and distilled; anhydrous ferric chloride, sublimed powder, Matheson Coleman and Bell, or Fisher Scientific Co.; biphenyl, *o*-, *m*-, and *p*-terphenyl, 4-chlorobiphenyl, terephthalic acid, and *p*-chlorobenzoic acid, Eastman Kodak Co.; *p*-quaterphenyl, K and K; 4,4′-biphenyldicarboxylic acid, Aldrich Chemical Co.; 4,4′-dichlorobiphenyl, Matheson Coleman and Bell; *n*-octane, 99 mole %, Phillips Petroleum Co., dried over sodium and distilled; *o*-dichlorobenzene, distilled from lithium hydride.

Apparatus.—Beckman DK-2 ultraviolet spectrophotometer (chloroform or cyclohexane); Beckman IR-7 or Perkin-Elmer Model 237 infrared spectrophotometer (carbon disulfide or 0.25–0.5% in potassium bromide); F and M Model 500 gas chromatograph, 6 ft., 20% silicone rubber on Chromosorb W, or 12 ft., 15% silicone rubber on Chromosorb W, or 20 ft., 15% silicone grease on Chromosorb W; X-ray diffraction apparatus, copper Kα radiation (λ 1.539 Å.).

***p*-Polyphenyl from Benzene–Ferric Chloride. 1. General Procedure.**—Water (1 mole) was added dropwise with stirring under nitrogen at 10–25° to a mixture of benzene (2 moles) and ferric chloride (1 mole). The reaction mixture was heated during 20 min. to 70 ± 3°; whereupon hydrogen chloride was rapidly evolved and the contents darkened. After 30 sec., the mixture was quickly cooled and filtered. The residue was washed with benzene and then triturated repeatedly with boiling concentrated hydrochloric acid until the filtrate was colorless. After the polymer was treated with hot 2 *M* sodium hydroxide, the acid triturations were repeated. The red-brown solid was washed thoroughly with distilled water, and dried at 140–150° for 2 hr. Precautions were taken to avoid contamination.

2. Low Molecular Weight Products.—The initial benzene filtrate from four reactions was washed with 3 *N* hydrochloric acid until the aqueous layer was colorless and then with water until the washings were neutral to litmus. After distillation of benzene from the dried organic layer, fractionation with an "Ace Minilab Apparatus" gave chlorobenzene, b.p. 125–131°, 3.5 g. The viscous liquid, 0.5 g., which remained was examined by gas chromatography and found to consist of a gross mixture. The major component, isolated by gas chromatography, was 4,4′-dichlorobiphenyl, m.p. 140–144°.[14] The infrared and ultraviolet spectra were essentially identical with those of the authentic material, m.p. 145–146°.

3. Analysis for Ferrous Chloride.—A mixture of benzene (2 moles), ferric chloride (1 mole), and water (1 mole) was allowed to react for 30 min. (see the general procedure). After filtration under nitrogen, the residue was stirred with 300 ml. of 3 *N* hydrochloric acid and filtered. The solid was subsequently heated with about 400 ml. of 6 *N* hydrochloric acid, and filtered. The original organic filtrate was extracted with two 50-ml. portions of 3 *N* hydrochloric acid. Dilution of the combined aqueous extracts to a volume of 1 l. was effected. Aliquots were titrated potentiometrically with 0.1 *N* ceric ammonium nitrate standardized with ferrous sulfate (Beckman pH meter, saturated calomel reference, and platinum indicator electrode). Ferrous ion was found to be present in the combined extract to the extent of 0.33 mole.

Characterization of *p*-Polyphenyl. 1. X-Ray Diffraction Pattern.—*d*-Spacing of 4.48, 3.82, 3.16, 7.96, and 2.07 Å in decreasing order of intensity, were obtained.[15]

2. Infrared Spectrum.—Absorption maxima were present at 767 (broad), 807, 1003, 1095, 1400 (broad), and 1481 cm.$^{-1}$. The infrared spectrum of the polymer possessing a high C/(H

(13) Melting points and boiling points are uncorrected. Elemental analyses were performed by Drs. Weiler and Strauss, Oxford, England.

(14) We wish to thank C. E. Stephan for the isolation and characterization of this compound.

(15) We are grateful to R. M. Lange for obtaining these data and to C. S. Smith for the use of the X-ray equipment.

+ Cl) atomic ratio (2.45) (Table II) was very similar to that of *p*-polyphenyl, except for a broad band at 1585 cm.$^{-1}$.

3. **Solubility.**—The polymer is essentially insoluble in boiling ethanol, ether, chloroform, xylene, and *o*-dichlorobenzene; 0.35% dissolved in xylene, and 0.4% in chloroform. The soluble material consisted partly of tar.

4. **Pyrolysis.**—The thermal decomposition was carried out *in vacuo* as previously described.[3,4] Infrared, ultraviolet, and gas chromatographic analyses were used in the identification of biphenyl, m.p. 69–70°, m.m.p. 69–70°; *p*-terphenyl, m.p. 209–210°, m.m.p. 209–210°; and 4-chlorobiphenyl ($\lambda_{max}^{CHCl_3}$ 256.5 mμ). *p*-Quaterphenyl melted at 304–305°, authentic material, m.p. 306–307°, m.m.p. 304–305°. The infrared and ultraviolet spectra ($\lambda_{max}^{CHCl_3}$ 299 mμ) were identical with those of authentic *p*-quaterphenyl. *p*-Quinquephenyl was characterized by the infrared and ultraviolet spectra ($\lambda_{max}^{CHCl_3}$ 309 mμ), and by m.p. 385–390°; authentic material, m.p. 382–386°; lit.[7] m.p. 395°. In addition, higher molecular weight sublimate was obtained whose infrared and ultraviolet spectra indicated a *p*-polyphenyl structure.

5. **Oxidation.**—An earlier procedure was followed.[4] Dimethyl terephthalate melted at 139–140°, m.m.p. with authentic material, 139–140°. The gas chromatogram and infrared spectrum indicated the absence of the 1,2- and 1,3-isomers in the unpurified dimethyl terephthalate. Dimethyl-4,4′-biphenyldicarboxylate was identified by the infrared spectrum and m.p. 210–212°; the mixture melting point with authentic ester was undepressed. The infrared spectrum, melting point (237°), and mixture melting point were used to characterize 4-chlorobenzoic acid.

6. **Thermal and Oxidative Stability.**—Three types of f benzene polymer (1 g. each) were placed in porcelain vessels and heated for 30-min. periods at temperatures which were increased by 50° increments in the 350–600° range. The data obtained are shown in Table II.

***p*-Polyphenyl–Ferric Chloride.**—A mixture of *p*-polyphenyl[3] (4 g.), ferric chloride (81.1 g.), and an appropriate solvent was stirred at 80 ± 5°. Work-up was by the standard procedure. The data are summarized in Table III.

***p*-Polyphenyl–Benzene–Ferric Chloride.**—A mixture of *p*-polyphenyl[3] (4 g., C/H atomic ratio 1.47), ferric chloride (162.2 g.), and benzene (156.2 g.) was stirred at the reflux temperature under nitrogen. Precautions were taken (weighing in a dry box, dry apparatus, etc.) to minimize the water content of the system. The reaction mixture was worked up by the usual procedure. The results are shown in Table IV. Table V contains the data for control experiments carried out under the same conditions, but with no added *p*-polyphenyl.

Dehydrogenation of 1,4-cyclohexadiene with Ferric Chloride.—Ferric chloride (1.62 g.) was added in portions with shaking to 1,4-cyclohexadiene (2 g.) while the temperature was kept at 1–43° by cooling. The liquid was decanted and subjected to gas chromatographic analysis. Benzene was identified by retention time and infrared spectrum. Also present were additional products possessing higher retention times.

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Polycondensation of Mercaptobenzenediazonium Salts

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Both 4- and 3-mercaptobenzenediazonium salts have been polymerized under various conditions to give red, insoluble infusible solids containing sulfide and diazosulfide bonds in equal amounts. On heating to 150–250°, about 80% of the nitrogen was lost. In order to characterize further the diazosulfide bond, several new diazosulfides have been synthesized.

One of the most useful procedures for the preparation of alkyl aryl sulfides is the reaction of aryl diazonium salts with alkyl mercaptide ions. It has, however, been long known that aryl mercaptide ions react with aryl diazonium salts to give diazosulfides.[1,2]

$$ArN_2^{\oplus} \xrightarrow{RS^{\ominus}} ArSR + N_2$$

$$ArN_2^{\oplus} \xrightarrow{Ar'S^{\ominus}} Ar'SN{=}NAr$$

We wish to report here on an investigation of the polymerization of mercaptodiazonium salts, an extension of recent work on polymerization of diazooxides.[3]

When 3- or 4-mercaptoanilines were diazotized and then buffered to neutrality by sodium acetate, red-brown polymer was obtained in each case. The insoluble polymers were found to contain about half the original nitrogen of the diazonium salt. The reaction apparently corresponds to the following stoichiometry.

$$2n\ {}^{\ominus}SC_6H_4N_2^{\oplus} \longrightarrow \underset{\text{II}}{\text{-(-}SC_6H_4SN{=}NC_6H_4\text{-)-}_n} + nN_2$$

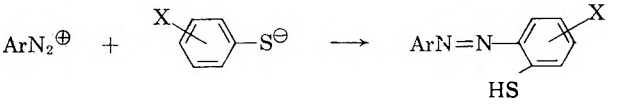
I (*p*- and *m*-)

The presence of the azo link is indicated by the color, by the infrared spectra bands at 1465 and 1580 cm.$^{-1}$ (diazosulfide), at 810 cm.$^{-1}$ (1,4-disubstituted benzene[4]) for *p*-II, and at 770 cm.$^{-1}$ (1,3-disubstituted benzene) for *m*-II, and by the substantial loss of nitrogen which occurred on heating at 150–250°.

$$\underset{p\text{-I}}{\text{-(-}SC_6H_4\text{-)-(-}SN_2C_6H_4\text{-)-}} \xrightarrow{250^\circ} \underset{p\text{-III}}{\text{-(-}SC_6H_4\text{-)-}_5\text{-(-}SN_2C_6H_4\text{-)-}} + N_2$$

The resulting polymer (*p*-III) showed the characteristic infrared peaks of poly(*p*-phenylene sulfide).[5]

The insolubility of the polymers, a weak infrared band at 870 cm.$^{-1}$ (1,2,4-trisubstituted benzene) for *p*-II, and the failure to evolve all nitrogen on heating is consistent with some azo coupling on carbon.



Such coupling would produce the trifunctional centers necessary for insoluble cross-linked polymer.

Of the three possible structures from self-condensation, diazo coupling on sulfur, diazo coupling on carbon, and diazo displacement by sulfur, it thus appears that

(1) A. Hantsch and H. Freese, *Ber.*, **28**, 3237 (1895).

(2) P. Jacobson, *ibid.*, **21**, 3104 (1888).

(3) J. K. Stille, P. Cassidy, and L. Plummer, *J. Am. Chem. Soc.*, **85**, 1318 (1963); T. Kunitake and C. C. Price, **85**, 761 *ibid.*, (1963).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 64.

(5) S. Tsunawaki and C. C. Price, *J. Polymer Sci.*, in press.

all three are involved in the formation of the polymer. There remains the interesting question as to why the ratio of diazo coupling on sulfur and diazo displacement by sulfur proceed at a ratio so nearly equal to one.

Experiment indicated that three different diazonium salts couple with thiophenol to give the diazosulfide as the only isolated product, although in yields of only about 50%.

$$ArN_2^{\oplus} + C_6H_5S^{\ominus} \longrightarrow ArN{=}NSC_6H_5$$

$$\downarrow \begin{matrix}1.\ \text{reduction}\\ 2.\ \text{oxidation}\end{matrix}$$

$$C_6H_5SSC_6H_5$$

IV. Ar = p-$NO_2C_6H_4$—
V. Ar = p-$NO_2C_6H_4SC_6H_4$—

VI. Ar = O_2N—(2,6-dichlorophenyl)

VII. Ar = p-$C_6H_5SC_6H_4$

In the case of VII, the diazosulfide was isolated only as an oil in 33% yield.

The data suggest to us that the diazo displacement reaction may be favored by electron-donating groups, a view proposed earlier from kinetic studies.[6] Thus dimerization of the initial zwitterion may occur by diazo displacement while subsequent reaction must then occur principally by coupling on sulfur.

$$2\ {}^{\ominus}SC_6H_4N_2^{\oplus} \longrightarrow [{}^{\ominus}SC_6H_4SC_6H_4N_2^{\oplus}) + N_2$$

$$\downarrow$$

II

Experimental

Polymerization of Sulfhydrylbenzene Diazonium Salts.—4-Aminothiophenol (3.13 g.) was diazotized, using 15 ml. of concentrated hydrochloric acid, 1.80 g. of sodium nitrite, 130 ml. of water, and 0.3 g. of urea. After neutralizing by addition of 30 ml. of 25% aqueous sodium acetate and 40 ml. of 4% aqueous sodium hydroxide, the mixture was stirred an additional 5 hr. and heated to 90°. The brown solid was collected by filtration, washed with hot water, and extracted with hot benzene. The red residue weighed 2.4 g. (82%), gradually darkened at 140°, but did not melt up to 300°. The infrared spectrum (KBr) showed absorptions at 670 (w), 810 (s), 870 (vw), 1000 (m), 1060 (m), 1080 (m), 1090 (w), 1160 (s), 1185 (m), 1230 (s), 1270 (w), 1290 (w), 1330 (w), 1380 (w), 1425 (m), 1465 (s), 1490 (m), 1580 (s), 1620 (w), and 3060 (w) cm.$^{-1}$. The residue did not dissolve in hot dimethylformamide, diphenyl ether, or nitrobenzene, although the solvents turned red.

Anal. Calcd. for C_6H_4SN: C, 58.98; H, 3.28; S, 26.24; N, 11.50. Found: C, 58.71; H, 3.82; S, 25.95; N, 11.51.

The red, benzene solution was concentrated and freeze dried to give 0.32 g. of red powder, m.p. 70–80°, mol. wt., 720. The infrared spectrum showed the same absorptions as that of the previous residue.

About 0.1 g. of the residue was heated in a vacuum sublimation flask with a finger type condenser at a fixed temperature for 1 hr. *in vacuo*. After heating at 250°, the residue was a red powder weighing 80.8% of the original weight.

Anal. Calcd. for $(C_6H_4S)_5$ $(C_6H_4SN_2)$: C, 63.87; H, 3.58; S, 23.42; N, 4.13. Found: C, 64.56; H, 3.14; S, 27.93; N, 4.37.

After heating at 150°, the residue was also a red powder weighing 84.2% of the original weight.

Anal. Calcd. for $(C_6H_4S)_4$ $(C_6H_4SN_2)$: C, 63.35; H, 3.57; S, 23.18; N, 4.90. Found: C, 63.80; H, 4.11; S, 27.43; N, 4.65.

The infrared spectra of these residues as potassium bromide disks were poorly resolved but showed absorption at 800, 1000, 1060, 1080, 1170, 1380, and 1460 cm.$^{-1}$, which were all observed in the spectra of poly(phenylene sulfide).[5]

3-Aminothiophenol (3.13 g.) was diazotized and polymerized by the same procedure as described in the previous experiment. The red residue weighed 1.8 g. (67%), gradually darkened above 120°, and softened at 250–290°. The infrared spectrum of this residue as a potassium bromide disk was poorly resolved but the characteristic absorption of 1,3-disubstituted benzenes was observed at 770 cm.$^{-1}$.

Anal. Calcd. for C_6H_4SN: C, 58.98; H, 3.78; S, 26.24; N, 11.50. Found: C, 58.83; H, 3.30; S, 26.19; N, 11.64.

The red extract was concentrated and freeze dried but gave only 0.01 g. of red paste.

Preparation of Diazosulfides. (a) **4-Nitrophenyldiazothiobenzene.**—4-Nitroaniline (13.8 g.) was diazotized, using 30 ml. of concentrated hydrochloric acid, 300 ml. of water, and 7.6 g. of sodium nitrite. After adding to a solution of 12.1 g. of thiophenol in 120 ml. of 5% sodium hydroxide, the yellow solid was collected by filtration and recrystallized twice from ethanol to give pink leaflets (12.2 g., 48%), m.p. 94–95° (lit.[1] m.p. 96–97°); $\lambda_{max}^{ethanol}$ (log ϵ); 223 mμ (4.00), 267 mμ (3.97), and 348 mμ (3.96).

Anal. Calcd. for $C_{12}H_9N_3O_2S$: C, 55.60; H, 3.49; S, 12.37; N, 16.20; mol. wt., 259.2. Found: C, 55.66; H, 3.73; S, 12.18; N, 15.89; mol. wt., 247.

The infrared spectrum (in KBr) showed peaks at 630 (w), 680 (s), 695 (w), 840 (vs), 860 (m), 975 (s), 1010 (w), 1060 (w), 1090 (m), 1100 (m), 1140 (w), 1305 (m), 1340 (vs), 1360 (w), 1390 (m), 1420 (s), 1430 (m), 1465 (m), 1510 (vs), 1575 (m), 1590 (m), and 3100 (w) cm.$^{-1}$.

Treating an alcoholic solution of the compound with sodium dithionate and then oxidizing with hydrogen peroxide gave a yellow solid which, after recrystallization from methanol, yielded white needles, m.p. 60–61°, undepressed on admixture with authentic diphenyl disulfide (m.p. 60–61°).

(b) **4-(4-Nitrophenylthio)phenyldiazothiobenzene**, m.p. 102° (dec.), was prepared in 49% (1.8 g.) yield, from 4-amino-4′-nitrodiphenyl sulfide (2.46 g.) by the same procedure as described.

Anal. Calcd. for $C_{18}H_{13}N_3O_2S_2$: C, 58.82; H, 3.57; N, 11.44; S, 17.46; mol. wt., 367.4. Found: C, 58.90; H, 3.62; N, 11.29; S, 17.41; mol. wt., 381.

The ultraviolet spectrum in ethanol solution showed λ_{max} (log ϵ) 213 (3.15), 238 (4.15) and 344 mμ (4.14). The infrared spectrum (in KBr) showed peaks at 685 (m), 700 (w), 740 (s), 760 (m), 830 (s), 845 (s), 1000 (m), 1020 (w), 1060 (w), 1075 (s), 1090 (w), 1110 (s), 1155 (w), 1170 (w), 1270 (w), 1330 (vs), 1360 (w), 1390 (w), 1420 (w), 1435 (m), 1470 (m), 1500 (s), 1570 (s), and 1585 (m) cm.$^{-1}$.

Reduction with sodium dithionate and then oxidation gave diphenyl disulfide.

(c) **4-Phenylthiophenyldiazothiobenzene**, a pink oil at 0°, mol. wt., 330 (theory 322.5), was prepared in 33% (5.2 g.) yield from 10.0 g. of 4-aminodiphenyl sulfide, keeping always under 0°. The ultraviolet spectrum in ethanol solution showed λ_{max} (log ϵ) 210 (4.47), 243 (4.42), and 354 mμ (4.25).

(d) **2,6-Dichloro-4-nitrophenyldiazothiobenzene.**—2,6-Dichloro-4-nitroaniline (2.07 g.) was diazotized, according to the procedure of Schoutissen[7] and added to a cold solution of thiophenol (1.2 g.) in 200 ml. of 4% aqueous sodium hydroxide. The mixture was extracted with cold ether. The ether was added to methanol and cooled in Dry Ice to give a yellow precipitate. After reprecipitating in the same way, recrystallization from ethanol gave pink needles (1.8 g., 55%), m.p. 75–76°.

Anal. Calcd. for $C_{12}H_7Cl_2N_3O_2S$: C, 43.93; H, 2.11; Cl, 21.61; N, 12.82; S, 9.77; mol. wt., 328.2. Found: C, 43.85; H, 2.12; Cl, 21.51; N, 12.70; S, 9.75; mol. wt., 330.

The ultraviolet spectrum in ethanol solution showed λ_{max} (log ϵ) 223 (4.10) and 317 mμ (3.91). The infrared spectrum (in KBr) had peaks at 680 (m), 695 (w), 705 (w), 735 (m), 740 (vw), 775 (s), 800 (m), 860 (w), 885 (m), 910 (m), 1015 (w), 1060 (m), 1140 (m), 1150 (m), 1180 (m), 1200 (m), 1270 (w), 1340 (vs), 1355 (w), 1380 (m), 1430 (m), 1440 (s), 1465 (m), 1500 (m), 1520 (s), 1570 (m), and 3090 (m) cm.$^{-1}$.

Treatment with sodium dithionate and then hydrogen peroxide also gave diphenyl disulfide.

(6) M. L. Crossley, R. H. Kienle, and C. H. Benbrook, *J. Am. Chem. Soc.*, **62**, 1400 (1940).

(7) H. A. J. Schoutissen, *J. Am. Chem. Soc.*, **55**, 4531 (1933).

Stereospecific Tautomerism in a 1,2-Dihydropyridine. A β-Benzomorphan Synthesis

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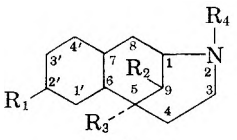
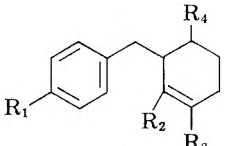
Bond tautomerism of 2-benzyl-1,3,4-trimethyl-1,2-dihydropyridine salts, controlled by salt form and solvent conditions, leads to *cis*- and *trans*-forms of 2-benzyl-1,3,4-trimethyl-2,3-dihydropyridinium salts which were used for stereospecific benzomorphan syntheses. A novel benzyl-migration is also described.

The configuration of the alkyl groups at position 9 of benzomorphans significantly affects the analgesic potency of these substances.[1] The more desirable *trans*- or β-form (I) is usually the lesser isomer in the Grewe syntheses,[2] where starting materials are Δ^3-tetrahydropyridines (II).



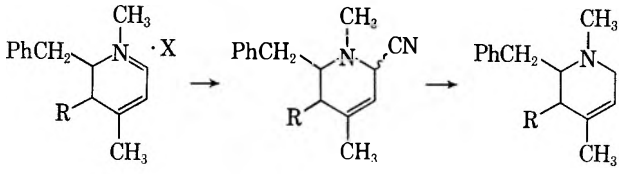
I



II

R_1 = H, -OH, -OCH_3
R_3, R_4 = -alkyl
R_2 = -H, -alkyl

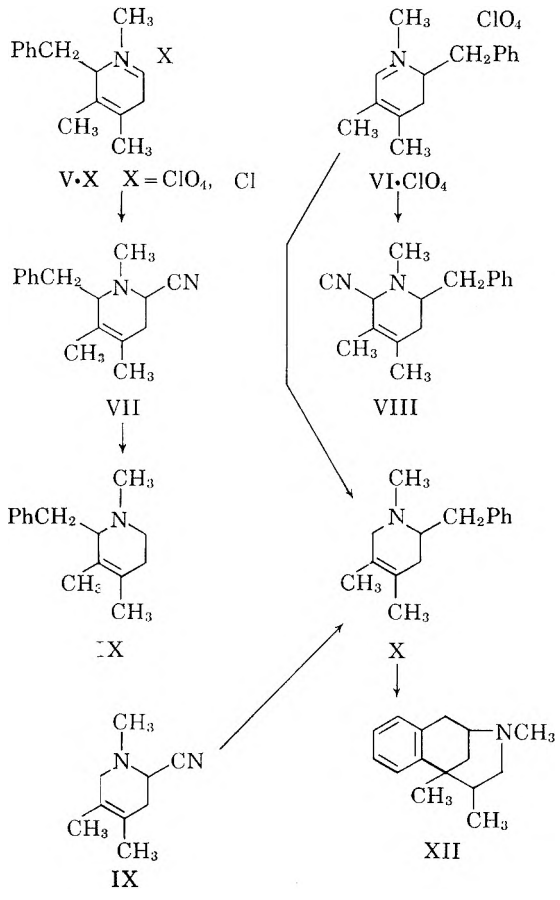
The desirability of having an intermediate which would undergo stereospecific ring closure to the β-benzomorphan prompted this investigation, and to this end the Δ^4-*cis* and Δ^4-*trans* isomers of 2-benzyl-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine (IV) were prepared by way of the corresponding imminium dienes (III). Migration of the benzyl group from position 2 to position 6 of the dihydropyridine ring also is described.



III·X III·CN IV

R = *cis*- or *trans*-CH_3
X = ClO_4, Cl

The crystalline perchlorate obtained from the reaction of the benzyl Grignard reagent with 1,3,4-trimethylpyridinium bromide proved to be a mixture of V-perchlorate and its isomer VI-perchlorate. The isomers could be cleanly separated by way of the salts of the cyano derivatives VII and VIII. Reduction with sodium borohydride gave IX and X and both oils were characterized through crystalline picrates. The structure of IX has been determined[3] and that of its precursor V-perchlorate is assigned by reason of the lack of a maximum in its ultraviolet absorption above 220 mμ. The structure of X is based on the degradation of its derived benzomorphan (XII) to 1-methylnaphthalene and on its n.m.r. spectrum which showed no vinylic hydrogen. It (X) was also synthesized by the action of the benzyl Grignard reagent on the cyano



V·X X = ClO_4, Cl
VI·ClO_4
VII
VIII
IX
X
XII

compound XI.[4] The structure of VI-perchlorate follows from its ultraviolet absorption maximum at 307 mμ (ε 4500), and from its lack of an ammonium band at *ca.* 4 μ in the infrared.[5]

The absence of a maximum in the ultraviolet absorption of V applies only to the salt freshly formed by acidifying a solution of the base. A freshly prepared solution of the perchlorate showed developing maxima at 265–270 mμ and at 300 mμ, thereby giving clear testimony to its instability in solution.[6,7] Attempts were made to force this transformation, and it was

(1) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

(2) R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949).

(3) E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).

(4) This compound is representative of a class of tetrahydropyridine derivatives not yet in the literature. This type compound is obtained readily by the action of sodium borohydride on a pyridinium salt in the presence of cyanide ion and will be the subject of a later report.

(5) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

(6) Previous work on double-bond mobilities in dihydropyridines has been limited to examples of 1,2- and 1,4-dihydropyridines substituted on the 3-position by groups capable of resonance interaction with ring unsaturation. The results were not useful in the present work. (a) K. Wallenfels, H. Schüly, and D. Hofmann, *Ann.*, **621**, 106 (1959). (b) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960, 2571 (1959). (c) W. Traber and P. Karrer, *ibid.*, **41**, 2066 (1958).

(7) Nucleophilic adducts have not been observed in the course of this work. However, see K. Wallenfels, H. Schüly, and D. Hofmann, *Ann.*, **621**, 188 (1959); A. G. Anderson and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958); ref. 6b.

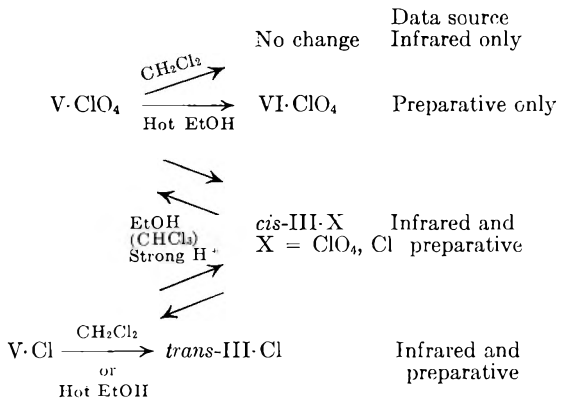


Figure 1

found that, by heating an alcohol solution of V-perchlorate for an hour under reflux, a 28% rearrangement to VI-perchlorate could be achieved. The remainder of the material was an oil with properties of a quaternary salt; it remains unidentified. The forcing conditions necessary to effect this isomerization rule out the possibility that VI-perchlorate originally isolated from the Grignard product was derived from V-perchlorate in the work-up. This unexpected and unwanted rearrangement was suppressed in strongly acid solutions, and was not that giving rise to the 300-mμ absorption mentioned.

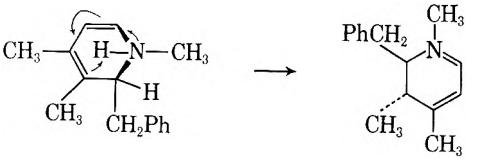
This latter material formed readily at room temperature, and was separated from unchanged V-perchlorate by way of the cyano derivatives,[8] crystalline VII-hydrobromide being separated from the unknown oily hydrobromide which was then transformed into a perchlorate. In this state it spontaneously lost hydrogen cyanide to give a crystalline perchlorate isomeric with V-perchlorate. The new salt had a maximum in the ultraviolet at 298 mμ (ε 4200). It easily reverted to starting material in solution and never amounted to more than 30% in an equilibrated acid solution. Reduction of the perchlorate gave a new tetrahydro isomer which readily isomerized in IX in hot hydrobromic acid, and which showed two C-methyl groups and one vinylic hydrogen. It gave the known benzomorphan,[9] isolated as the methiodide in 67% yield, on ring closure. Comparison of the benzomorphan with its β isomer (see text following) put its configuration on a firm basis and permitted assignment of the *cis* structure to the precursor diene (*cis* III-perchlorate).

When a hydrochloric acid solution of the V-chloride–*cis*-III-hydrochloride mixture was layered with chloroform and refluxed, the nature of the bond rearrangements was profoundly altered. By the action of sodium cyanide on the resulting salt, a crystalline base was obtained in 70% yield. An acid-induced loss of hydrogen cyanide was followed by formation of a crystalline perchlorate isomeric with V-perchlorate. It showed a maximum absorption in the ultraviolet at 282 mμ (ε 5800). Its reduction gave a tetrahydro derivative which showed vinylic hydrogen and two C-methyl groups by n.m.r. spectra and which readily isomerized to IX in hot hydrobromic acid. Ring closure of the hydrochloride with aluminum chloride gave an 82% recovery of a benzomorphan, the structure of which was confirmed by degradation to 1,2-dimethylnaphthalene.[9] On the basis of the rate of methiodide formation[1] relative to that of the previously obtained isomer, it was assigned the β configuration. Thus the rearrangement of the hydrochloride under these conditions yielded *trans*-III-chloride. In contrast to *cis*-III-chloride, *trans*-III-chloride is stable in acid solution and a return to V-chloride could not be effected.

The experimental evidence cited so far has included only as much as was necessary for describing the conditions of the three rearrangements and identification of the compounds involved. The relationships shown in Fig. 1 are taken in part from infrared data, and repeat what has been described except for calling attention to the differences in the behavior of V-perchlorate and V-chloride. As can be seen, the perchlorate is stable in the aprotic solvent methylene chloride, but isomerizes in the presence of a proton source, namely the alcohol usually present in chloroform, to the extent of 0.75%.

In like manner *cis*-III-perchlorate is stable in methylene chloride, but reverts to V-perchlorate in chloroform–0.75% ethanol. The equilibrium is thus approached from both sides, and the infrared diagrams become equivalent. The chloride of V, on the other hand, shows only as transients those bands at 5.86 and 5.96 μ, which characterize V-perchlorate. Within an hour, bands at 6.01 and 6.26 μ characteristic of *trans*-III-chloride become dominant. Even in the hot alcohol solution which promoted the V-perchlorate to VI-perchlorate isomerization, V-chloride again yields *trans*-III-chloride.

The key to these differences probably lies in the absorption, or lack of it, in the 4-μ region of the infrared.[5] The perchlorate of V lacks absorption in this region, whereas V-chloride has a broad band at 4.0–4.3 μ. If, on the basis of the ammonium bands, V-chloride is partly thus,



III

with *trans* arrangement of benzyl and N-methyl groups, a 1,5-hydrogen transfer[10] would account for the formation of *trans*-III. In the case of the immonium salt, V-perchlorate, or with V-chloride in a strongly acid solution where the immonium structure might be favored, an equilibrium between Δ^3 and Δ^4 is obviously not only easily achieved, but strongly favors the *cis* arrangement for the alkyl groups; the most obvious implication is that the benzyl group inhibits the approach of the proton donor to the sterically less favored position.

The bases of the salts which have been described can be obtained by decomposition of the salts with strong alkali, but insufficient base or even a trace of weak base in suspensions of V-perchlorate or VI-perchlorate in alcohol yields the corresponding pyridinium and tetra-

(8) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(9) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

(10) A six-center concept has been used to explain the thermal isomerization of 1,3-dienes. J. Wolinsky, B. Chollar, and M. D. Baird, *J. Am. Chem. Soc.*, **84**, 2775 (1962). G. Büchi and E. M. Burgess, *ibid.*, **84**, 3104 (1962).

hydropyridine salts.[11] The identities of the former follow from their quaternary nature, analytical values, and absorption characteristics. Heating in alcohol solution alone is enough to cause disproportionation of VI-perchlorate.

A prediction based on the relative stabilities of the carbanions[12] would favor initial formation of the *exo–endo* diene from VI-salts and from the *cis*- and *trans*-III-salts. In fact only *trans*-III-base was clearly *exo–endo* as shown by its n.m.r. spectrum, with four vinylic hydrogens and one C-methyl group. The other two bases were mixtures, as shown by comparison of their infrared data with those of the bases, V and *trans*-III. The relevant data are given in Fig. 2.

Bases V and VI were recovered unchanged from ethereal solutions of lithium aluminum chloride, but *trans*-III was reduced to *trans*-IV in 71% yield under these conditions. Reduction by hydride reagent in solvents incapable of supplying the proton necessary to form the immonium ion appears anomalous. (The possibility of a pseudobase appears ruled out by the absence of 2.7–2.8-μ absorption.) Compounds V and VI were readily reduced by sodium borohydride in alcohol to give IX and X, respectively. It will be noted that in two of these examples, *trans*-III and VI, the reduction must have occurred after migration of both bonds and raises the question of a possible concerted tautomerism. It is interesting that the single bond shift implicit for V in the basic reduction medium, can also be observed on acidification of a solution of the base (disappearance of ultraviolet maxima), whereas development of salt maxima are rapid in the other two cases, *trans*-III and VI, where concerted migration in basic media is suspected. Analogous systems provide examples of stepwise,[13] or possibly concerted[6b] bond migrations, and Opitz and Merz[14] give an example of initial N-protonation, followed by two probable stepwise bond shifts.[15]

The successful use of cyanide ion[4] as a competitor nucleophile in hydride reductions may eventually yield more information, and another potentially useful approach was initiated by Lyle, Nelson, and Anderson[16] in the use of deuterium to mark the nucleophilic site on the dihydropyridine ring. But because of the possibility of bond shifts due to proton abstraction, both methods seem limited to disproving an apparently concerted diene tautomerism.

Experimental

Microanalyses are by the Analytical Services Unit of this laboratory, Harold McCann, director. N.m.r. spectra, 60 Mc., are with tetramethylsilane as internal reference standard; τ values are averaged; integrated benzene areas were used as standards. Ultraviolet spectra are by a Cary recording spectrophotometer, Model 14, and infrared spectra are by a Perkin-Elmer Infracord, Model 137. Melting points are uncorrected.

(11) For disproportionation of a Hantzsch base see O. Mumm, *Ann.*, **529**, 115 (1937); O. Mumm and J. Diederichsen, *ibid.*, **538**, 195 (1939).

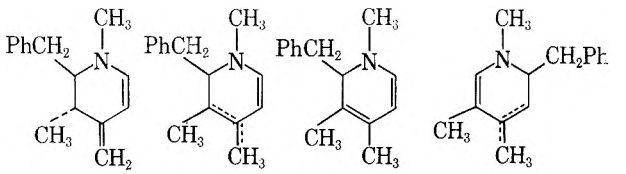
(12) See A. Schriesheim and C. A. Rowe, Jr., *J. Am. Chem. Soc.*, **84**, 3160 (1962).

(13) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *ibid.*, **78**, 430 (1956); W. S. Johnson, V. J. Bauer, and R. W. Frank, *Tetrahedron Letters*, 72 (1961).

(14) G. Opitz and W. Merz, *Ann.*, **652**, 139 (1962).

(15) For other examples of C- and N-protonation see R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962), and references therein.

(16) R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Tetrahedron Letters*, (13) 553 (1962).



trans-III	*cis*-III	V	VI
302 (14200)	282 (4600)	275 (4100)	
	300–315 (4400)	325 (3800)	312 (3600)
6.17 (s)	6.06 (s)	6.05 (s)	6.04 (s)
	6.18 (m)		6.14 (m)
6.25 (sh)	6.32 (s), 6.24 (sh)	6.32 (s), 6.23 (sh)	6.32 (s), 6.24 (sh)

Fig. 2. Ultraviolet maxima, mμ (ε). Infrared μ, (s)trong, (m)edium, (sh)oulder.

Mixture of 2-Benzyl-1,3,4-trimethyl-2,5-dihydropyridinium (V) and 6-Benzyl-1,3,4-trimethyl-5,6-dihydropyridinium (VI) Perchlorates.—The Grignard reagent from 64 ml. (0.56 mole) of benzyl chloride in 500 ml. of ether solution was added to 68 g. (0.34 mole) of N-methyl-3,4-lutidinium bromide, previously layered with ether, and the suspension stirred for 1 hr. The grey adduct no longer showed a yellow spot on mashing with a stirring rod. The suspension was poured onto a mixture of 105 ml. of 60% perchloric acid and ice while agitating vigorously. The salt partly crystallized, and the ether was decanted and crystallization aided by triturating the oily solid several times with 30–60° petroleum ether. It was recovered by filtering through a sintered-glass funnel, washing twice with water, and twice with chloroform. After drying overnight, it was again washed twice with chloroform. The solid weighed 62 g. and melted at 150–154°. From the aqueous acid–chloroform mother liquors, another 12 g. was obtained, m.p. 130–180°. The total crystalline yield was 70%. The main fraction could not be completely freed of the isomer (infrared evidence) by recrystallization from acetic acid, and the melting point was variable. The analytical sample melted at 143–146°.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.45; H, 6.37.

6-Benzyl-1,3,4-trimethyl-5,6-dihydropyridinium perchlorate (VI·ClO$_4$) was readily obtained from the lesser fraction by recrystallization from acetic acid. It melted at 196–199° with a slight sinter at 193°. Ultraviolet data for this salt was obtained by dissolving the sample in a little alcohol containing a drop of 60% perchloric acid, λ_{max} 307 mμ (ε 4500); λ_{min} 235 mμ (ε1100). Without acid, absorption at 275 mμ was evident. Disproportionation evidence is presented (p. 1872). Infrared bands (μ) in Nujol were at 5.96 (m), 6.26 (s), 8.09 (m), and 8.36 (m). The last two peaks were valuable in detecting this compound in mixtures.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.55; H, 6.35.

Base from VI-perchlorate was obtained as an oil from the action of sodium hydroxide in dilute alcohol and was recovered from ether. In an ethereal solution it was held for 30 min. with lithium aluminum hydride, recovered, and converted back to the perchlorate for a 60% recovery. The neat oil showed an infrared (μ) pattern of peaks 6.04 (s), 6.14 (m), 6.24 (sh), 6.32 (s) which varied with different samples and, together with n.m.r. results, indicates a mixture. In ethanol, λ_{max} 312 mμ (ε3600); λ_{min} 245 mμ (ε 2800).

N.m.r. data: 4.25 τ (=CH—) 0.7H; 5.2 τ (=CH—) 0.7H; 8.25 τ [=C(CH$_3$)—C(CH$_3$)=] 5.5H.

A sample of the cyano derivative made from the perchlorate was found to be an oil; hence there is no question of contamination of the cyano base described next.

2-Benzyl-6-cyano-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (VII).—To 31.8 g. of crude VII-perchlorate, wet with water and layered with ether, was added a solution of 7.5 g. (1.5 × theory) of sodium cyanide dissolved in 35 ml. of water. The solid disappeared on shaking. Hydrogen chloride was passed into the ethereal solution with precipitation of an oil which crystallized. Instability precluded solution in a hot solvent. It was purified by triturating in acetone, wt., 24.9 g. (89%), m.p. (rapid heating) 119–121° (gas). The oil from the acetone filtrate yielded 0.92 g. (2.9%) of VI-perchlorate.

Anal. Calcd. for $C_{16}H_{21}N_2Cl$; C, 69.42; H, 7.65. Found: C, 69.55; H, 7.56.

The weakness of the cyano base is shown by dissociation of the salt in aqueous solution yielding the free base. The base was obtained solid from ether solution and was purified by recrystallization from petroleum ether (30–60°). It melted at 59.5–62°.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 80.06; H, 9.03; N, 11.69.

In ethanolic solution at room temperature the hydrochloride rapidly underwent change. Ultraviolet absorption at 262 mμ increased to a maximum value, ε 4400, in 20 min. The base showed no peak above 220 mμ except for benzene peaks at about 260 mμ (ε 500).

2-Benzyl-1,3,4-trimethyl-1,2-dihydropyridine (V) and Its Perchlorate (V·ClO$_4$).—(The cyano group was eliminated without accompanying tautomerism by means of stannic chloride. The crystalline tin salt was not characterized.) The hydrochloride of VII, 0.26 g., partly dissolved in 4 ml. of dilute alcohol, was treated with 0.2 ml. of stannic chloride. The tin salt separated from the solution crystalline, m.p. 157–159°. It was converted to the base with sodium hydroxide and the base recovered with ether. Infrared bands (μ) for the neat oil were at 6.05 (s), 6.23 (sh), 6.32 (s). Conversion to the perchlorate gave a salt which, in Nujol mull or chloroform, showed no absorption at about 4 μ, with bands at 5.86 and 5.96 μ, with only weak absorption at 6.25 μ, and no maxima in 8.0–8.4-μ region (Nujol mull). These were the criteria used in establishing the absence of its isomers. The perchlorate, dissolved in ethanol acidified with perchloric acid, showed only benzene maxima above 220 mμ. Made alkaline with sodium hydroxide, the solution showed two peaks in ultraviolet, λ_{max} 275 mμ (ε 4100), 325 (3800); λ_{min} 240 (3000), 302 (3100).[17] Reacidification gave back the original curve. When the perchlorate was dissolved in ethanol, absorption at 268 mμ rose to a constant value, ε 4500, in 2 hr. at room temperature. The perchlorate was recovered (93%) from base held for 8 min. in ethereal lithium aluminum hydride solution.

Rearrangement of 2-Benzyl-1,3,4-trimethyl-2,5-dihydropyridinium (V) Perchlorate to 6-Benzyl-1,3,4-trimethyl-5,6-dihydropyridinium (VI) Perchlorate.—2-Benzyl-6-cyano-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (VII) hydrochloride (1.0 g.) was converted to the base and thence to the perchlorate. (This crystalline material was blank in the 6-μ region, hence still retained the cyano group, but subsequent attempts to make it showed the characteristic absorption of the dihydro salt.) It was dissolved in 1.0 ml. of 95% ethanol and 0.05 ml. of acetic acid and the solution refluxed for 1.5 hr. The solution yielded 0.33 g. of crystals melting at 165–185°. Recrystallized from acetic acid, it weighed 0.26 g. (28%) and melted at 185–191°. The infrared diagram and a mixture melting point established its identity. The remainder of the material was principally a quaternary salt which in alcohol absorbed at 265–270 mμ.

2-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (IX) has been obtained in 72% yield by the action of sodium borohydride on a solution of V in alcohol, in 78% yield by a similar reduction of VII, and in 71% yield by reduction of V-perchlorate with lithium aluminum hydride. All yields are as the picrate which has been reported.[3]

6-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (X). A.—This compound was obtained by the action of lithium aluminum hydride on a suspension of VI-perchlorate in ether in 85% yield, and by sodium borohydride reduction of its derived base in alcohol in 73% yield. Both yields are as the picrate salt which was purified from alcohol, m.p. 130–132°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.73; H, 5.21.

N.m.r. data: No absorption in the 4–6-τ region; 8.45 τ [—C(CH$_3$)=C(CH$_3$)—] 6H.

B.—The cyano compound, obtained by action of sodium borohydride and cyanide ion on 3,4-lutidine methiodide, reacted with the benzyl Grignard reagent to yield an oil which gave a picrate. By means of mixture melting point and infrared diagram of the derived base, it was found to be identical to the previously described X-picrate.

Disproportionations. A.—2-Benzyl-1,3,4-trimethyl-2,5-dihydropyridinium (V) perchlorate, 0.5 g. (0.0016 mole), in 0.5 ml. of 95% alcohol and 0.005 g. (0.00025 equiv.) of magnesium oxide on heating gave a solution which was boiled for 10 min. The solvent was removed and the remaining oil shaken with aqueous sodium carbonate solution and ether. The oil from the ether was converted to 0.14 g. of picrate, identified by mixture melting point and the infrared diagram of the derived base as the tetrahydro compound IX. The material unaffected by base crystallized. Purified from alcohol, it weighed 0.16 g. (64%), m.p. 113–115°. In ethanol solution, it showed a maximum at 275 mμ (ε 8000), unchanged by alkali. A Nujol mull had bands (μ) at 6.17 (s) and 6.35 (m).

Anal. Calcd. for $C_{15}H_{18}ClNO_4$: C, 57.78; H, 5.82. Found: C, 57.65; H, 5.88. On this evidence the compound is **2-benzyl-1,3,4-trimethylpyridinium perchlorate.**

B.—6-Benzyl-1,3,4-trimethyl-5,6-dihydropyridinium (VI) perchlorate, 0.5 g. in 1.5 ml. of 95% ethanol, and 0.005 g. of magnesium oxide was boiled for 15 min. On cooling the solution, crystals separated, wt., 0.24 g. (97%), m.p. 193–197°. Recrystallized, it melted at 195–197°. It had λ_{max}^{EtOH} 272 mμ (ε 6700). On making the solution alkaline, this peak was not affected but broad absorption appeared at 355 mμ (ε 1100). Bands (μ) in a Nujol mull were at 6.11 (s) and at 6.24 (m).

Anal. Calcd. for $C_{15}H_{18}ClNO_4$: C, 57.78; H, 5.82. Found: C, 57.64; H, 5.80. This evidence identifies this compound as **6-benzyl-1,3,4-trimethylpyridinium perchlorate.**

Alcohol was removed from the preceding filtrate; the remaining oil decomposed with sodium carbonate as before. The base yielded a picrate, wt., 0.29 g. (82%), m.p. 128–130°. By mixture melting point it was proved to be identical with the sample of X-picrate described earlier. Disproportionation (about 10%) also resulted from refluxing an alcohol solution of VI-perchlorate for 3 hr.

Rearrangements Using 2-Benzyl-6-cyano-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (VII) Hydrochloride.—The facile loss of hydrogen cyanide made use of this compound equivalent to that of its parent V-salt in acid solution.

A. ***cis*-2-Benzyl-1,3,4-trimethyl-2,3-dihydropyridinium (III) Perchlorate.**—The hydrochloride of VII, 3.0 g., dissolved on heating in 27 ml. of 2.2 *N* hydrochloric acid; the solution was boiled for 6 min. with loss of hydrogen cyanide. The yellow solution was chilled to 7° and an equally cold solution of 4.0 g. of sodium cyanide in 20 ml. of water was added rapidly. The yellow color vanished and an oil separated. The oil was taken into ether and the solution shaken with 1.8 ml. of 8.8 *N* hydrobromic acid. The crystalline hydrobromide of VII separated. After filtering, washing with 3 ml. of water, and drying under reduced pressure, it weighed 2.2 g. (63%), m.p. 138–140° (gas). Identity was established by reconversion to VII.

Anal. Calcd. for $C_{16}H_{21}N_2Br$: C, 59.82; H, 6.59. Found: C, 59.75; H, 6.43.

Sodium cyanide, 1.0 g., in 4 ml. of cold water was then added to the cold filtrate and the separated oil (*cis*-III·CN) shaken into ether. It was recovered by removing the ether under reduced pressure, taken up in petroleum ether (30–60°) to remove aqueous material, and recovered again under reduced pressure. The yellow cyano derivative weighed 0.85 g. (33%). It was converted to the perchlorate by triturating with 0.6 ml. of 60% perchloric acid and then adding water. Hydrogen cyanide was lost and the salt crystallized. It was washed with water, dried, and washed with acetic acid to remove a little color, wt., 0.9 g. (26% over-all), m.p. 118–125°. In ethanol containing perchloric acid, λ_{max} 298 mμ (ε 4400); λ_{min} 235 mμ (ε1300). Infrared bands (μ) in Nujol at 6.01 (s), 6.29 (s), and 8.18 (m). A weak band at 5.86 μ is due to V-perchlorate and is increased by recrystallization from acetic acid or from alcohol.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.36; H, 6.65.

Lithium aluminum hydride reduction of residual perchlorate of this rearrangement yielded all four tetrahydro isomers, IX, *cis*-IV, X, and *trans*-IV, the latter being in trace amount. Identification was by v.p.c. The base from ***cis*-III-perchlorate** appeared in the infrared to be principally V. The neat oil showed bands (μ) at 6.06 (s), 6.18 (m), 6.24 (sh), and 6.32 (s). A return to the perchlorate gave back V-perchlorate.

B. **2-Benzyl-6-cyano-1,3,4-trimethyl-1,2,3,4-tetrahydropyridine (*trans*-III·CN).**—Two grams of VII-hydrochloride in 8 ml. of 6 *N* hydrochloric acid layered with 16 ml. of chloroform was heated to the reflux temperature of the chloroform layer, with solution of the solid and loss of hydrogen cyanide. After refluxing for 4 hr., the chloroform was distilled from the pale yellow acid solution. Reduced to a small volume under reduced pressure, a little ammonium chloride separated. Sodium cyanide, 0.9 g. in 7 ml. of cold water, was added to the chilled oil and

(17) Extensive use has been made of the double peak characteristic of 1,2-dihydropyridines as opposed to the single band shown by the 1,4-isomers, ref. 6a,c. Cross conjugation involving the 3-substituent has been considered, ref. 6b, but this explanation is obviously not relevant here.

triturated, with formation of the solid product which was dissolved in ether. After removing ether under reduced pressure, the crystalline product was filtered from cold alcohol. It weighed 1.23 g. (70.5%) and melted at 88–90°.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 80.15; H, 8.64; N, 11.80.

To the alcohol filtrate was added dilute perchloric acid with recovery of 0.42 g. (19%) of crystalline material. The infrared diagram showed a mixture of VI- and V-perchlorates.

One gram of VII-hydrochloride was heated in 1.0 ml. of 95% ethanol and 0.05 ml. of acetic acid. These are conditions for rearranging V-perchlorate to VI-perchlorate, but none of the latter could be recovered. Instead, a 32% yield of the previous cyano derivative resulted from the action of sodium cyanide on the solution. The oily portion was converted to an oily perchlorate which showed loss of cyanide (strong absorption in the 6-μ region) but no bands at 8.09 and 8.36 μ characteristic of VI-perchlorate.

trans-2-Benzyl-1,3,4-trimethyl-2,3-dihydropyridinium (*trans*-III) Perchlorate.—The previously described cyano compound, 0.51 g., was treated with 1.1 ml. of 2.2 *N* hydrochloric acid with formation of another crystalline material, probably the salt. It dissolved over the next 12 min., accompanied by liberation of hydrogen cyanide (vapor test with alkaline sodium picrate solution) and a lowering of the solution temperature. After an additional 20 min., the addition of 0.3 ml. of 60% perchloric acid gave an oil which crystallized, wt., 0.62 g. (93%), m.p. 115–118°. Recrystallized from alcohol, it melted at 116–118°. In ethanol it showed λ_{max} 282 mμ (5800); λ_{min} 230 mμ (ε1600). Infrared maxima (μ) in Nujol were at 6.00 (m), 6.26 (s), and 8.26 (m).

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.50; H, 6.36.

N.m.r. data: 1.65 τ [—N(CH₃)=CH—] 1H; 7.9 τ [—C(CH₃)=] 3H; 9.9 τ [—CH(CH₃)—] 3H. The perchlorate was recovered (90%) after refluxing in alcohol–acetic acid; neither the condition of the V-perchlorate–VI-perchlorate rearrangement nor did heating the hydrochloride salt in hydrochloric acid under conditions of the V-chloride–*cis*-III-chloride rearrangement result in change. The perchlorate likewise showed no rearrangement in chloroform.

Spectroscopic Evidence of the Formation of *trans*-III-Chloride from V-Chloride.—The hydrochloride made by passing hydrogen chloride into a methylene chloride solution of V showed the 5.86-μ, 5.96-μ double peaks characteristic of V-perchlorate, as well as 6.26-μ absorption with a broad band at about 4.2 μ. In an hour at room temperature peaks at 6.00 and 6.26 μ, characteristic of *trans*-III-chloride, were dominant with the 4.2-μ absorption still present. The addition of perchloric acid resulted in elimination of the 4.2-μ absorption and appearance of a peak at 3.6 μ, which was found by means of a blank to be due to hydrogen chloride. Positive identification was made by means of the crystalline cyano derivative but recovery was poor. The oily hydrochloride made from *trans*-III-base also showed absorption in the 4.2-μ region. The neat oil did *not* show absorption in this region.

Spectroscopic Evidence for the V-Perchlorate–*cis*-III-Perchlorate Tautomerism.—A solution of V-perchlorate in chloroform (alcohol stabilized) showed development of 6.01- and 6.29-μ bands, reaching an equilibrium with the original 5.86- and 5.96-μ bands in about 4 hr. This same equilibrium was reached by development of the 5.86- and 5.96-μ bands in a chloroform solution of *cis*-III-perchlorate in approximately the same time. In methylene chloride this equilibration was not observed.

trans-2-Benzyl-1,3-dimethyl-4-methylene-1,2,3,4-tetrahydropyridine (*trans*-III) was obtained as an oil by the action of sodium hydroxide on *trans*-III-perchlorate. In ethanol, λ_{max} 302 mμ (ε14,200); λ_{min} 255 mμ (ε3300). Infrared maxima (neat) (μ) at 6.17 (s), and 6.25 (sh).

N.m.r. data: 4.15 τ (—CH=) 1H; 5.05 τ (—CH=) 1H; 5.40 τ, 5.65 τ (=CH₂) 2H.

trans-2-Benzyl-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine (*trans*-IV).—Sodium borohydride, 0.58 g., was added to a cold suspension of 2.7 g. of 2-benzyl-6-cyano-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine with vigorous gas evolution. The temperature was maintained below 23°. After 2 hr. the suspension was chilled and 10 ml. of 3 *N* hydrochloric acid added portionwise with gas evolution. The solid in suspension successively became an oil, solidified, and dissolved. The acid solution was heated briefly to 50°. The solvent was removed under reduced pressure, sodium carbonate solution added, and the base taken into ether. The crystalline salt separated as hydrogen bromide was passed into the ethereal solution; it was washed with acetone, wt., 2.7 g. (81%), m.p. 191–197°. Recrystallized from alcohol it melted at 198–199°.

Anal. Calcd. for $C_{15}H_{22}NBr$: C, 60.81; H, 7.49. Found: C, 60.70; H, 7.31.

This hydrobromide was also recovered in 88% yield by the action of lithium aluminum hydride on *trans*-III-perchlorate, and in 71% yield by the action of lithium aluminum hydride on *trans*-III in ether solution. The picrate was made and purified from alcohol. It melted at 114–116°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.60; H, 5.68.

N.m.r. data: 4.6 τ [—C(CH₃)=CH—] 1H; 8.2 τ [—C(CH₃)=] 3H; 8.6 τ [—CH(CH₃)—] 3H.

cis-2-Benzyl-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine (*cis*-IV).—The perchlorate of *cis*-III, 1.3 g., was added to a cold solution of 0.2 g. of lithium aluminum hydride in 11 ml. of ether. The solid rapidly dissolved. After decomposition of the excess reagent with ethyl acetate–water, the solution of the base in ether was shaken with 0.48 ml. (1 × theory) of 8.8 *N* hydrobromic acid. The oil which separated was freed of water under reduced pressure, dissolved in absolute ethanol, and again freed of solvent. The salt was recovered crystalline from acetone–ether. A second crop brought the weight to 0.73 g. (58%). Purified by adding ether to a solution in absolute ethanol, it melted 170–171°. The same material was obtained by the action of sodium borohydride on the oily cyano derivative (*cis*-III-CN).

Anal. Calcd. for $C_{15}H_{22}NBr$: C, 60.81; H, 7.49. Found: C, 60.93; H, 7.57.

N.m.r. data: 4.7 τ (=CH—) 1H; 8.3 τ [—C(CH₃)=] 3H; 8.65 τ [—CH(CH₃)—] 3H.

Isomerizations of *cis*-IV- and *trans*-IV-Hydrobromides to IX-Hydrobromide.—A solution of 0.10 g. of *cis*-IV-hydrobromide in 0.4 ml. of 8.8 *N* hydrobromic acid was held in the steam bath for 2 hr. The base was recovered, then converted to the picrate (wt., 0.11 g.) which by mixture melting point was proved to be IX-picrate. In like manner 0.10 g. of *trans*-IV-hydrobromide yielded 0.12 g. of IX-picrate. Infrared diagrams confirmed these results.

2,4,9-Trimethyl-6,7-benzomorphan (XII) and Degradation to 1-Methylnaphthalene.—A solution of the oily hydrobromide of X in 20 ml. of 8.8 *N* hydrobromic acid was heated at reflux temperature for 5 hr. The solution was chilled, made alkaline with sodium hydroxide solution, and 3.4 g. of oil recovered with ether. In acetone solution the crude benzomorphan, 2.2 g., was converted to an oily methiodide which was heated in aqueous suspension with excess thallous hydroxide until the thallous iodide became granular. After filtering the solid, the solution was made alkaline with sodium hydroxide, boiled for 30 min., cooled, and extracted with ether to give 1.3 g. of methine base. Converted to the hydrobromide, an oil, this salt absorbed about 1 mole of hydrogen in alcohol over Adams catalyst. The oily product was converted to the base and heated with 10% palladium–charcoal at 270° with distillation of an oil which showed about 12% 1-methylnaphthalene by v.p.c.

α-2,5,9-Trimethyl-6,7-benzomorphan.[18]—An oily adduct formed when 0.2 g. of *cis*-IV-hydrobromide was added to a suspension of 0.2 g. of aluminum chloride in 0.5 ml. of carbon disulfide. The adduct was gummy but on triturating became an oil in about 2 min. After 3 hr. at room temperature the suspension was chilled and water added dropwise; carbon disulfide was decanted from the white mush which was then washed with ether. Excess sodium hydroxide dissolved the aluminum hydroxide, and the basic product was recovered from petroleum ether (30–60°), wt., 0.14 g. The base in acetone solution was converted to a crystalline methiodide in 67% over-all yield, m.p. 214–220°. Recrystallized from alcohol–ethyl acetate, it melted at 218–222°, and a mixture melting point and infrared diagram showed it to be identical to the previously characterized sample.[9]

β-2,5,9-Trimethyl-6,7-benzomorphan.—The hydrobromide of *trans*-IV, 2.7 g., was added to a suspension of 2.8 g. of aluminum chloride in 8 ml. of carbon disulfide. The solids dissolved into an oily adduct on triturating. After 4 hr. the mixture was decomposed as in the above experiment to give 1.75 g. of an oil which, in acetone with methyl iodide, yielded a crystalline salt, wt., 2.7 g. (82% over-all), m.p. 225–231° (gas). Recrystallized from water, it melted at 232–239° with a sinter at 196°. Dried

(18) Configuration assignments for the α- and β-benzomorphans were made by E. L. May and will be included in a subsequent publication.

overnight at 100° under oil pump vacuum it lost 0.97% water and melted at 240–241° with a sinter at 201°.

Anal. Calcd. for $C_{16}H_{24}NI$: C, 53.78; H, 6.77. Found: C, 53.92; H, 6.59.

1,3-Dimethyl-1-(2-dimethylaminoethyl)-1,2-dihydronaphthalene Hydrobromide.—The methiodide of the β-benzomorphan, 1.8 g., was converted to the methohydroxide with thallous hydroxide. After filtering the thallous iodide the aqueous solution was taken to an oil under reduced pressure and the base then heated in a bath at 170° (0.5 mm.) with distillation of a colorless oil at about 120° (0.5 mm.). In ether solution with hydrogen bromide it gave a crystalline salt, wt., 1.4 g. (88% over-all), m.p. 170–174° (gas). Recrystallized from acetone, it melted at 175–177°.

Anal. Calcd. for $C_{16}H_{24}NBr$: C, 61.93; H, 7.80. Found: C, 62.12; H, 8.12. An ethanol solution showed λ_{max} 265 mμ (ε 9000).

1,3-Dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene hydrobromide was obtained by reduction of the above salt in alcohol with Adams catalyst. It was recrystallized by adding ethyl acetate to a solution in alcohol–acetone, m.p. 202–205°.

Anal. Calcd. for $C_{16}H_{26}NBr$: C, 61.53; H, 8.39. Found: C, 61.81; H, 8.47.

1,2-Dimethylnaphthalene was recovered as the picrate in 18% yield as one of the products resulting from the 280° palladium–charcoal decomposition of the tetrahydronaphthalene base from the preceding hydrobromide.[9] Identification was by a mixture melting point with a known sample.

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The Synthesis of Tryptophan Peptides

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The preparation of blocked and free dipeptides containing tryptophan and the synthesis of tryptophan benzyl ester are described.

In connection with our work on the specific cleavage of proteins at the tryptophyl residue, we found it necessary to prepare various peptides containing tryptophan as model compounds.

The only studies so far reported in the synthesis of tryptophan peptides are the early work of Abderhalden[1] and the work of Smith[2] on the synthesis of protected tryptophyl peptides through carbobenzoxy tryptophyl chloride, and the preparation of tryptophylglycine[3] and arginyltryptophan[4,5a] as intermediates in the partial synthesis of α and β MSH.[5b]

All the protected tryptophan peptides listed in Table I and the corresponding free peptides listed in Table II previously have not been reported in the literature. They were synthesized by coupling carbobenzoxy-L-tryptophan with the appropriate amino acid benzyl ester by the dicyclohexylcarbodiimide (DCC) method.[6]

The blocked dipeptides containing C-terminal tryptophan were prepared similarly from the appropriate carbobenzoxy-L-amino acid and L-tryptophan benzyl ester, except for carbobenzoxy-L-prolyl-L-tryptophan which was synthesized from carbobenzoxypropyl chloride[7] and free L-tryptophan.

Tryptophan benzyl ester hydrochloride has not been synthesized previously probably owing to the instability of tryptophan at the acid pH values and high temperature needed for esterification. However, we succeeded in synthesizing this compound in 80% yield in one step by a modification of Erlanger's method.[8] The method was to pass phosgene through a suspension of tryptophan in dioxane until the tryptophan was completely dissolved, being converted to the N-carboxy-anhydride.[9] About half the dioxane was distilled so as to remove the excess of phosgene. Benzyl alcohol–ether was added and two to three moles of gaseous hydrogen chloride per mole residue of tryptophan were passed through at 0°. After standing overnight, the ester precipitated. All of the benzyl esters used in this study were synthesized by this method.

The unblocked peptides listed were obtained by catalytic hydrogenation of the blocked peptides in the presence of palladium on charcoal.

The free peptides were chromatographically pure (butanol–acetic acid–water, 25:6:25). On basic hydrolysis all gave tryptophan and the appropriate amino acid in a 1:1 ratio.

Experimental

All melting points are uncorrected. Prior to analysis the free peptides were dried at 80° *in vacuo*, over phosphorus pentoxide. Other compounds were dried *in vacuo* over phosphorus pentoxide at room temperature.

L-Tryptophan Benzyl Ester Hydrochloride.—Dry phosgene was passed at room temperature through a suspension of L-tryptophan (20.4 g.) in anhydrous dioxane (330 ml.) until a clear solution was obtained (about 45 min.). Phosgene was removed by a stream of dry nitrogen and half of the solvent was distilled *in vacuo* at 45°.

Benzyl alcohol (50 ml.) and dry ether (250 ml.), previously saturated with 2–3 moles of gaseous hydrogen chloride per mole residue of tryptophan at 0°, were added, and the solution was left overnight at room temperature. The ester which separated was filtered off and washed with ether. The product was recrystallized from hot water; yield, 80%; m.p. 222°, $[\alpha]^{25}D$ +4° (*c* 2, methanol).

Anal. Calcd. for $C_{18}H_{18}N_2O_2 \cdot HCl$: C, 65.45; H, 5.78; N, 8.48. Found: C, 65.55; H, 5.83; N, 8.28.

Carbobenzoxy-L-tryptophan *p*-Nitrophenyl Ester.—Cbz-L-tryptophan (34 g.) was dissolved in ethyl acetate and *p*-nitrophenol (14 g.) was added. The solution was cooled to 0° and dicyclohexylcarbodiimide (20.5 g.) was added. After 2 hr. at room tem-

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TABLE I

BLOCKED DIPEPTIDES OF L-TRYPTOPHAN

Dipeptide[g]	Yield, %	M.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	$[\alpha]^{25}D$[a]
Z-L-Ala-L-try OBZ	78	105[b]	$C_{29}H_{29}N_3O_5$	69.72	5.85	8.41	69.52	6.00	8.60	−22
Z-L-Leu-L-try OBZ	80	110[b]	$C_{32}H_{35}N_3O_5$	70.92	6.51	7.76	70.81	6.40	7.82	−27
Z-L-Phe-L-try OBZ	70	135[b]	$C_{35}H_{33}N_3O_5$	73.02	5.78	7.30	72.80	5.79	7.10	− 4
Z-L-Pro-L-try	70	183[c]	$C_{24}H_{25}N_3O_5$	66.20	5.74	9.65	66.35	5.78	9.80	−20
Z-L-Try-L-try OBZ	90	75[d]	$C_{32}H_{34}N_4O_5$	72.30	5.50	9.09	72.10	5.65	8.87	− 9
Z-L-Val-L-try OBZ	85	129[d]	$C_{31}H_{33}N_3O_5$	70.58	6.26	7.96	70.65	6.38	8.08	−24
Z-L-Try-L-ala OBZ	80	153[e]	$C_{29}H_{29}N_3O_5$	69.72	5.85	8.41	69.77	5.97	8.38	−22
Z-L-Try-L-leu OBZ	83	114[d]	$C_{32}H_{35}N_3O_5$	70.92	6.51	7.76	71.20	6.53	8.00	−34
Z-L-Try-L-phe OBZ	89	130[f]	$C_{35}H_{33}N_3O_5$	73.02	5.78	7.30	72.90	5.90	7.58	−22
Z-L-Try-L-try OMe	70	196[e]	$C_{31}H_{30}N_4O_5$	69.13	5.50	10.50	69.15	5.48	10.30	−13
Z-L-Try-L-tyr OBZ	85	110[d]	$C_{35}H_{33}N_3O_6$	71.05	5.62	7.10	70.97	5.80	7.02	−23
Z_2-L-Tyr-L-try OMe	78	176[f]	$C_{37}H_{35}N_3O_8$	68.40	5.40	6.50	68.35	5.71	6.60	− 8

[a] *c* 1, methyl alcohol. Recryst. solvent: [b] Ethyl acetate–ether. [c] Ethanol. [d] Ethyl acetate–petroleum ether. [e] Ethyl acetate. [f] Methanol. [g] Abbreviations: Z = C_7H_7OCO, BZ = $C_6H_5CH_2$.

TABLE II

FREE DIPEPTIDES OF L-TRYPTOPHAN

Peptide	Yield, %	$[\alpha]^{25}D$	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Recrystallization solvent
L-Ala-L-try	85	+19[a]	$C_{14}H_{12}N_3O_3$	61.08	6.22	15.26	61.20	6.30	15.38	Ethyl alcohol–ethyl acetate
L-phe-L-try	78	+ 6[b]	$C_{20}H_{21}N_3O_3H_2O$	65.04	6.23	11.38	65.20	6.35	11.53	Methyl alcohol–ethyl alcohol
L-pro-L-try	85	−35[d]	$C_{16}H_{19}N_3O_3H_2O$	60.18	6.58	13.16	59.88	6.60	13.40	Water–ethyl alcohol
L-Try-L-try	80	−12[c]	$C_{22}H_{22}N_4O_3$	67.67	5.68	14.35	67.56	5.80	14.62	Ethyl alcohol–ethyl acetate
L-Try-L-ala	95	+28[a]	$C_{14}H_{12}N_3O_3$	61.08	6.22	15.26	60.92	6.45	15.05	Water–ethyl alcohol
L-Try-L-leu	93	+18[a]	$C_{12}H_{23}N_3O_3$	64.33	7.30	13.24	64.50	7.50	13.48	Water–ethyl alcohol
L-Try-L-phe	85	+30[b]	$C_{20}H_{21}N_3O_3H_2O$	65.04	6.23	11.38	65.30	6.40	11.54	Methyl alcohol–ethyl alcohol
L-Try-L-tyr	88	+ 8[c]	$C_{20}H_{21}N_3O_4$	65.38	5.76	11.44	65.23	5.67	11.22	Ethyl alcohol–ethyl acetate

[a] *c* 1, water. [b] *c* 1, methyl alcohol. [c] *c* 1, ethyl alcohol. [d] *c* 1, 6 *N* HCl.

perature, the dicyclohexylurea was filtered off and washed with ethyl acetate. The filtrate was evaporated to dryness and the crystalline residue was recrystallized from hot ethanol; yield, 85%; m.p. 105°, $[\alpha]^{25}D$ −4.5° (*c* 5, dimethylformamide).

Anal. Calcd. for $C_{25}H_{24}N_3O_6$: C, 65.35; H, 4.57; N, 9.15; neut. equiv., 459. Found: C, 65.19; H, 4.22; N, 9.03; neut. equiv., 457.

The neutral equivalence value was determined by titration in ethanol with 0.1 *M* sodium methoxide using thymol blue as indicator.[10]

Carbobenzoxy-L-tryptophyl-L-alanine Benzyl Ester.—To a solution of L-alanine benzyl ester hydrochloride (21.5 g., 0.1 mole) in 150 ml. of dichloromethane was added triethylamine (14.4 ml.) and the solution was mixed with another solution of carbobenzoxy-L-tryptophan (33.8 g., 0.1 mole) in 150 ml. of dichloromethane at 0°. Then 20.5 g. of dicyclohexylcarbodiimide was added, and the solution was stirred overnight at room temperature. Dicyclohexylurea was removed by filtration, and the filtrate was washed with 0.5 *N* hydrochloric acid, water, 5% sodium bicarbonate solution, and finally dried over sodium sulfate. The solvent was evaporated *in vacuo*. Upon adding ether, the residue crystallized, and was recrystallized from ethyl acetate; yield, 80%; m.p. 153°, $[\alpha]^{26}D$ −27° (c 1, methanol).

Anal. Calcd. for $C_{29}H_{29}N_3O_3$: C, 69.72; H, 5.85; N, 8.41. Found: C, 69.77; H, 5.97; N, 8.38.

The other protected tryptophyl dipeptides were made similarly (Table I).

(10) M. Wilchek and A. Patchornik, *Bull. Res. Council Israel*, **11A**, 239 (1962).

Carbobenzoxy-L-phenylalanyl-L-tryptophan Benzyl Ester.—This compound was prepared from carbobenzoxy-L-phenylalanine and L-tryptophan benzyl ester hydrochloride in the manner described earlier. The filtrate was washed with water, 0.5 *N hot* hydrochloric acid, *hot* water, 5% sodium bicarbonate solution, water, and dried over sodium sulfate. The solvent was evaporated *in vacuo*. Upon adding petroleum ether, the oily residue crystallized and was recrystallized from ethyl acetate–ether; yield, 70%; m.p. 135°, $[\alpha]^{25}D$ −4° (*c* 5, methanol).

Anal. Calcd. for $C_{35}H_{33}N_3O_5$: C, 73.02; H, 5.78; N, 7.30. Found: C, 72.80; H, 5.99; N, 7.10.

The remaining tryptophan dipeptides were prepared similarly. Yields and analytical data are given in Table I.

L-Tryptophyl-L-alanine.—A solution of carbobenzoxy-L-tryptophyl-L-alanine benzyl ester (5 g.) in 80% methanol–water was hydrogenated in the presence of 0.5 g. of 10% palladium on charcoal for 4 hr. The catalyst was removed by filtration. The filtrate was evaporated *in vacuo* and, upon adding ethanol, the peptide crystallized, and was recrystallized from water–ethanol; yield, 95%, $[\alpha]^{25}D$ +28° (*c* 1, water).

Anal. Calcd. for $C_{14}H_{12}N_3O_3$: C, 61.08; N, 6.22; N, 15.26. Found: C, 60.92; H, 6.45; N, 15.05.

All of the N and C terminal tryptophan peptides are soluble in methanol. The remaining free peptides were made similarly. Yields and analytical data are given in Table II.

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Urea–Formaldehyde Condensation Products. I. Urons[1]

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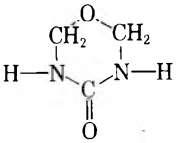
The synthesis of the parent member of the "Uron" class, tetrahydro-4*H*-1,3,5-oxadiazin-4-one, was effected by the acid-catalyzed hydrolysis of tetrahydro-3,5-bis(methoxymethyl)-4*H*-1,3,5-oxadiazin-4-one. A compound previously reported to be tetrahydro-3,5-dimethyl-4*H*-1,3,5-oxadiazin-4-one was shown to be 1,3-dimethyl-1-methoxymethylurea. The synthesis of tetrahydro-3,5-dimethyl-4*H*-1,3,5-oxadiazin-4-one was effected by the hydrogenolysis of tetrahydro-3,5-bis(methoxymethyl)-4*H*-1,3,5-oxadiazin-4-one in the presence of Raney nickel.

In 1936 Kadowaki[2] assigned the name "Uron" to a cyclic urea (I), tetrahydro-4*H*-1,3,5-oxadiazin-4-one, and described the preparation of N,N′-bis(methoxymethyl)uron (II), tetrahydro-3,5-bis(methoxymethyl)-4*H*-1,3,5-oxadiazin-4-one.



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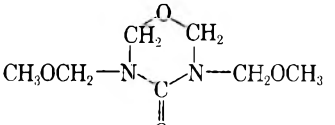


II

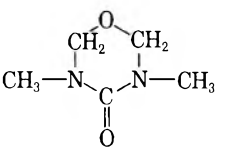
Until now there has been some uncertainty concerning the nature of the so-called "Urons" and in fact I itself has recently been referred to by Marsh[3] as a "hypothetical substance" presumably because it has never been reported.

We repeated Kadowaki's preparation and obtained, as he did, a product having the correct carbon, hydrogen, and nitrogen content for II; however, the methoxyl analysis was much too high and the total formaldehyde was much too low for this structure. In addition, the infrared absorption spectrum of this material had a strong NH band at 2.98 μ which remained even when the product was fractionated carefully. An examination of this product by vapor phase chromatography clearly showed that Kadowaki had a mixture of two major and several minor components.

By the use of a preparative vapor phase chromatographic column the isolation of pure II was easily effected since it came off the column last. The product was identified as II by elemental, methoxyl, and total formaldehyde analyses, and a molecular weight determination.

Since attempts to prepare I by the cyclization of 1,3-bis(hydroxymethyl)urea were unsuccessful, an attempt was made to cleave selectively the methoxymethyl groups of II by acid hydrolysis, using a dilute solution of dimedone since this reagent is acidic and will also tie up the released formaldehyde as methylenebisdimedone. After hydrolyzing, the insoluble methylenebisdimedone was filtered off and from the filtrate a colorless, crystalline solid melting at 170–171° was obtained. This material was identified as the long-sought parent "Uron," I, by elemental analysis, total formaldehyde, and molecular weight determinations.

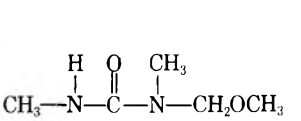
Kadowaki[2] also reported the preparation of a low-melting compound, N,N′-dimethyluron (III), tetrahydro-3,5-dimethyl-4*H*-1,3,5-oxadiazin-4-one, by the reaction of 1,3-dimethylurea with formaldehyde followed by cyclization; this claim was supported by excellent analytical data.



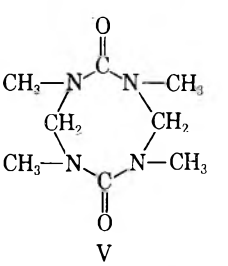
III

In 1958 Becher and Griffel[4] reported on the infrared absorption spectra of several compounds of the "Uron" class, citing Kadowaki's article and publishing a spectrum in the 6–15-μ region of a product which they assumed to be III. We repeated the preparation of Becher and Griffel and found that the infrared absorption spectrum of the product had a strong NH band at 2.99 μ. A comparison with the spectrum reported by Becher and Griffel showed that both spectra were identical in the 6–15-μ region. Elemental, methoxyl and total formaldehyde analyses showed that the compound obtained by Becher and Griffel was actually 1,3-dimethyl-1-methoxymethylurea (IV).

Numerous attempts were made to prepare III by Kadowaki's procedure but in every case the products were IV and the known compound tetramethyldimethylenediureid[2] (V).



IV



V

Since III was not obtained by either the procedure of Kadowaki or of that of Becher and Griffel, an attempt was made to prepare it by the hydrogenolysis of II in the presence of Raney nickel. This resulted in a low-melting crystalline solid which was subsequently identified as III; compound III had the same melting point as that originally reported by Kadowaki.[2]

Experimental

All melting points are uncorrected.

Tetrahydro-4*H*-1,3,5-oxadiazin-4-one (I).—A mixture of 2.0 g. (0.0105 mole) of II, 5.70 g. (0.0407 mole) of dimedone and 600 ml. of water was maintained at boiling temperature for 20 min., then cooled to room temperature, and filtered to separate the methylenebis(dimedone). The filtrate was concentrated at 1 mm., while

(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September 1962.

(2) H. Kadowaki, *Bull. Chem. Soc. Japan*, **11**, 248 (1936).

(3) J. T. Marsh, *Textile Recorder*, **79**, 55 (July, 1961).

(4) H. J. Becher and F. Griffel, *Chem. Ber.*, **91**, 2032 (1958).

maintaining the temperature below 30°, to a volume of 20 ml. and filtered again to remove additional methylenebis(dimedone); the filtrate was again concentrated at 1 mm. to remove the remaining water. The residue (1.10 g.), a tacky solid, on trituration with an acetone–ethanol mixture gave a crystalline solid (0.30 g., m.p. 158–165°); recrystallization from acetonitrile gave colorless needles, m.p. 170–171°; infrared (Nujol mull): 3.15, 3.27, 3.45, 5.95, 6.50, 6.95, 7.15, 7.27, 7.57, 8.60, 8.80, 9.07, 9.55, 9.72, 10.07, 11.50, 12.35 μ.

Anal. Calcd. for $C_3H_6N_2O_2$: C, 35.3; H, 5.95; N, 27.40; CH_2O (total), 58.64; mol. wt., 102. Found: C, 35.06; H, 6.07; N, 27.11; CH_2O (total), 58.64; mol. wt., 104.6 ± 10.

Tetrahydro-3,5-bis(methoxymethyl)-4*H*-1,3,5-oxadiazin-4-one (II). A. Method of Kadowaki.[2]—This procedure gave a liquid which on distillation *in vacuo* through a 6-in. Vigreux column gave 101.7 g. of product. (54%), b.p. 127–137° at 4 mm., $n^{25}D$ 1.4675; infrared (film): 2.95, 3.42, 3.55, 6.02, 6.70, 6.87, 7.20, 7.50, 7.75, 8.57, 9.35, 9.80, 10.35, 10.75, 11.05, 11.87, 12.42, 12.95, 13.32, 14.27 μ.

Anal. Calcd. for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42; N, 14.74; CH_3O, 32.60; CH_2O (total), 63.05. Found: C, 44.05; H, 7.49; N, 14.61, CH_3O, 37.16; CH_2O (total), 57.8; CH_2O (free), none.

B. Isolation by Vapor Phase Chromatography.—Samples (50 μl.) of the reaction mixture prepared by the Kadowaki procedure were injected into an F&M Model 500 gas chromatograph containing a 12-ft. column packed with 20% silicon gum rubber on Chromosorb W, a flux calcined diatomaceous earth, while using a helium flow rate of 50 ml. per minute. The temperature conditions were maintained as follows: injection part, 270°, block, 300°, and column, 200°. Using these conditions it was found that pure II ($n^{25}D$ 1.4705) had a retention time of 15.4 min. (peak height); samples of II were collected in a tube cooled to −60°; infrared (film): 3.37, 3.50, 5.97, 6.66, 6.82, 7.20, 7.50, 7.75, 8.57, 9.32, 9.80, 10.32, 10.75, 11.05, 12.45, 13.35, 14.25 μ.

Anal. Calcd. for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42; N, 14.74; CH_3O, 32.60; CH_2O (total), 63.05. Found: C, 44.04; H, 7.39; N, 14.76; CH_3O, 32.49; CH_2O (total), 63.66.

Tetrahydro-3,5-dimethyl-4*H*-1,3,5-oxadiazin-4-one (III).—An amount of 95.1 g. (0.50 mole) of II was dissolved in sufficient methanol to make 400 ml. of solution. The solution was charged to a 1-l. stainless steel autoclave together with 15 g. of Raney nickel and shaken at 150–165° for 10 min. and at 200° for 8 hr.; the autoclave was then cooled to room temperature and vented.

The methanolic solution on concentration *in vacuo* gave 59.8 g. of crude product which on analysis by vapor phase chromatography showed three components; the last component was identified as starting material.

Distillation of the crude product under reduced pressure gave five fractions boiling over a range of 74–90° at less than 1 mm.; vapor phase analysis of each fraction showed that no clear-cut separation was obtained. However, the second fraction (6.4 g., b.p. 74–77° at less than 1 mm.) had the greatest concentration of the first component. When this fraction was cooled at −60° to induce crystallization and twice recrystallized from ether at −60°, the resulting solid (m.p. 36.4°, $n^{26}D$ 1.4808) was found to be chromatographically pure and identified as III; infrared (film): 3.40, 3.47, 6.05, 6.60, 6.82, 7.00, 7.15, 7.57, 7.95, 8.17, 9.05, 9.25, 9.65, 10.35, 12.40, 13.32 μ.

Anal. Calcd. for $C_5H_{10}N_2O_2$: C, 46.10; H, 7.74; N, 21.55; CH_2O (total), 46.1. Found: C, 45.90; H, 7.75; N, 21.45; CH_2O (total), 46.8.

The second component was not isolated; it is believed to be tetrahydro-1,3,5-trimethyl-4*H*-1,3,5-triazin-4-one because the addition of pure tetrahydro-1,3,5-trimethyl-4*H*-1,3,5-triazin-4-one to the crude product greatly increased the peak height of the second component.

Tetrahydro-1,3,5-trimethyl-4*H*-1,3,5-triazin-4-one.—An amount of 17.6 g. (0.20 mole) of 1,3-dimethylurea was dissolved in 33.2 g. (0.41 mole) of 37% formaldehyde and 31.0 g. (0.40 mole) of 40% aqueous methylamine was added dropwise while maintaining the temperature below 35°. The reaction mixture was refluxed for 18 hr. and concentrated at 15 mm. to remove the water. The residue (29.0 g.) was distilled at 0.30 mm. through a micro Vigreux column and the fraction (7.35 g.) boiling at 65–67° was collected and identified as tetrahydro-1,3,5-trimethyl-4*H*-1,3,5-triazin-4-one.

Anal. Calcd. for $C_6H_{13}N_3O$: C, 50.39; H, 9.09; N, 29.35. Found: C, 50.33; H, 9.09; N, 29.35.

1,3-Dimethyl-1-methoxymethylurea (IV).—The procedure used was that described by Becher and Griffel.[4] Distillation of the crude material through a 5-in. Vigreux column gave 75.3 g. (65%) of a colorless liquid (b.p. 99–100° at 1 mm., $n^{25}D$ 1.4626); infrared (film): 2.98, 3.40, 3.55, 6.10, 6.53, 7.10, 7.30, 7.73, 8.0, 8.15, 8.52, 8.70, 9.20, 9.35, 9.70, 10.32, 10.57, 11.06, 11.85, 12.55, 13.00 μ.

Anal. Calcd. for $C_5H_{12}O_2$: C, 45.4; H, 9.15; N, 21.2; CH_3O, 23.45; CH_2O (total), 22.7. Found: C, 46.1; H, 9.33; N, 21.64; CH_3O, 24.19; CH_2O (total), 23.2.

Acknowledgment.—The authors wish to thank Dr. Jessie Gove for the infrared data, and Dr. James Parsons for assistance with the vapor phase chromatography. They also wish to thank the late Mr. Oliver Sundberg and Mr. John Kobliska, and their associates, for the microanalyses.

Polyfunctional Aliphatic Compounds. IV. The Cyclization of Nitriles by Halogen Acids. A New Synthesis of Thiazoles

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α-Cyanoalkyl thiocyanates, prepared from α-chloroalkyl and α-(4-toluenesulfonyloxy)alkyl cyanides, are shown to undergo cyclization to derivatives of 2-bromo-4-aminothiazole by means of hydrogen bromide. Hydrogen chloride is unsatisfactory as a cyclizing agent whereas hydrogen iodide causes further reduction and leads directly to derivatives of the previously inaccessible 4-aminothiazoles. Attempts to apply this synthesis to the preparation of selenazoles were unsuccessful.

In earlier papers,[1,2] we have shown that the cyclization reaction of α,ω-dinitriles can be used effectively for the synthesis of pyridine and isoquinoline compounds. For example, 3-hydroxyglutaronitrile is cyclized to 2-amino-6-bromopyridine hydrobromide by hydrogen bromide and 2-cyanobenzyl cyanide with the same reagent leads exclusively to 3-amino-1-bromoisoquinoline hydrobromide.

All previous work[3] dealing with the action of anhydrous hydrogen halides on dinitriles of the type under discussion has been devoted largely to systems in which the two nitrile groups were joined by a carbon

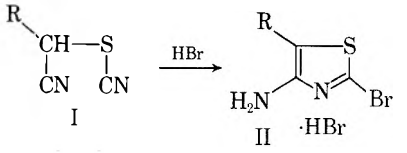
(1) Part II, F. Johnson, J. P. Panella, A. A. Carlson, and D. H. Hunneman, *J. Org. Chem.*, **27**, 2473 (1962).

(2) Part III, F. Johnson and W. A. Nasutavicus, *ibid.*, **27**, 3953 (1962).

(3) This has been summarized in part II (ref. 1).

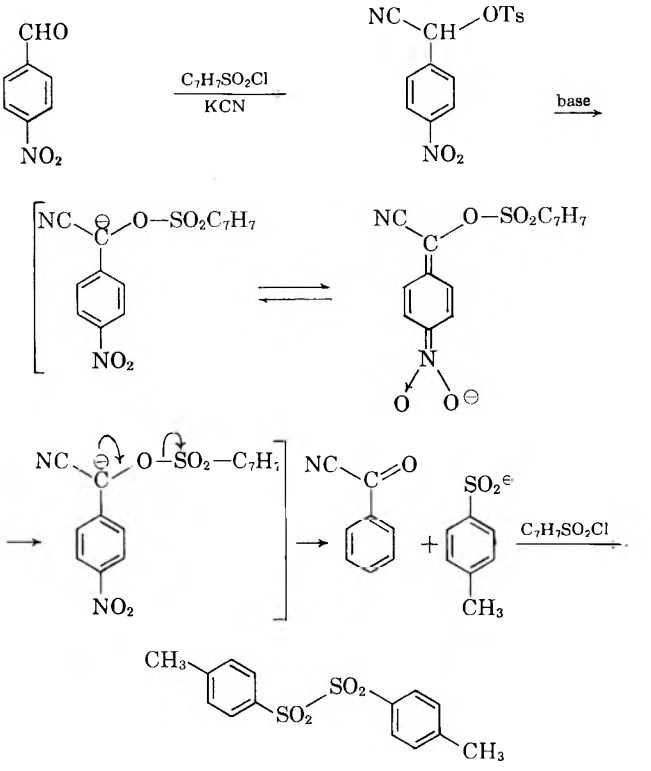
chain.[4] We now report studies where the latter has been modified by the incorporation of a heteroatom, namely sulfur or selenium.

In view of the fact that the electron-accepting and electron-donating effect of divalent sulfur appear to be similar to those of a 1,2-phenylene group, it seemed likely that the cyclization of the appropriate cyano thiocyanates also might proceed in one specific direction. In addition, if the cyclization were to be analogous to that of 2-cyanobenzyl cyanide then α-cyanoalkyl thiocyanates should lead to derivatives of the essentially inaccessible 4-aminothiazoles. We now report that this is the case and that the reaction of these dinitriles (I) with anhydrous hydrogen bromide proceeds exclusively to give 4-amino-2-bromothiazole hydrobromides (II).



Cyanoalkyl Thiocyanates.—Of the required starting materials (I) only those where R = H or C_6H_5 were known in the previous literature. The former compound had been reported[5] to be of use as a solvent for polyacrylonitrile (no preparative details were given), while Brintzinger and Schmahl[6] had described it as a solid, m.p. 96–98°. They claimed its preparation by the action of potassium cyanide on chloromethylsulfenyl chloride in acetic acid. The phenyl homolog (I, R = C_6H_5) had been prepared[7,8] twice previously by the action of ammonium thiocyanate on α-bromobenzyl cyanide in alcohol. This latter method, obviously capable of much wider application, had the disadvantage of requiring α-halonitriles, materials often having disagreeable properties. Nevertheless, Taylor[9] has pointed out that the analogous α-cyanoalkyl arylsulfonates are handled more easily and can be used as effectively as α-haloalkylnitriles in substitution reactions. As they also seemed to have the added benefit of easy preparation[10] from the corresponding aldehydes, these at first appeared to be our starting materials of choice.

However, although we were able to prepare the previously known α-cyanoalkyl 4-toluenesulfonates, the method[10] failed completely to give solid products when applied to 2-methoxy-, 2,4-dimethoxy-, 4-chloro-, 3- and 4-nitro-, or 4-acetaminobenzaldehyde, terephthaldehyde, cinnamaldehyde, or furfural. The use of methanesulfonyl chloride or benzenesulfonyl chloride in place of 4-toluenesulfonyl chloride in the reaction with 4-chlorobenzaldehyde was equally unsuccessful. In most of these cases a noncrystallizable viscous sirup was isolated and only when using 4-nitrobenzaldehyde could any solid material be obtained. This, however, proved to be 4-tolyl disulfone, undoubtedly formed by the following sequence.



Properties of this material were in good agreement with those previously recorded[11,12] for this substance. The base-catalysed elimination of sulfinate ion from sulfonate esters of this type has been well documented by Loudon[10] and by Taylor.[9] However disulfone formation has not been observed previously, and the above reaction represents an alternate pathway for the disappearance of sulfinate anion. In the case of 4-chlorobenzaldehyde, further treatment of the crude reaction mixture with ammonium thiocyanate did give a very small amount of the required α-cyano-4-chlorobenzyl thiocyanate. This, however, was the only example of the aldehydes listed previously, where any conversion to the desired product could be achieved.

In those instances where the preparation of the α-cyanoalkyl 4-toluenesulfonate failed, recourse had to be made to the α-chloroalkyl cyanides. These were prepared by the action of thionyl chloride on the cyanohydrins of a selection of the preceding aldehydes according to known procedures.[13,14]

Whereas it was possible to convert the α-chloroalkylnitriles and α-cyanoalkyl 4-toluenesulfonates to the α-cyanoalkyl thiocyanates with thiocyanate ion in boiling alcohol, it was found that usually anhydrous dimethylformamide was a much more suitable solvent. Using this medium, the reactions were complete inside thirty minutes at room temperature, and the products, generally obtained in high yield, required little purification.

(4) The only exceptions are thiocyanogen [A. Söderback, *Ann.*, **419**, 217 (1919); **465**, 184 (1928)] and the N,N′-dicyanoguanidines [D. W. Kaiser, U. S. Patent 2,630,433 (1953); J. J. Roemer and D. W. Kaiser, U. S. Patent 2,658,893 (1953)].

(5) R. C. Houtz (to E. I. du Pont de Nemours and Co.), U. S. Patent 2,404,727 (1946).

(6) H. Brintzinger and H. Schmahl, *Chem. Ber.*, **87**, 314 (1954).

(7) A. Kretov and A. Panchenko, *J. Russ. Phys. Chem. Soc.*, **61**, 1975 (1929); *Chem. Abstr.*, **24**, 4769.

(8) D. G. Coe, M. M. Gale, R. P. Linstead, and C. J. Timmons, *J. Chem. Soc.*, 123 (1957).

(9) E. C. Taylor, G. A. Berchtold, N. A. Goeckner, and F. G. Stroehmann, *J. Org. Chem.*, **26**, 2715 (1961).

(10) J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 1780 (1959).

(11) T. P. Hilditch, *ibid.*, 1524 (1908).

(12) E. v. Meyer, R. Nacke, and M. Gmeiner, *J. prakt. Chem.* **63**, [ii] 167 (1901).

(13) W. H. Davies, A. W. Johnson, and H. A. Piggott, *J. Chem. Soc.*, 352 (1945).

(14) A. H. Cook, J. Downer, and B. Hornung, *ibid.*, 502 (1941).

TABLE I

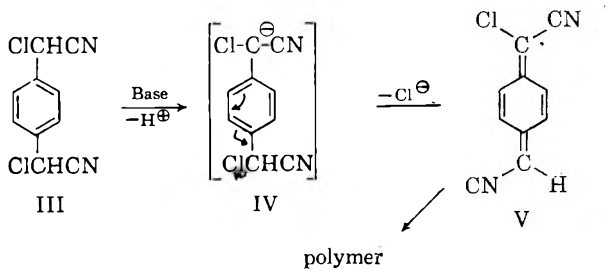
PREPARATION OF α-CYANOALKYL THIOCYANATES USING DIMETHYLFORMAMIDE AS REACTION MEDIUM

RCH(CN)SCN

R	Cryst. from[a]	M.p., °C.	Yield, %	Formula	Analyses Calcd. C	H	N	S	Found C	H	N	S
C_6H_5	E–P	78–80	83	$C_9H_6N_2S$[b]	..	...	..	..	..	...	..	..
2-ClC_6H_4	E–P	86–88	89	$C_9H_5ClN_2S$	51.8	2.4	13.4	15.4	51.8	2.4	13.4	15.3
4-ClC_6H_4	E–P	78–80	83	$C_9H_5ClN_2S$	51.8	2.4	13.4	15.4	51.8	2.0	13.3	15.4
2,4-$Cl_2C_6H_3$	MC–P	136–138	96	$C_9H_4Cl_2N_2S$	44.5	1.7	11.5	13.2	44.2	1.6	11.4	13.3
2-$CH_3OC_6H_4$	MC–P	104–105	91	$C_{10}H_8N_2OS$	58.8	3.9	13.7	15.7	58.8	3.9	13.5	15.9
2-$NO_2C_6H_4$	MC–P	87–89	74	$C_9H_5N_3O_2S$	49.3	2.3	19.2	14.6	49.1	2.3	19.1	14.7
4-$CH_3CONHC_6H_4$	...	136–140	49	$C_{11}H_9N_3OS$[c]	..	...	..	..	..	...	..	..

[a] Solvent key: E = ether; P = petroleum ether (b.p. 30–60°); MC = methylene chloride. [b] Known compound; yield when ethanol used as solvent was 45%. [c] This material resisted purification by crystallization and was used as such for further work.

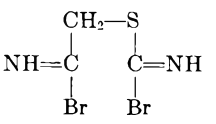
A few failures were observed. α-Cyano-β-phenylethyl 4-toluenesulfonate reacted with ammonium thiocyanate in boiling ethanol to give a dark red solid which lacked a band in its infrared spectrum for the –SCN group, and from the same reaction in dimethylformamide only traces of starting material could be isolated. The reaction of α,α′-dichlorobenzene-1,4-bisacetonitrile (III) with ammonium thiocyanate in dimethylformamide was accompanied by some vivid color changes and the deposition of ammonium chloride, but only an extremely insoluble amorphous brown powder was obtained. The latter showed nitrile but no thiocyanate absorption in the infrared spectrum. It is possible that this product is polymeric in nature having been formed from the *p*-xylylene derivative (V) shown below.

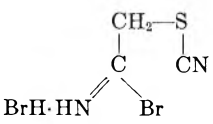


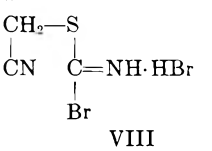
Finally, the parent compound (I, R = H) deserves some attention. It was prepared easily by refluxing chloroacetonitrile with ammonium thiocyanate in ethanol for a few hours, and proved to be a highly mobile liquid which could not be induced to crystallize at room temperature. Besides giving good elemental analytical data, its infrared spectrum showed bands at 4.40 and 4.57 μ in agreement with structure I (R = H). As Brintzinger, *et al.*,[6] claimed this material to be a solid, we repeated their experiments. Although it was possible to isolate some yellow crystals of m.p. 160–170° (with effervescence) which had no infrared absorption bands in the 4–5-μ region, we were unable to obtain any compound corresponding to that of these authors.

Table I lists the α-cyanobenzyl thiocyanates prepared for cyclization studies.

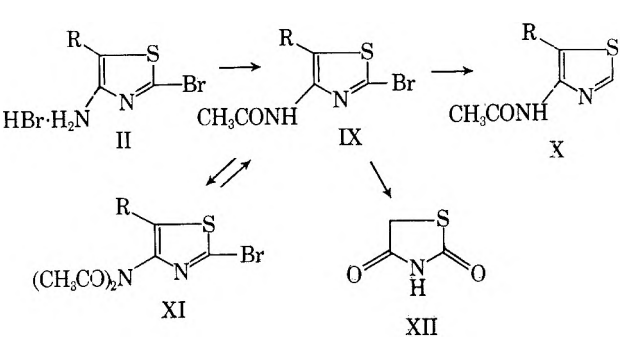
Thiazoles.—The reaction of the α-cyanoalkyl thiocyanates with hydrogen bromide in an inert solvent (usually acetic acid or ether) occurred quite readily, in most instances a highly crystalline salt being obtained. These hydrolyzed rapidly in moist air but were found to be stable indefinitely at room temperature in a dry atmosphere. The product (II, R = H) from I (R = H), to which most attention was given, had a good analysis for a compound containing two bromine atoms. That this is indeed the hydrogen bromide salt of a bromoaminothiazole and not an open chain analog such as VI, VII, or VIII, is suggested by the evidence that its infrared spectrum shows no absorption in the 4–5-μ region but does show considerable similarity to the hydrobromide salt of 3-amino-1-bromoisoquinoline around 3 μ. In addition, structure VI seems unlikely, as previous attempts[15] to isolate the monohydrobromide adducts of simple nitriles have failed. If formed at all, they appear to disproportionate into nitrile and







the nitrile dihydrobromide. Treatment of II (R = H) with acetic anhydride containing pyridine afforded a bromoacetaminothiazole (IX) which on hydrogenation led to 4-acetaminothiazole (X, R = H). The physical properties of the latter agreed well with those published[16] for this compound, and by direct comparison, were completely dissimilar to those of 2-acetaminothiazole. Clearly then the cyclization of I (R = H) by hydrogen bromide leads to 4-amino-2-bromothiazole hydrobromide and not to the alternate 2-amino-4-bromothiazole salt, a result in agreement with the corresponding cyclization[2] of 2-cyanobenzyl cyanide. By analogy, similar structural assignments were made to those cyclized products prepared from

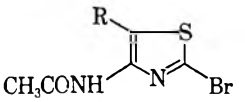


(15) F. Klages and W. Grill, *Ann.*, **594**, 21 (1956).

(16) H. Erlenmeyer and D. Markees, *Helv. Chim. Acta*, **29**, 1229 (1946).

TABLE II

PREPARATION OF 4-ACETAMINO-2-BROMOTHIAZOLES



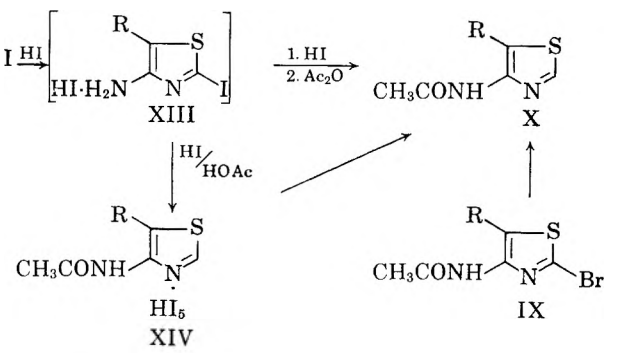
R	Method	Cryst. from[a]	M.p., °C.	Yield, %	Formula	Analyses: Calcd. C	H	Br	N	S	Found C	H	Br	N	S
H	A	A–P	165	86	$C_5H_6BrN_2OS$	27.2	2.3	36.1	12.7	14.5	27.1	2.0	35.9	12.7	14.7
C_3H_7	B	MC–P	107–109	43	$C_8H_{11}BrN_2OS$	36.5	4.2	30.4	10.6	12.2	36.6	3.9	30.3	10.6	12.3
C_6H_5	C	EE	160–162	74	$C_{11}H_9BrN_2OS$	44.5	3.1	26.9	9.4	10.8	44.5	3.0	27.1	9.2	10.7
2-ClC_6H_4	B	EE	120–121	55	$C_{11}H_8BrClN_2OS$	39.8	2.4	..	8.4	9.7	39.5	2.3	..	8.4	9.7
4-ClC_6H_4	B	EE	182–183	80	$C_{11}H_8BrClN_2OS$	39.8	2.4	24.1	8.4	9.7	39.7	2.4	24.3	8.4	9.8
2,4-$Cl_2C_6H_3$	B	EE–P	134–136	94	$C_{11}H_7BrCl_2N_2OS$	36.3	2.0	..	7.7	8.8	36.0	1.7	..	7.7	8.9
2-$CH_3OC_6H_4$	C	EE	143–145	83	$C_{12}H_{11}BrN_2O_2S$	44.0	3.4	24.4	8.6	9.8	43.6	3.4	24.2	8.4	9.7
2-$NO_2C_6H_4$	A	EE	118–120	20	$C_{11}H_8BrN_3O_3S$	38.6	2.4	23.4	12.3	9.4	38.4	2.1	23.8	12.1	9.3
4-$CH_3CONHC_6H_4$	C	ET	229–233	88	$C_{13}H_{12}BrN_3O_2S$	44.1	3.4	22.6	11.9	9.1	43.9	3.3	22.4	12.0	8.8

[a] Solvent key: A = acetone; ET = ethanol; EE = ethyl acetate; others as in Table I.

I where R = alkyl or aryl. In general, these materials were characterized as their 4-acetamino derivatives by treatment with acetic anhydride, and the latter are listed in Table II. In some cases, if base was excluded during the acetylation step and the mixture heated, an N,N-bisacetylamino compound (XI) could be isolated as the sole product. This was converted easily to the monoacetyl compound by a mild basic hydrolysis.

Some solvolysis reactions of II (R = H) also were examined and appear to be rather complex. Treatment with water almost immediately led to a very insoluble substance which was unaffected by acetic anhydride in the presence of hydrogen bromide and acetic acid. Its elemental analysis corresponds well with that required by $C_3H_5BrN_2OS$, and from its infrared spectrum and the fact that it releases bromide ion on treatment with sodium hydrogen carbonate we have assigned to it the structure 4-imino-2-oxothiazolidine hydrobromide. Treatment of II (R = H) with sodium hydrogen carbonate solution gave a bright yellow insoluble material which within minutes began to decompose, changing eventually to a mottled purple substance which could not be recrystallized without further decomposition. If following the subsidence of effervescence, the moist material was immediately transferred to an excess of acetic anhydride in pyridine, a highly crystalline product could be isolated, which, from its elemental analysis is assigned the empirical formula $C_8H_{13}BrN_4O_6S_2$. Further work on the material is continuing. Lastly, boiling II (R = H) with hydrochloric acid led to thiazolidine-2,4-dione (XII), identified by comparison with an authentic sample.[17]

The action of other halogen acids on I also was examined. The reaction of hydrogen iodide was more complex than that of hydrogen bromide. Thus, I (R = H) treated with hydrogen iodide in acetic acid initially gave a brown solid which quickly redissolved with the liberation of iodine. Addition of acetic anhydride after one hour then afforded 4-acetaminothiazole directly. When acetic anhydride was omitted and the reaction mixture was allowed to stand overnight, a black crystalline precipitate was formed. From its elemental analysis and its conversion by a basic solution of sodium thiosulfate to 4-acetaminothiazole, it appears to be a hydrogen iodide periodide (XIV, R = H) of the latter substance. Presumably these reactions proceed through a 4-amino-2-iodothiazole salt (XIII, R = H) which then undergoes reductive deiodination[18] by the excess of hydrogen iodide present. Reductive cleavage



of the thiocyanate group also occurs for besides the expected 4-acetaminothiazole (X, R = 2, 4-$Cl_2C_6H_3$), hydrogen iodide treatment of I (R = 2, 4-$Cl_2C_6H_3$) affords some 2,4-dichlorobenzyl cyanide.[19] The former product was identified by hydrogenation of 4-acetamino-2-bromo-5-(2,4-dichlorophenyl)thiazole (IX, R = 2, 4-$Cl_2C_6H_3$) using a palladium catalyst, which removed only bromine from the molecule.

By contrast, hydrogen chloride treatment of I (R = H) in acetic acid did not lead to the desired 4-amino-2-chlorothiazole compounds. A precipitate did appear but acetylation with acetic anhydride afforded only a small amount of a compound containing no chlorine, whose elemental analysis is in agreement with that of $C_5H_6N_2SO_2$. The infrared spectrum of the material showed bands at 3.05, 3.22, 5.90, and 6.17 μ which suggests that it may be 4-acetamino-2-oxo-4-thiazoline. No further work was done with this compound.

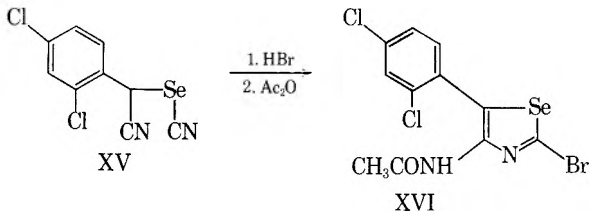
Selenazoles.—An attempt was made to extend the above cyclization procedures to the preparation of 1,3-selenazoles. Cyanomethyl selenocyanate, prepared from potassium selenocyanate and chloroacetonitrile in boiling alcohol, when treated with hydrogen bromide

(17) W. Davies, J. A. Maclaren, and L. R. Wilkinson, *J. Chem. Soc.*, 3491 (1950).

(18) Such facile deiodination in the thiazole series is not unprecedented. Y. Garreau [*Compt. rend.*, **230**, 448 (1950)] observed that 2-amino-4-iodo-5-methylthiazole was reduced to 2-amino-5-methylthiazole by a mixture of hydrogen chloride and allyl alcohol.

(19) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).

in ether, deposited selenium. After treatment of the reaction mixture with acetic anhydride, no 4-acetamino-2-bromoselenazole could be isolated. α-Cyano-2,4-dichlorobenzyl selenocyanate (XV) behaved in much the same manner. However, in this case a trace of a substance was obtained after acetylation whose infrared spectrum resembled that of the corresponding thiazole (IX, R = 2, 4-$Cl_2C_6H_3$). Unfortunately, insufficient material was obtained for analysis but it does appear to be the required XVI. Hydrogen chloride in the case of



XV XVI

XV caused selenium deposition and did not lead to any selenazole compound.

The reactions presented in this paper represent a new approach to the synthesis of thiazoles and in particular to 4-aminothiazoles. Although a number of 2,4-diaminothiazoles are known,[17,20-24] only a few derivatives of 4-aminothiazole itself have been reported. The previously mentioned 4-acetaminothiazole and its precursor 4-acetamino-2-chlorothiazole were prepared by Erlenmeyer and Markees[16] while 4-amino-2,5-diphenylthiazole, the only known free 4-aminothiazole, was synthesized by Taylor, *et al.*[25] Nevertheless, no general synthetic pathway to these materials has been described before, and the methods presented here now make them easily available.

Further reactions of these compounds will be presented in a later paper.

Experimental

Melting points were determined on a Fisher-Johns melting point block and are not corrected. Infrared spectra were recorded on a Baird spectrophotometer Model no. 4-55 as films or as Nujol mulls. Hydrogen bromide (30–33%) in acetic acid was used as supplied by Eastman Kodak.

α-Chloro-2-methoxybenzyl Cyanide.—2-Methoxybenzaldehyde (82 g.) was added to a solution of sodium bisulfite (100 g.) in water (750 ml.). The mixture which became homogeneous almost immediately was cooled to 12° and treated with a solution of potassium cyanide (45 g.) in water (100 ml.), with stirring during 30 min. This reaction solution was then extracted with ether (two 200-ml. portions) and organic phase dried over anhydrous magnesium sulfate. After removal of the latter, pyridine (5 ml.) was added, followed by a solution of thionyl chloride (80 g.) in ether (100 ml.). The second reagent was added during 40 min. at room temperature and thereafter the mixture was refluxed for 6 hr. The ether layer was removed by decantation, washed twice with water (two 100-ml. portions), and, after drying over anhydrous magnesium sulfate, evaporated to give a brown oil (79 g.). Distillation of this liquid under reduced pressure afforded only one fraction (45.4 g.), b.p. 113° (0.5 mm.), $n^{25}D$ 1.5430, which solidified after standing at room temperature for two weeks, m.p. 40–42°. A sample redistilled for analysis boiled at 123° (3.3 mm.), $n^{25}D$ 1.5429.

Anal. Calcd. for C_9H_8ClNO: C, 59.5; H, 4.4; Cl, 19 5; N, 7.7. Found: C, 59.7; H, 4.5; Cl, 19.4; N, 7.7.

α-4-Dichlorobenzyl Cyanide.—The procedure used was exactly the same as that of the preceding example. From 4-chlorobenzaldehyde (21.1 g.) there was obtained a crude brown oil (24.5 g.) which when distilled under reduced pressure afforded pure α,4-dichlorobenzyl cyanide (17.5 g.), b.p. 85–87° (0.18 mm.), $n^{25}D$ 1.5575.

Anal. Calcd. for $C_8H_5Cl_2N$: C, 51.6; H, 2.7; Cl, 38.1; N, 7.5. Found: C, 51.5; H, 2.8; Cl, 38.2; N, 7.5.

4-Acetamino-α-chlorobenzyl Cyanide.—4-Acetamino-α-cyanobenzyl alcohol, m.p. 80°, was prepared in quantitative yield from 4-acetaminobenzaldehyde according to the procedure of Buck.[26] It exhibited bands in the infrared spectrum at 2.95 (–OH) and 6.01 μ (acetamino). Nitrile absorption was not apparent between 4 and 5 μ, but this is not unusual with α-hydroxynitriles. This material (7 6 g.) was suspended in dry ether (50 ml.), and triethylamine (4.1 g.) added, followed by a solution of thionyl chloride (15 g.) in ether (20 ml.). The latter was added dropwise during 20 min. and the suspended solid turned a yellow color but not dissolve. The mixture was refluxed for 1.5 hr. and water then added, whereupon all solid present went into solution. The ether phase was separated, washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness. The resulting brown material was crystallized from methylene chloride–ether (with charcoal decolorizing) to give a yellow solid, m.p. 120–122° (4.15 g.). A sample recrystallized for analysis had m.p. 124–127°.

Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.6; H, 4.3; Cl, 17.0; N, 13.4. Found: C, 57.8; H, 4.1; Cl, 17.0; N, 13.4.

α,α′-Dichlorobenzene-1,4-bisacetonitrile.—Terephthalaldehyde (6.5 g.) was added to liquid hydrogen cyanide (50 ml.). After stirring for 1 min., the mixture became homogeneous, then within 3 min. a solid began to precipitate. Two hours later, the excess hydrogen cyanide was removed *in vacuo* and the residual solid, presumed to be terephthalaldehyde biscyanohydrin, suspended in ether (25 ml.). Thionyl chloride (18 g.) in ether (25 ml.) was added dropwise and the mixture refluxed for 2 hr. The solution was washed with water (five 10-ml. portions), dried over magnesium sulfate, and the ether removed by distillation. The resulting solid (8.5 g.), m.p. 100–120°, when crystallized from methylene chloride–carbon tetrachloride afforded crystals (2.1 g.), m.p. 132–135°. Recrystallization from ether–petroleum ether (b.p. 30–60°) led to the pure material, m.p. 139–141°. Its infrared spectrum showed a band at 4.41 μ.

Anal. Calcd. for $C_{10}H_6Cl_2N_2$: C, 53.4; H, 2.7; Cl, 31.5; N, 12.4. Found: C, 53.1; H, 2.6; Cl, 31.3; N, 12.4.

α-Cyano-β-phenylethyl 4-Toluenesulfonate.—Phenyl acetaldehyde (24 g.) in 50% ethanolic solution was poured onto 4-toluenesulfonyl chloride (19 g.) and to this paste was added potassium cyanide (6.5 g.) in water (25 ml.) with cooling and stirring. After standing 5° overnight, the solid (12 g.) which had precipitated was removed by filtration and recrystallized from ethanol to give pure α-cyano-β-phenylethyl 4-toluenesulfonate (2.7 g.), m.p. 77–78°.

Anal. Calcd. for $C_{16}H_{15}NO_3S$: N, 4.6; S, 10.6. Found: N, 4.7; S, 10.9.

4-Tolyl Disulfone.—4-Nitrobenzaldehyde (15 g., 0.1 mole) and 4-toluenesulfonyl chloride (19 g., 0.1 mole) were dissolved in dioxane (100 ml.) and the resulting solution treated dropwise with potassium cyanide (6.5 g., 0.1 mole) in water (25 ml.). After standing overnight the mixture was diluted with a large volume of water and extracted with methylene chloride (two 100-ml. portions). This extract was dried over magnesium sulfate and evaporated to small bulk. Dilution with acetone then afforded a white crystalline precipitate (1.4 g.), m.p. 205–206°. Several recrystallizations raised the melting point to 210–211° (reported[11] m.p. 212°). The infrared spectrum of this substance showed bands at 7.46 and 8.79 μ, characteristic of a sulfone group.

Anal. Calcd. for $C_{14}H_{14}O_4S_2$: C, 54.2; H, 4.55; S, 20.7. Found: C, 54.3; H, 4.2; N, 20.9.

α-Cyanoalkyl Thiocyanates (I).—The requisite α-chloroalkyl cyanide or α-cyanoalkyl 4-toluenesulfonate (0.02 mole) was dissolved in anhydrous dimethylformamide (10 ml.) and a solution of dry sodium or ammonium thiocyanate (0.021 mole) in the same solvent (10 ml.) added in one portion at room temperature.

(20) K. Gapanathi and A. Venkataraman, *Proc. Ind. Acad. Sci.*, **22A**, 359 (1945).

(21) S. C. De and P. K. Datta, *Sci. Cult.* (Calcutta), **11**, 150 (1945); *Chem. Abstr.*, **40**, 1804 (1946).

(22) A. H. Land, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **11**, 617 (1946).

(23) R. M. Dodson and H. W. Turner, *J. Am. Chem. Soc.*, **73**, 4517 (1951).

(24) B. H. Chase and J. Walker, *J. Chem. Soc.*, 4443 (1955).

(25) E. C. Taylor, J. A. Anderson, and G. A. Berchtold, *J. Am. Chem. Soc.*, **77**, 5444 (1955).

(26) J. S. Buck, *ibid.*, **55**, 3388 (1933).

In most cases precipitation of ammonium or sodium chloride or the corresponding 4-toluenesulfonate salt was complete in half an hour. The mixture was then filtered into ice–water and the precipitate collected and crystallized from the appropriate solvent.

Cyanomethyl Thiocyanate.—To a solution of sodium thiocyanate (40.5 g., 0.5 mole) in methanol (250 ml.) there was added chloroacetonitrile (37.75 g., 0.5 mole) in one portion. The mixture was refluxed for 22 hr., with good stirring and the sodium chloride (28 g.) then removed by filtration. The filtrate was evaporated under reduced pressure to remove methanol and the water-soluble residue taken up in methylene chloride, dried over calcium chloride, and stirred with decolorizing charcoal. The methylene chloride was then evaporated under reduced pressure. This procedure was necessary to remove traces of basic inorganic salts which, if still present when the crude product was distilled, led to an explosion.

The pale brown liquid was twice distilled through a 6-in. Vigreux column to give pure cyanomethyl thiocyanate, b.p. 100–101° (1.5 mm.) (30.9 g., yield 62.0%). A sample redistilled for analysis boiled at the same temperature and pressure and had $n^{25}D$ 1.5088.

Anal. Calcd. for $C_3H_2N_2S$: C, 36.7; H, 2.1; N, 28.6; S, 32.7. Found: C, 36.6; H, 1.9; N, 28.6; S, 32.9.

1-Cyanobutyl Thiocyanate.—To a mixture of butyraldehyde (21.6 g., 0.3 mole) and benzenesulfonyl chloride (53 g. 0.3 mole) there was added dropwise with stirring a solution of potassium cyanide (19.5 g., 0.3 mole) in water (45 ml.). After stirring for 2 hr., the reaction mixture was poured into methylene chloride and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure. The residual sirup (64 g.) was added to a solution of ammonium thiocyanate (18 g., 0.245 mole) in ethanol (120 ml.) and the whole stirred at 40° for 4 hr. A yellow solid (7 g.) which had separated was removed by filtration (this material was not investigated), and the filtrate concentrated under reduced pressure. The semisolid residue was stirred vigorously with ether and the undissolved solid removed by filtration. The ethereal extract was washed three times with water, dried over anhydrous magnesium sulfate, and the ether removed evaporatively. The liquid thus obtained was distilled and that fraction (11.6 g.) distilling at 85–98° (0.5 mm.) collected. Redistillation at the same pressure afforded pure 1-cyanobutyl thiocyanate (10.6 g., yield 25%), b.p. 95°, $n^{25}D$ 1.4805. Its infrared spectrum showed absorption bands at 4.45 and 4.60 μ.

Anal. Calcd. for $C_6H_8N_2S$: C, 51.4; H, 5.8; N, 20.0; S, 22.9. Found: C, 51.5; H, 5.8; N, 19.9; S, 23.0.

Cyanomethyl Selenocyanate.—A solution of potassium selenocyanate (30 g.) in water (90 ml.) was added, in one portion, to chloroacetonitrile (31.5 g.) in methanol (250 ml.) and the mixture refluxed overnight. The solvents were removed under reduced pressure, and the residual sludge of oil and salt extracted with methylene chloride. The extract was stirred with anhydrous magnesium sulfate, and the methylene chloride and excess chloroacetonitrile then removed under reduced pressure. The dark red oily product was fractionally distilled and that portion (15.4 g.) boiling at 131–134° (0.45 mm.) collected. Refractionation of this material through a 4-in. Vigreux column gave a fairly pure sample of cyanomethyl thiocyanate (13.3 g.), b.p. 118° (0.3 mm.). Its infrared spectrum showed bands at 4.44 (nitrile) and 4.62 μ (selenocyanate).

Anal. Calcd. for $C_3H_2N_2Se$: C, 24.8; H, 1.4; N, 19.3. Found: C, 25.0; H, 1.6; N, 19.4.

A later fraction (3.6 g.), b.p., 138–140° (0.45 mm.) obtained from the first distillation showed only a single band (at 4.44 μ) in its infrared spectrum and we consider this to be biscyanomethyl selenide derived undoubtedly from some potassium selenide impurity in the potassium selenocyanate.

2,4-Dichloro-α-cyanobenzyl Selenocyanate.—2,4-Dichloro-α-cyanobenzyl 4-toluenesulfonate (6.05 g.) dissolved in dimethylformamide (50 ml.) was treated with solution of potassium selenocyanate (2.5 g.) in water (7.5 ml.). The mixture was allowed to stand at room temperature for 20 hr. and then poured into ice–water. The solid precipitate was removed by filtration and dried (4.3 g., 89%). A sample recrystallized from methylene chloride–ether had m.p. 151–152° (softening at 142°). Its infrared spectrum showed absorption bands at 4.45 (–CN) and 4.62 μ (–SeCN).

Anal. Calcd. for $C_9H_4Cl_2N_2Se$: C, 37.3; H, 1.4; N, 9.7. Found: C, 37.2; H, 1.4; N, 9.6.

Cyclization of Dinitriles with Hydrogen Bromide. Method A.—The α-cyanoalkyl thiocyanate was dissolved in ten to twenty times its weight of dry ether, and anhydrous hydrogen bromide passed through the solution at 0° for 1.5 hr., or until precipitation of the solid appeared complete. The solid was removed by filtration under a dry atmosphere and then added to an excess of a 2:1 mixture of acetic anhydride–pyridine. After 2 hr. at room temperature, the mixture was poured into 20% aqueous sodium acetate and stirred for a short period. The resulting solid was removed by filtration, washed with water, and dried, then recrystallized from the appropriate solvent.

Treatment of cyanomethyl thiocyanate (3 g.) in this way led to the immediate deposition of a faintly yellow crystalline solid (6.6 g.) with no definite melting point. It decomposed slowly at 140–180°. Its infrared spectrum showed bands at 3.25, 3.88, 6.40, and 6.65 μ. 3-Amino-1-bromoisoquinoline hydrobromide had corresponding bands in the same regions.

Anal. Calcd. for $C_3H_4Br_2N_2S$: C, 13.9; H, 1.6; Br, 61.5; N, 10.8; S, 12.3. Found: C, 13.8; H, 1.7; Br, 61.0; N, 10.6; S, 12.4.

Method B.—The α-cyanoalkyl thiocyanate was dissolved in three times its weight of glacial acetic acid and added to a solution of acetic acid containing three equivalents of hydrogen bromide with stirring at 10°. After 2 hr., a fivefold excess of acetic anhydride was added at the same temperature, and 2 hr. later the mixture poured into water containing a little pyridine. The precipitate was then treated as under method A.

Method C.—This was identical with method B, except that a 3:1 mixture of acetic anhydride–pyridine was used to effect acetylation.

4-(N,N-Bisacetylamino)-2-bromo-5-phenylthiazole.—α-Cyanobenzyl thiocyanate (1.0 g.) in benzene (30 ml.) was treated with hydrogen bromide for 45 min. and the precipitate collected and added to acetic anhydride (5 ml.). After heating for 30 min. at 100°, the product was isolated in the usual way. Recrystallization from ethyl acetate gave the pure compound (1.59 g., 82%), m.p. 150–151°. Its infrared spectrum showed a band at 5.80 μ.

Anal. Calcd. for $C_{13}H_{11}BrN_2O_2S$: Br, 23.6; N, 8.3; S, 9.5. Found: Br, 23.6; N, 8.3; S, 9.3.

4-(N,N-Bisacetylamino)-2-bromo-5-(4-chlorophenyl)thiazole.—Using exactly the same procedure as before α-cyano-4-chlorobenzyl thiocyanate (1.3 g.) was converted to the title compound in 92% yield. The product was recrystallized from ethyl acetate, m.p. 202–204°.

Anal. Calcd. for $C_{13}H_{10}BrClN_2O_2S$: C, 41.8; H, 2.7; N, 7.5; S, 8.6. Found: C, 41.7; H, 2.5; N, 7.7; S, 8.5.

A sample (1.0 g.) of this material in ethanol (35 ml.) was refluxed for 30 min. with sodium hydrogen carbonate (0.23 g.) in water (10 ml.). Evaporative removal of the ethanol followed by dilution with water led to 4-acetamino-2-bromo-5-(4-chlorophenyl)thiazole (0.8 g.) identical in all respects with the material prepared as described earlier.

4-Acetaminothiazole.—A solution of 4-acetamino-2-bromothiazole (0.22 g.) in ethanol (75 ml.) containing sodium acetate (84 mg.) was stirred in an atmosphere of hydrogen with a 10% palladium-on-charcoal catalyst (50 mg.) for 3 hr. At the end of this time, hydrogen absorption ceased and the catalyst and solvent were removed in the usual way. Extraction of the residue led to 4-acetaminothiazole (0.12 g.), m.p. 176–178° (reported[16] m.p. 175–176°), which crystallized as flat blades from carbon tetrachloride. The infrared spectrum of this material with bands at 3.10 and 5.94 μ was completely different from that of a specimen of 2-acetaminothiazole of m.p. 203°.

Anal. Calcd. for $C_5H_6N_2OS$: C, 42.2; H, 4.3; N, 19.7; S, 22.6. Found: C, 42.1; H, 4.2; N, 19.4; S, 22.5.

The Action of Hydrogen Iodide on Cyanomethyl Thiocyanate. (a).—A solution of cyanomethyl thiocyanate (2.0 g.) in acetic acid (10 ml.) was added dropwise to 13% hydrogen iodide in acetic acid (50 ml.). The dark brown solid that appeared quickly redissolved and after 1 hr. acetic anhydride (10 ml.) was added and the solution stirred for 2 hr. Isolation of the product by dilution with water and methylene chloride extraction afforded 4-acetaminothiazole (0.7 g.), m.p. 174–178°, identical with a specimen prepared by the procedure described previously.

(b).—When reaction was carried out as in method A but the addition ofacetic an hydride was omitted, and the reaction allowed to proceed for 24 hr., a highly crystalline black precipitate formed

(4.7 g.). This was removed by filtration and washed with methylene chloride.

Recrystallization proved difficult and the material was analyzed as such.

Anal. Calcd. for $C_5H_7I_5N_2OS$: C, 7.7; H, 0.9; I, 81.6; N, 3.6. Found: C, 7.7; H, 0.6; I, 79.6; N, 4.1.

A specimen (0.5 g.) of this material treated with a mixture of sodium hydrogen carbonate and sodium thiosulfate solutions afforded 4-acetaminothiazole (82 mg., 91%), m.p. 175–178°.

4-Acetamino-5-(2,4-dichlorophenyl)thiazole. (a).—To α-cyano-2,4-dichlorobenzyl thiocyanate (1.2 g.) suspended in glacial acetic acid (10 ml.) there was added dropwise at 5° a solution (12 g.) of hydrogen iodide (10–12%) in the same solvent. After an additional 30 min. at this temperature, acetic anhydride (3 ml.) was added and the liquid allowed to stand for 2 hr. at room temperature, then poured into 20% sodium acetate solution. Extraction with methylene chloride afforded a noncrystallizable gum which was redissolved in methylene chloride and percolated through a silica gel (5 g.) column. The initial eluate yielded an oil which slowly crystallized affording 2,4-dichlorobenzyl cyanide (50 mg.), m.p. 57–58° (reported[19] m.p. 58–59°). The infrared spectrum of this material had a band at 7.07 μ characteristic of a methylene group in a benzyl cyanide system.

Further elution of the column with ethyl acetate led to a second oil which when recrystallized from methylene chloride–ether afforded 4-acetamino-5-(2,4-dichlorophenyl)thiazole (0.35 g.), m.p. 115–116°. This material did not depress the melting point of a specimen prepared according to the procedure following.

Anal. Calcd. for $C_{11}H_8Cl_2N_2OS$: C, 46.0; H, 2.8; Cl, 24.7; N, 9.8; S, 11.2. Found: C, 46.0; H, 2.6; Cl, 24.5; N, 9.7; S, 11.2.

(b).—4-Acetamino-2-bromo-5-(2,4-dichlorophenyl)thiazole (1.0 g.) was dissolved in ethanol (60 ml.) containing potassium hydroxide (0.23 g.) and the resulting solution stirred under hydrogen in the presence of a 10% palladium-on-charcoal catalyst (0.15 g.). Hydrogen absorption had almost ceased after 2 hr. and the catalyst and solvent were removed by the usual methods. The residue was extracted with methylene chloride, and the extract concentrated and diluted with ether. Cooling to 5° caused crystallization of the product (0.45 g., 59% yield). A further crystallization from ethyl acetate gave the pure substance, m.p. 116–117°. Its infrared spectrum was identical with that of the material prepared by method a.

The Action of Hydrogen Chloride on Cyanomethyl Thiocyanate.—Cyanomethyl thiocyanate (0.1 g.) in ether (5 ml.) was saturated at room temperature with hydrogen chloride. After 1 hr. the yellow precipitate was removed and heated with acetic anhydride (~5 ml.) until solution was complete. The mixture was then poured into sodium acetate solution and the product isolated by methylene chloride extraction. Crystallization of the latter from acetone–petroleum ether (b.p. 66–67°) led to fine white needles, m.p. 202–206° (20 mg.).

Anal. Calcd. for $C_5H_6N_2O_2S$: C, 38.0; H, 3.8; N, 17.7; S, 20.3. Found: C, 38.1; H, 3.6; N, 17.5; S, 20.3.

Solvolysis Experiments with 4-Amino-2-bromothiazole Hydrobromide. (a).—The hydrobromide (1.0 g.) was stirred vigorously with water (15 ml.) for 15 min. and the undissolved solid removed by filtration and dried (0.5 g.), m.p. >280°. Its infrared spectrum showed bands at 5.92 and 6.20 μ.

Anal. Calcd. for $C_3H_5BrN_2OS$: C, 18.3; H, 2.6; Br, 40.6; N, 14.2; S, 16.3. Found: C, 18.4; H, 2.5; Br, 40.4; N, 14.1; S, 16.0.

(b).—The hydrobromide (4.0 g.) was added, with stirring, in one portion to 10% sodium hydrogen carbonate solution (200 ml.). As soon as effervescence had subsided, the solid was removed and, while still damp, added to a mixture of pyridine (20 ml.) and acetic anhydride (20 ml.) and the resulting mixture stirred for 1 hr. The clear solution was poured into water and the product isolated by methylene chloride extraction. The resulting brown gum crystallized easily from methanol and gave a highly crystalline solid (1.0 g.), m.p. 178–180° (effervesces at 110–120°). Two further crystallizations afforded the pure material, m.p. 184–185°, as large diamonds. Its infrared spectrum showed absorption at 2.97, 3.05, 3.11, 3.12, 5.92, and 6.52 μ.

Anal. Calcd. for $C_8H_{13}BrN_4O_6S_2$: C, 23.7; H, 3.2; Br, 19.7; N, 13.8; S, 15.8. Found: C, 23.5; H, 3.2; Br, 20.0; N, 13.8; S, 16.0.

(c).—The hydrobromide (0.5 g.) was refluxed with 5 *N* hydrochloric acid (10 ml.) for 3 hr. Evaporation of the solution to dryness followed by crystallization of the residue from ether–petroluem ether (b.p. 30–60°) afforded colorless prisms of thiazolidine-2,4-dione, m.p. 126–127° undepressed on admixture with an authentic specimen.

The Action of Hydrogen Bromide on α-Cyano-2,4-dichlorobenzyl Selenocyanate.—The selenocyanate (0.4 g.) was suspended in glacial acetic acid (4 ml.) and stirred while hydrogen bromide in acetic acid (1 g., 30% hydrogen bromide) was added dropwise. The reaction mixture immediately became homogeneous and turned a dark brown color. After 30 min., an excess of acetic anhydride was added and the solution then allowed to stand a further 3 hr. The mixture was poured into 20% sodium acetate solution and deposited selenium removed by filtration. The filtrate was processed by methylene chloride extraction which led to a small amount of a sirup. On standing in the refrigerator, this deposited crystals (6 mg.), m.p. 170° (softening at 160°). Its infrared spectrum showed bands at 3.09 and 6.00 μ.

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Hydrogenation of Diels–Alder Adducts of Anthracene[1]

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In the presence of ruthenium catalyst, hydrogen attacks selectively only one aromatic ring in 9,10-dihydroanthracene-9,10-endo-α,β-succinic anhydride (I). Several diesters and an N-substituted imide were prepared from the resulting hydrogenation product (II). In the presence of Raney nickel, the action of hydrogen on I is nonselective. In contrast to I, hydrogenation of 11-methylol-9,10-dihydro-9,10-ethanoanthracene in the presence of ruthenium catalyst proceeds with attack on both aromatic rings. This difference is attributed to steric effects.

The Diels–Alder condensation of anthracene with dienophiles is a reversible, temperature-dependent reaction.[2] At higher temperatures, usually above 200°, the equilibrium is shifted in favor of the polycyclic hydrocarbon.[3] Pyrolysis of anthracene adducts has been suggested as a means of purifying anthracene or unsaturated alcohols.[4] The low thermal stability of these adducts excludes their use as potential starting materials for the preparation of polymers. It was thought that hydrogenation of one or both benzene

(1) Paper presented before the Division of Fuel Chemistry, 143rd National Meeting of the American Chemical Society, Cincinnati, Ohio, January, 1963.

(2) For numerous references, see M. C. Kloetzel, *Org. Reactions*, **4**, Chap. 1 (1948).

(3) (a) W. E. Bachmann and M. C. Kloetzel, *J. Am. Chem. Soc.*, **60**, 481 (1938); (b) R. Norman Jones, C. J. Gogek, and R. W. Sharpe, *Can. J. Research*, **26B**, 719 (1948).

(4) C. W. Smith and R. T. Holm, U. S. Patent 2,761,883 (1956).

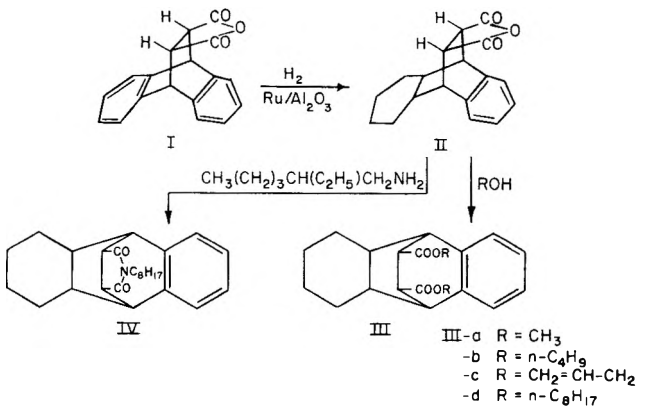
TABLE I

DIESTERS (III) AND N-SUBSTITUTED IMIDE (IV)

Formula	Yield, %	B.p., °C. and $n^{25}D$	M.p., °C.	Molecular formula	Calculated	Found
III-a	77		145–147[a]	$C_{20}H_{24}O_4$	C 73.14	73.49
					H 7.37	7.53
III-b	85	220–225 (1.5 mm.) 1.5710		$C_{26}H_{36}O_4$	C 75.69	75.13
					H 8.80	8.62
III-c	72	201–203 (0.5 mm.) 1.5420		$C_{24}H_{28}O_4$	C 75.76	75.86
					H 7.42	7.62
III-d	88	245–248 (0.4 mm.) 1.5025		$C_{34}H_{52}O_4$	C 77.82	77.67
					H 9.99	10.01
IV	76	190–232 (0.6 mm.)	72–74[b]	$C_{26}H_{33}NO_2$	C 79.34	79.36
					H 8.96	9.08
					N 3.56	3.30

[a] Recrystallized from hexane–ethyl acetate (10:1). [b] Recrystallized from petroleum ether (30–60°).

rings in these adducts would prevent the pyrolytic reversal reaction and produce compounds of higher thermal stability. This was found to be the case when two anthracene adducts, 9,10-dihydroanthracene-9,10-*endo*-α,β-succinic anhydride (I)[5] and 11-methylol-9,10-dihydro-9,10-ethanoanthracene (VIII),[6] were hydrogenated in the presence of ruthenium catalyst. Hydrogenation of adduct I under high pressure at 145–150° in the presence of ruthenium-on-alumina catalyst led to the absorption of three moles of hydrogen per mole of I, producing 1,2,3,4,4a,9,9a,10-octahydroanthracene-9,10-α,β-succinic anhydride (II).



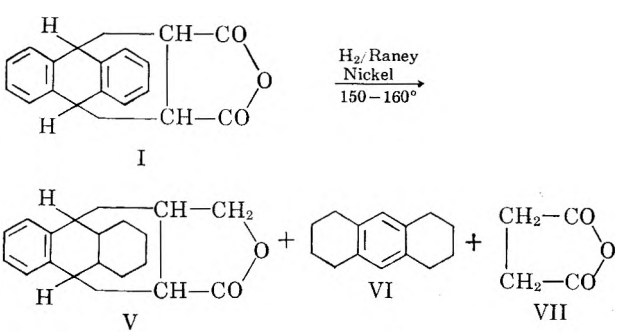
The infrared and ultraviolet spectra were consistent with structure II. The ultraviolet spectrum was that of an *ortho*-disubstituted benzene, and the infrared showed absorption bands characteristic of anhydride and *ortho*-disubstituted benzene groups.

Under the conditions employed, only one benzene ring was hydrogenated. The failure of the second benzene ring to undergo hydrogenation can be explained by steric effects as follows. The molecule of adduct I, which contains a *meso*-dihydroanthracene skeleton, is nonplanar. It has been shown that 9,10-dihydroanthracene is bent about the line joining carbon atoms 9 and 10, each half of the molecule being planar but the two halves inclined to each other at an angle of approximately 145°.[7,8] Assuming that addition of hydrogen to the benzene rings requires a flatwise adsorption of the unsaturated ring against the catalytic surface, it is likely that, due to the bent configuration of adduct I and to the hindering effect of the bulky anhydride group, only one of the benzene rings can be hydrogenated.[9] Inspection of the Godfrey molecular model of the adduct (I) confirms these expectations.

The hydrogenated adduct II, m.p. 145–165°, was a mixture of stereoisomers, and no attempt was made to separate them and determine their configuration. Several derivatives of interest as potential plasticizers or pesticides, such as the diesters (III-a, -b, -c, -d) and the N-substituted imide (IV), which were prepared by standard procedures from II, are listed in Table I.

The foregoing results show that in the presence of a ruthenium catalyst, a selective hydrogenation occurred, resulting in the reduction of the aromatic ring but not affecting the succinic anhydride group of the adduct (I). In contrast, the anhydride group is attacked when a substituted succinic anhydride[10,11] is hydrogenated in the presence of palladium or platinum catalyst, the products obtained being hydroxylactones, lactones, and β-methyl acids. The reduction of adduct I in the presence of Raney nickel at 160° was also nonselective, providing a mixture of compounds. These were 1,2,3,4,4a,9,9a,10-octahydro-9,10-ethanoanthracene-11-methylol-12-carboxylic acid lactone (V), produced by an attack on the aromatic ring and the anhydride group; s-octahydroanthracene (VI); and succinic anhydride (VII).

Products VI and VII could have been formed either by hydrogenolysis or thermal decomposition of the



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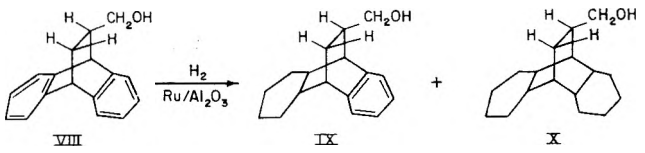
adduct (I) followed by hydrogenation of the intermediates.

The lactone (V), m.p. 125–145°, was a mixture of stereoisomers.

In contrast to I, the hydrogenation of 11-methylol-9,10-dihydro-9,10-ethanoanthracene (VIII) in the presence of ruthenium catalyst proceeds further, with some reduction of both aromatic rings, affording a mixture of 11-methylol-9,10-ethano-1,2,3,4,4a,9,9a,10-octahydroanthracene (IX) and 11-methylol-9,10-ethanoperhydroanthracene (X) in a variable ratio depending upon the reaction time.



VIII IX X

Hydrogenation of both aromatic rings of VIII occurred, since the hindering effect of the hydroxymethyl group is smaller than that of the rigid and bulky anhydride group of I. As in the previous case, no attempt was made to separate the stereoisomers.

Experimental

1,2,3,4,4a,9,9a,10-Octahydroanthracene-9,10-α,β-succinic Anhydride (II).—A mixture of 83 g. of 9,10-dihydroanthracene-9,10-endo-α,β-succinic anhydride (I) (m.p. 261–262°),[3a] 250 ml. of dioxane, and 6.0 g. of 5% ruthenium-on-alumina catalyst was placed in an "Aminco" autoclave, and hydrogen was admitted up to 1350 p.s.i. The vessel was shaken and heated for 16 hr. at 145–148°, after which the absorption of hydrogen ceased. The amount of hydrogen absorbed corresponded to about 3 moles of hydrogen per mole of I. After cooling, the catalyst was removed by filtration and washed with acetone. The filtrate and the washing were combined, and the solvents were removed by distillation, first at atmospheric pressure, then under vacuum. The solid residue, after washing with petroleum ether (30–60°), gave 71 g. (84%) of 1,2,3,4,4a,9,9a,10-octahydroanthracene-9,10-α,β-succinic anhydride (II), m.p. 145–165°. A sample of the anhydride, crystallized from ethyl acetate–petroleum ether, melted at 175–177°. Infrared absorption maxima: 5.45, 5.70, and 13.0 μ. Ultraviolet absorption spectrum in methylene chloride: λ_{max} 247 mμ (ε 248), 253 (270), 260 (297), 263 (216), and 267 (230).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; mol. wt., 282.3. Found: C, 76.67; H, 6.57; mol. wt. (alkaline titration), 283.3.

In order to determine its heat stability, II was heated for 6 hr. in air to 230–240°. A slight discoloration, but no degradation, occurred.

In a second experiment, a modified procedure was employed for purifying the crude hydrogenation product. After separation from the catalyst and removal of the solvent, the solid residue was heated with 5% sodium hydroxide for 5 min. on a steam bath. After cooling and washing with ether to remove the nonacidic products, the aqueous layer was acidified with 15% hydrochloric acid. The precipitated solid, after washing with water and drying, gave the adduct (II) in a yield of 85%.

Hydrogenation of 9,10-Dihydroanthracene-9,10-α,β-succinic Anhydride in the Presence of Raney Nickel.—An "Aminco" bomb was charged with 27.6 g. of the adduct (I), 250 ml. of ethyl alcohol, and 10 ml. of Raney nickel catalyst, and hydrogen was admitted under 1330 p.s.i. at 25°. The bomb was shaken and heated at 160° for 20 hr. The amount of hydrogen absorbed corresponded to about 13.5 moles of hydrogen per mole of the starting adduct. After cooling, the solution of the hydrogenated product was separated from the catalyst by filtration, and the catalyst was washed with ether. The filtrates were combined and the solvents removed, first at atmospheric pressure, then under vacuum. The residue, composed of an oil and a solid, was treated with ethyl alcohol. The solid, insoluble in alcohol, was separated by filtration to give 4.8 g. of *s*-octahydroanthracene. The filtrate, after removal of the solvent by distillation, gave 20 g. of an oil.

In order to separate acidic products from nonacidic, the oil (18 g.) was heated on a steam bath with 120 ml. of 10% sodium hydroxide solution for 2 hr., and, after cooling, was extracted with ether. The nonacidic product, after elimination of ether, gave an additional 5.6 g. of *s*-octahydroanthracene. The total of s-octahydroanthracene isolated from the reaction mixture amounted to 10.4 g., or 56%. The alkaline solution was acidified with concentrated hydrochloric acid, and the precipitated solid was separated by filtration. The aqueous filtrate, after ether extraction and removal of the solvent, afforded 0.4 g. of succinic acid. The precipitated solid (6.0 g.) was crystallized several times from ethyl acetate to yield 1,2,3,4,4a,9,9a,10-octahydro-9,10-ethanoanthracene-11-methylol-12-carboxylic acid lactone, m.p. 125–145°. Infrared absorption maxima: 5.7 (lactone) and 13.0 μ (*ortho*-disubstituted benzene ring).

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 79.74; H, 7.67.

Hydrogenation of 11-Methylol-9,10-dihydro-9,10-ethanoanthracene (VIII).—A mixture of 54 g. (0.228 mole) of 11-methylol-9,10-dihydro-9,10-ethanoanthracene (m.p. 105–108°) (VIII),[12] 250 ml. of ethyl alcohol, and 4.0 g. of 5% ruthenium-on-alumina catalyst was placed in an autoclave, and hydrogen was admitted up to 1630 p.s.i. The vessel was shaken and heated for 6 hr. at 150°, after which the absorption of hydrogen ceased. The amount of hydrogen absorbed corresponded to about 3.8 moles of hydrogen per mole of adduct. After removal of the catalyst and solvent, the residue was distilled to yield 46 g. (84%) of a colorless oil, b.p. 150–175° (0.6 mm.), $n^{25}D$ 1.5480, consisting of a mixture of 11-methylol-9,10-ethanol-1,2,3,4,4a,9,9a,10-octahydroanthracene and 11-methylol-9,10-ethanoperhydroanthracene in an approximate ratio of 3 to 1.

Anal. Calcd. for $3(C_{17}H_{22}O) + C_{17}H_{28}O$: C, 83.89; H, 9.70; mol. wt., 244. Found: C, 83.87; H, 10.20; mol. wt., 248. (From determination of the hydroxyl content by acetylation method.)

Upon cooling, the oil solidified partially. The separated solid, 11-methylol-9,10-ethanoperhydroanthracene, crystallized from hexane, melted at 102–104°. The infrared and ultraviolet spectra of the solid product showed complete disappearance of the aromatic ring.

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.80; H, 11.36. Found: C, 82.71; H, 11.59.

A thermal stability test of the hydrogenated adducts IX and IX + X was conducted as follows: Samples of the products were heated separately in air for 4 hr. at 235–240°. The products became colored, and according to infrared spectra, partial oxidation to the aldehydes occurred (infrared, 5.85 μ). However, no change in the carbon skeleton of the products was observed.

In a similar hydrogenation run, the crude product was separated from the catalyst, a fresh portion of the catalyst (4.0 g.) was added, and the mixture was hydrogenated further at 160° for an additional 17 hr. The reaction mixture contained approximately 30% of IX and 70% of X.

Acknowledgment—This work was carried out by the Coal Chemicals Research Project, sustained by the United States Steel Corporation, to whom the author is grateful for permission to publish these results.

(12) Prepared by the method of H. Krzikalla and E. Woldan, German Patent 740,142 (1943).

The Mechanism of the Reaction between Dehydroacetic Acid and Alkylamines

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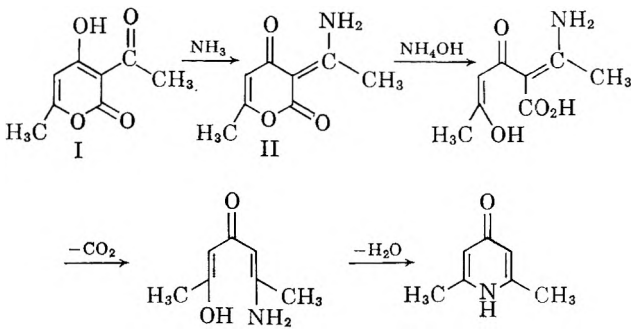
In a study of the conversion of dehydroacetic acid to N-substituted lutidones by reaction with alkylamines, two compounds have been obtained which are considered to be intermediates in the reaction. A mechanism for the reaction is suggested and its relation to a general mechanism for the conversion of γ-pyrones to γ-pyridones is considered.

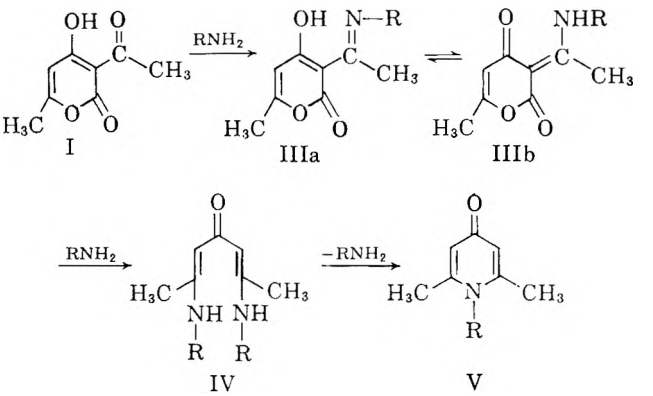
The reaction of dehydroacetic acid with ammonia or primary amines to form lutidones has been known for many years.[1,2] However, during this time there has been no comprehensive study of the reaction mechanism. In 1890, Feist[3] proposed structure II for the compound formed from dehydroacetic acid and ammonia and suggested the following mechanism for its subsequent conversion into lutidone with excess



ammonia. An analogous mechanism may be assumed for the corresponding reaction with alkylamines.

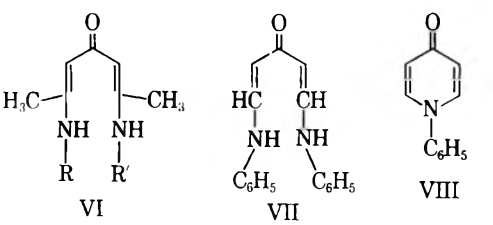
We recently undertook a study of the mechanism of the conversion of dehydroacetic acid into N-substituted lutidones and isolated two intermediates. Dehydroacetic acid reacted with an equivalent amount of aqueous methylamine forming a crystalline compound (m.p. 127–128°), with the empirical formula $C_9H_{11}NO_3$. Ultraviolet spectrum was similar to that of dehydroacetic acid [λ_{max}^{EtOH}, 235 mμ (log ε 4.08) and 311 (log 4.16)]. The compound was readily converted back to dehydroacetic acid in dilute hydrochloric acid. This evidence suggested that this compound was the Schiff base (IIIa) formed by addition of methylamine to the carbonyl group of the acetyl side chain. N.m.r. spectrum (deuteriochloroform) showed three methyl groups, one of which was a doublet, and, since the coupling constant (J = 5.0 c.p.s.) was the same as that for the N-methyl group in N-methylacetamide, the compound probably exists in the tautomeric form IIIb.[4] The compound yielded N-methylacetamide when oxidized with potassium permanganate.

When III (R = Me) was treated with methylamine it was converted into bis-2,7-methylaminohepta-2,5-dien-4-one (IV, R = Me). The n.m.r. spectrum of this compound also exhibited the N-methyl group as a doublet (J = 5.0 c.p.s.). The heptadienone was converted directly into N-methyllutidone with the elimination of one equivalent of methylamine by boiling in water. Similarly dehydroacetic acid when heated with excess methylamine was converted directly into bis-2,7-methylaminohepta-2,5-dien-4-one (IV). Under these conditions none of the intermediate (III) accumulated. The same series of reactions was observed when ethylamine was used.



The mechanism of the conversion of dehydroacetic acid to N-methyl- or N-ethyllutidone can be described by the series of reactions I → III → IV → V.

The simplest mechanism for the conversion of the compound IIIb to the diaminoheptadienone (IV) would be an attack by a molecule of the amine on carbon atom 6, opening the pyrone ring which, after decarboxylation, would yield product IV. In order to verify this mechanism, we attempted to prepare the dienones (VI, R ≠ R′). On treatment of compound III (R = Et) with an equimolar quantity of methylamine a mixture of products resulted. From this mixture,

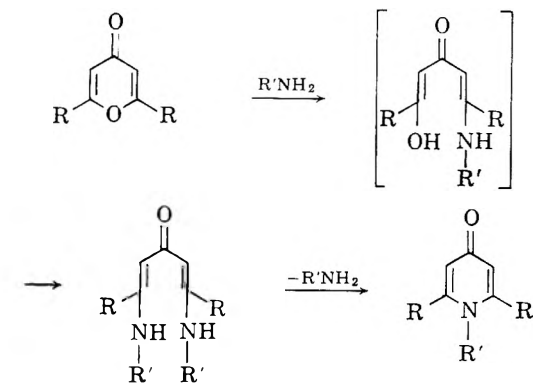


3-ethylidene(α-methylamino)-6-methylpyran-2,4-dione (IIIb, R = Me) was isolated. Using an excess of methylamine the reaction with III (R = Et) yielded bis-2,7-methylaminohepta-2,5-dien-4-one (IV, R = Me) in greater than 50% yield. Similar results were obtained on treatment of III (R = Me) with ethylamine. In no case were mixed dienones IV (R ≠ R′) isolated. A major difficulty in a study of these reaction mixtures is the ease of conversion of the dienones

(1) L. Haitinger, *Ber.*, **18**, 452 (1885).
(2) See references in K. Dimroth, *Angew. Chem.*, **72**, 333 (1960).
(3) F. Feist, *Ann. Chem.*, **257**, 253 (1890).
(4) S. Iguchi, *et al.*, *Chem. Pharm. Bull.* (Tokyo), **7**, 323 (1959), have reported the formation of compounds of type IIIa from the reaction between dehydroacetic acid and various alkylamines and amino acids. However in the case of IIIa (R = Me) the melting points quoted for both the hydrated and anhydrous form of the product were exactly those of N-methyllutidone. On repeating their experimental procedure we obtained a product with the physical constants quoted and we identified this as N-methyllutidone (melting point, mixture melting point, ultraviolet, and n.m.r.).

to the N-substituted lutidones. This aspect of the work is still under review.

A considerable amount of literature exists on the conversion of γ-pyrones to γ-pyridones.[2,5] In the normal course of the reaction no intermediates were obtained, the γ-pyridone being isolated directly. However, Borsche and Bonacker[6] in 1921 observed that in the reaction of aniline with γ-pyrone bisoxymethyleneacetone dianilide (VII) was obtained. This compound could then be converted to N-phenyl-γ-pyridone (VIII). Subsequent work by Campbell, *et al.*,[7] showed that heptadienones could be obtained when 2,6-dimethyl-γ-pyrone reacted with higher alkylamines and more recently Conley, *et al.*,[8] have prepared the heptadienones IV (R = Me and R = Et) by treating 2,6-dimethyl-γ-pyrone with the alkylamine in the cold. In a recent review[5] it has been suggested that the isolation of these diaminoheptadienones does not necessarily mean that they are intermediates in the formation of the lutidone. However, we have now isolated the compounds IV (R = Me and R = Et) under the reaction conditions normally used for the preparation of the lutidone.[9] This would suggest that IV is indeed an intermediate. It would appear from our results that the mechanism proposed by Cavalieri[10] must be modified, as suggested by Conley, *et al.*,[8] to include IV as an intermediate. This is illustrated in Scheme 1.



SCHEME I

Experimental[11,12]

3-Ethylidene-(α-methylamino)-6-methylpyran-2,4-dione (IIIb, R = Me).—Dehydroacetic acid (10.0 g.) was dissolved in 30% aqueous methylamine (10 ml.) and the solution was warmed on a steam bath. After 10 min. the reaction mixture was cooled and the crystals which had formed were collected (9.5 g.). Recrystallization from ethanol gave 3-ethylidene(α-methylamino)-6-methylpyran-2,4-dione as prisms (6.6 g.), m.p. 126–127°.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.65; H, 6.12; N, 7.70. Found: C, 59.65; H, 5.97; N, 7.70. λ_{max}^{EtOH}, 235 mμ (log ε 4.08) and 311 (4.16); infrared($CHCl_3$), 5.90, 6.03, 6.18, and 6.34 μ. N.m.r. ($CDCl_3$), τ values: 4.38 (singlet, 1H); 6.84 (center of doublet, 3H); 7.38 (singlet, 3H); 7.9 (singlet, 3H).

Oxidation of 3-Ethylidene(α-methylamino)-6-methylpyran-2,4-dione.—A solution of the foregoing compound (1.80 g.) in water (50 ml.) was stirred while 150 ml. of 5% aqueous potassium permanganate was slowly added. The temperature of the reaction was not allowed to rise above 30°. After the permanganate solution had been added, the stirring was continued for a further 30 min. The manganese dioxide then was filtered and washed well with water. The filtrate was acidified with dilute hydrochloric acid and evaporated to dryness under reduced pressure. The residue was dissolved in absolute ethanol and the insoluble potassium chloride was filtered and washed with ethanol. The filtrate was evaporated under reduced pressure and the residue chromatographed on an alumina column. N-Methylacetamide (88 mg., 12%) was eluted with benzene–chloroform (1:3).

Treatment of 3-Ethylidene(α-methylamino)-6-methylpyran-2,4-dione with Methylamine.—The compound (III, R = Me) (0.663 g.) was dissolved in 40% aqueous methylamine by gently warming on a steam bath. When solution was complete the warming was continued and after about 5 min. crystals precipitated. The reaction mixture was cooled and the crystals were collected (0.546 g.), m.p. 158–160°. Recrystallization from absolute ethanol gave bis-2,7-methylaminohepta-2,5-dien-4-one as needles, m.p. 162–163°.

Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.56; H, 9.59; N, 16.66. Found: C, 64.56; H, 9.77; N, 16.30. λ_{max}^{EtOH} 372 mμ (log ε 4.37); infrared ($CHCl_3$), 6.13 and 6.35 μ. N.m.r. ($CDCl_3$), τ values: 5.39 (singlet, 2H); 7.10 (center of doublet, 6H); 8.15 (singlet, 6H).

N-Methyllutidone (V, R = Me).—Bis-2,7-methylaminohepta-2,5-dien-4-one (IV, R = Me) (0.338 g.) was dissolved in water (10 ml.) and the resulting solution heated under reflux. The methylamine which formed was passed into picric acid solution (0.520 g. of picric acid in 10 ml. of ethanol). After 1 hr. the reaction was stopped and the methylamine picrate collected (0.375 g.), m.p. 210–211°, unchanged on mixing with an authentic sample. The reaction mixture was cooled and the white needles which separated were collected (0.211 g.), m.p. 247–248°, identical in all respects (melting point, mixture melting point, infrared spectrum, and ultraviolet spectrum) with a known sample of N-methyllutidone.

Bis-2,7-methylaminohepta-2,5-dien-4-one (IV, R = Me).—Dehydroacetic acid (10.0 g.) was dissolved in 40% aqueous methylamine (25 ml.) and the resulting solution was warmed on a steam bath. After 10 min. the reaction mixture was cooled and the crystals which had formed were collected and recrystallized from ethanol yielding bis-2,7-methylaminohepta-2,5-dien-4-one (4.2 g.), m.p. 160–162°. The original mother liquor gave a second crop of crystals (0.7 g.), m.p. 246–248°, identified as N-methyllutidone (melting point, mixture melting point, and ultraviolet spectrum).

3-Ethylidene(α-ethylamino-6-methylpyran-2,4-dione (III, R = Et).—Dehydroacetic acid (10.0 g.) was dissolved in 70% aqueous ethylamine (10 ml.) and the resulting solution was warmed on a steam bath. After 10 min. the reaction mixture was cooled and the crystals which formed were collected (11.0 g.). Recrystallization from ethyl acetate gave 3-ethylidene(α-ethylamino)-6-methylpyran-2,4-dione (6.5 g.), m.p. 87–88°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.58; H, 6.71; N, 7.70. Found: C, 61.39; H, 6.79; N, 7.30. λ_{max}^{EtOH} 236 mμ (log ε 4.03) and 311 (4.18); infrared ($CHCl_3$), 5.90, 6.02, 6.24, and 6.33 μ. N.m.r. ($CDCl_3$), τ values: 4.42 (singlet, 1H); 6.6 (center of multiplet, 2H); 7.40 (singlet, 3H); 7.92 (singlet, 3H); 8.69 (center of triplet, 3H).

Reaction of 3-Ethylidene(α-ethylamino)-6-methylpyran-2,4-dione (III, R = Me) with Ethylamine.—The foregoing compound (0.698 g.) was dissolved in 70% aqueous ethylamine (5 ml.) and the resulting solution was warmed on a steam bath for 3 hr. At the end of this time crystals had formed. After cooling, the crystals were collected and recrystallized from absolute ethanol yielding bis-2,7-diethylaminohepta-2,5-dien-4-one as needles (0.488 g.), m.p. 90–91°.

Anal. Calcd. for $C_{11}H_{20}N_2O$: C, 67.29; H, 10.27; N, 14.27. Found: C, 67.61; H, 10.52; N, 14.51. λ_{max}^{EtOH} 375 mμ (log ε 4.47); infrared ($CHCl_3$), 6.13 and 6.35 μ. N.m.r. ($CDCl_3$), τ values: 5.42 (singlet, 2H); 6.8 (center of multiplet, 4H); 8.15 (singlet, 6H); 8.82 (center of triplet, 6H).

N-Ethyllutidone (V, R = Et).—Bis-2,7-ethylaminohepta-2,5-dien-4-one (0.51 g.) was dissolved in water (8 ml.) and heated under reflux. The ethylamine which formed was flushed out with nitrogen into picric acid solution (0.677 g. of picric acid in 5 ml. of methanol). After 3 hr. the picrate which had formed was

(5) H. Meislich in "Pyridine and its Derivatives," Part III, E. Klingsberg, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 549.

(6) W. Borsche and I. Bonacker, *Ber.*, **54**, 2678 (1921).

(7) K. N. Campbell, A. B. Spooner, and B. K. Campbell, Abstracts of the 118th National Meeting of the American Chemical Society, 1950.

(8) R. T. Conley, E. Nowoswiat, and W. G. Reid, *Chem. Ind.* (London), 1157 (1959).

(9) K. N. Campbell, B. K. Campbell, and J. Ackerman, *J. Org. Chem.*, **15**, 221 (1950).

(10) L. F. Cavalieri, *Chem. Rev.*, **41**, 525 (1947).

(11) All melting points are uncorrected.

(12) N.m.r. spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as an internal reference.

collected and recrystallized from methanol yielding ethylamine picrate (0.52 g.), m.p. 167–169°, unchanged on mixing with an authentic sample. The original reaction mixture was evaporated to dryness under reduced pressure and the residue was recrystallized from ethyl acetate. After two recrystallizations N-ethyllutidone (0.20 g.), m.p. 160–162°, was obtained.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.45; H, 8.68; N, 9.27. Found: C, 71.04; H, 8.64; N, 9.39.

Bis-2,7-ethylaminohepta-2,5-dien-4-one (IV, R = Et).—Dehydroacetic acid (5.0 g.) was dissolved in 70% aqueous ethylamine (25 ml.) and warmed on a steam bath for 30 min. On cooling, crystals precipitated and these were collected (4.0 g.), m.p. 89–90°. Recrystallization from ethanol gave pure bis-2,7-ethylaminohepta-2,5-dien-4-one as needles, m.p. 90–91°.

Acknowledgment.—The author wishes to thank Professor David Shemin for his invaluable help. This work was supported by grants from the National Institutes of Health, U. S. Public Health Service (A-1101), and National Science Foundation.

The Mechanism of the Lithium Aluminum Hydride Cleavage of Alkyl Tosylate

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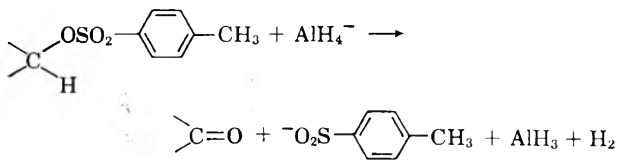
The cleavage of *trans*-9-decalylcarbinyl tosylate with lithium aluminum deuteride does not introduce deuterium into the *trans*-9-decalylcarbinol or the *p*-tolyl disulfide formed by reduction *p*-toluenesulfinate ion generated in the cleavage reaction. It is concluded that the cleavage reaction occurs by nucleophilic attack of aluminohydride ion on sulfonate sulfur.

A common side reaction in the lithium aluminum hydride reduction of alkyl tosylates is cleavage with regeneration of the parent alcohol.[1,2] The most likely stoichiometry for this process involves the formation of *p*-toluenesulfinate ion with the liberation of hydrogen. *p*-Toluenesulfinic acid and its reduction products have been isolated from the reaction when cleavage is the predominant course of the reaction.[1]

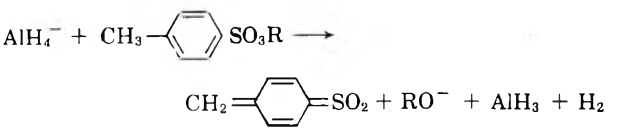
Three possible mechanisms for the cleavage reaction may be considered. The most likely is direct nucleophilic attack on sulfonate sulfur by aluminohydride ion to give an isomer of *p*-toluenesulfinic acid and alkoxide ion. Subsequent reaction with a hydride donor would liberate hydrogen to give *p*-toluenesulfinate ion. There are numerous examples of nucleophilic attack on sulfonate sulfur[3] and this mechanism requires no further comment.

A more speculative mechanism involves the base-catalyzed elimination of the elements of *p*-toluenesulfinic acid to give an intermediate carbonyl compound which would be rapidly reduced in a second step.



This type of elimination has been observed in the reaction of α-*p*-toluenesulfonyloxy ketones with alkoxides[4] and in the conversion of an α-*p*-toluenesulfonyloxylactam to an α-ketolactam with potassium *tert*-butoxide.[5]

The third possible mechanism involves a quinonoid intermediate generated by proton abstraction from the methyl group of the *p*-toluenesulfonate portion of the molecule.



This intermediate would presumably be reduced to *p*-toluenesulfinate by a hydride donor.

To test these mechanisms we have examined the products from the cleavage of an alkyl tosylate with lithium aluminum deuteride. The first mechanism predicts no deuterium incorporation in the recovered alcohol or the *p*-toluenesulfinate and its reduction products. The second mechanism requires incorporation of deuterium at the carbinol carbon atom and the third mechanism requires incorporation of deuterium into the methyl group of *p*-toluenesulfinic acid and its reduction products.

trans-9-Decalylcarbinyl tosylate was chosen as the alkyl tosylate because it is readily available and it has been shown to yield considerable cleavage product, *trans*-9-decalylcarbinol, upon lithium aluminum hydride reduction.[6,7] In the present investigation, the reduction of *trans*-9-decalylcarbinyl tosylate with lithium aluminum deuteride afforded *trans*-9-decalylcarbinol in 25% yield and *p*-tolyl disulfide in 2.5% yield. There was also a quantity of oil obtained which was undoubtedly deuterated *trans*-9-methyldecalin.[6,7] It was found that the *trans*-9-decalylcarbinol contained 0.03 atom of deuterium per molecule.[8] This evidence argues against the cleavage reaction proceeding by way of the aldehyde.

It is conceivable that part of the cleavage reaction occurs by attack of *p*-toluenethiolate ion, formed by reduction of *p*-toluenesulfinate, on sulfonate sulfur to give *p*-tolyl *p*-toluenethiolsulfonate. However, this seems unlikely because the reaction of *cis*-3-benzyloxy-*trans*-9-decalycarbinyl tosylate with benzyl mercaptide ion gives the benzyl thioether.[6]

(1) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).
(2) D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951).
(3) For a leading reference, see J. F. Bunnett and J. Y. Bassett, Jr., *J. Org. Chem.*, **27**, 2345 (1962).
(4) A. S. Kende, *Org. Reactions*, **11**, 285 (1960).
(5) W. G. Kofron, Ph.D. thesis, University of Rochester, 1960.
(6) A. S. Hussey, H. O. Liao, and R. H. Baker, *J. Am. Chem. Soc.*, **75**, 4727 (1953).
(7) W. G. Dauben, J. B. Rogan, and E. J. Blanz, Jr., *ibid.*, **76**, 6384 (1954).
(8) Deuterium analysis were carried out by the falling drop method by Josef Nemeth, Urbana, Ill.

The details of the formation of *p*-tolyl disulfide are not clear. It must be formed from *p*-toluenesulfinate ion originating in the cleavage reaction since the reaction of lithium *p*-toluenesulfonate with lithium aluminum hydride did not give *p*-toluenethiol or *p*-tolyl disulfide under the conditions used for the reduction of *trans*-9-decalylcarbinyl tosylate. It has been claimed that *p*-tolyl disulfide is a primary reaction product from the lithium aluminum hydride reduction of *p*-toluenesulfinic acid.[9] However, disulfides are readily reduced by lithium aluminum hydride[9,10] and in the present case the *p*-tolyl disulfide was probably formed by air oxidation of the corresponding thiol.

By comparing the infrared spectrum of the *p*-tolyl disulfide, obtained from the lithium aluminum deuteride reduction of *trans*-9-decalylcarbinyl tosylate, with spectra of known mixtures of *p*-tolyl disulfide-α,α'-d_2 and normal *p*-tolyl disulfide, it was found to contain less than 0.2 atom of deuterium per molecule. The analysis is complicated by the fact that monodeuterated species might be present in the sample and the authentic *p*-tolyl disulfide-α,α'-d_2 (described in the Experimental section) contained approximately 1.6 atoms of deuterium per molecule. However, the results indicate that the cleavage reaction does not proceed to the extent of 10% through the quinonoid intermediate.

The results are consistent with the lithium aluminum hydride cleavage of alkyl tosylates occurring by nucleophilic attack of aluminohydride ion on sulfonate sulfur. The evidence does not exclude the possibility of nucleophilic attack on oxygen. However, this alternative is less attractive since there seems to be no analogy for nucleophilic attack on oxygen of alkyl tosylates.

Experimental[11]

trans-9-Decalincarboxylic acid was prepared by the procedure of Koch and Haaf[12] using 88% formic acid and 98% sulfuric acid as suggested by Pincock, Grigat, and Bartlett.[13]

trans-9-Decalylcarbinol.—*trans*-9-Decalincarboxylic acid was reduced as described by Dauben, Tweit, and MacLean[14] to yield *trans*-9-decalylcarbinol, m.p. 76–77° (lit.[14] m.p. 77–78°).

trans-9-Decalylcarbinyl Tosylate.—*trans*-9-Decalylcarbinol was converted to the tosylate, m.p. 139–141° (lit.[14] m.p. 139.7–141.7°), as previously described.[14]

Reaction of *trans*-9-Decalylcarbinyl Tosylate with Lithium Aluminum Deuteride.—To a slurry of 281 mg. of lithium aluminum deuteride in 30 ml. of *n*-butyl ether was added 1.00 g. of *trans*-9-decalylcarbinyl tosylate and the resulting mixture was heated under reflux with stirring for 14 hr. The cooled reaction mixture was hydrolyzed with water and the inorganic salts were dissolved with 6 *N* hydrochloric acid. The layers were separated and the aqueous layer was extracted four times with ethyl ether. The organic extracts were combined and washed with 5% sodium hydroxide, then water. The ether solution was dried over sodium sulfate and the ethyl ether was flash-distilled after which the *n*-butyl ether was distilled at atmospheric pressure. The residue was chromatographed on 15 g. of Woelm neutral alumina, grade I. Elution with 100 ml. of 60–90° petroleum ether gave some oil which was discarded. Elution with 40 ml. of benzene (3%)–petroleum ether yielded 10 mg. (2.6%) of *p*-tolyl disulfide, m.p. 43–44°, after sublimation (lit.[15] m.p. 46°). Elution with 100 ml. of benzene gave a trace of gum and elution with 100 ml. of ether gave 131 mg. (25%) of *trans*-9-decalylcarbinol, m.p. 76–77°. The infrared spectrum was identical with that of an authentic sample. Deuterium analysis showed 0.03 atom of deuterium per molecule.[8]

The infrared spectrum of the *p*-tolyl disulfide was identical with that of an authentic sample. The absorbancies at 1040 cm.$^{-1}$ (absent in *p*-tolyl disulfide-α,α'-d_2) and 1020 cm.$^{-1}$ were compared for a series of known mixtures of *p*-tolyl disulfide and *p*-tolyl disulfide-α,α'-d_2 and 0.2 atom of deuterium per mole would have been detected.

Toluene-α-*d*[16] was prepared by the reaction of benzylmagnesium chloride with impure deuterium oxide. The toluene-α-*d* was found to contain 0.78 ± 0.04 atom of deuterium per molecule by mass spectral analysis.[17]

p-Toluenesulfonyl Chloride-α-*d*.—Toluene-α-*d* was chlorosulfonated by a standard procedure.[18] From 92 g. of toluene-α-*d* there was obtained 30 g. (16%) of *p*-toluenesulfonyl chloride-α-*d*, m.p. 67–68°, after two crystallizations from petroleum ether.

p-Toluenethiol-α-*d*.—*p*-Toluenesulfonyl chloride-α-*d* was reduced with zinc dust using the procedure of Adams and Marvel.[19] From 15 g. of *p*-toluenesulfonyl chloride-α-*d* there was obtained 3.0 g. (30%) of *p*-toluenethiol-α-*d*, m.p. 42–43°, after crystallization from petroleum ether and sublimation (lit.[20] m.p. 42–43°).

p-Tolyl disulfide-α,α'-d_2 was prepared by the bromine oxidation[21] of *p*-toluenethiol-α-*d*. A stirred solution of 1.0 g. of *p*-toluenethiol-α-*d* in 100 ml. of ether was cooled to −10° and treated with 2.0 g. of bromine. Stirring was continued for 20 min. while the bromine color was discharged after which the ether was removed under reduced pressure. The residue was crystallized from aqueous ethanol and sublimed to yield 0.65 g. (66%) of *p*-tolyl disulfide-α,α'-d_2, m.p. 43–44°. The infrared spectrum showed peaks at 2200 and 1430 cm.$^{-1}$ not present in normal *p*-tolyl disulfide and greatly diminished bands at 1450, 1380, 1210, 1105, and 1040 cm.$^{-1}$ present in *p*-tolyl disulfide.

Attempted Reduction of Lithium *p*-Toluenesulfonate with Lithium Aluminum Hydride.—A slurry of 0.706 g. of anhydrous lithium *p*-toluenesulfonate and 0.76 g. of lithium aluminum hydride in 30 ml. of *n*-butyl ether was heated under reflux for 3 days. The cooled reaction mixture was hydrolyzed with water and the inorganic salts were dissolved with 6 *N* hydrochloric acid. The layers were separated and the aqueous layer was extracted four times with ethyl ether. The organic extracts were combined and extracted with 5% sodium hydroxide solution. The ether solution was dried over sodium sulfate and distilled to a volume of 0.3 ml. Neither *p*-toluenethiol nor *p*-tolyl disulfide could be detected by thin-layer chromatography on silica gel with petroleum ether (b.p. 60–90°) as solvent. Under these conditions both *p*-toluenethiol (R_f 0.45) and *p*-tolyl disulfide (R_f 0.32) were readily determined in known samples.

The basic extracts were acidified and extracted with ether. The ether extracts were evaporated to a small volume and neither *p*-toluenethiol nor *p*-tolyl disulfide could be detected by thin-layer chromatography.

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(10) R. C. Arnold, A. B. Lien, and R. M. Alm, *J. Am. Chem. Soc.*, **72**, 731 (1950).

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(17) We are greatly indebted to Donald F. Swinehart of this department for the mass spectral analysis.

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The Spectra of Thermochromic Substances. I[1]

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The spectra of three thermochromic substances, rubrene, tetracyclone, and dimethylfulvene, have been examined over a range of temperature from −195 to 95°. As the temperature is lowered, rubrene spectra grow more intense and shift toward the red; tetracyclone absorption increases slightly and shifts toward the red; dimethylfulvene absorption increases but shows no red shift. When concentrations are corrected for thermal expansion, only the rubrene shows a notable increase in extinction coefficient.

Thermochromism is the visible, reversible change of color with temperature shown by several classes of molecules, most of them complex. The change may be spectacular, as with bianthrone, whose solutions turn from colorless to deep green on heating; for other reported thermochromic compounds the change in color ranges from slight to noticeable. Only for bianthrone, the spiropyrans, and the disulfides have the mechanisms of the thermochromic transitions been extensively studied.[3]

Possible mechanisms include: (1) a temperature-dependent equilibrium between differently colored forms, such as keto–enol, lactim–lactam, monomer–dimer, or equilibria involving configuration isomers, ring opening or the formation of ionic species or free radicals; (2) extension of conjugation in twisted or overcrowded molecules; (3) extrinsic effects such as thermal solvent expansion, temperature-sensitive solvent–solute interaction, or absorption band broadening caused by thermal redistribution of molecular rotation energy levels; (4) thermal excitation to low lying triplet states; (5) temperature-dependent fluorescence. A further possibility for solid materials is change in crystal state.

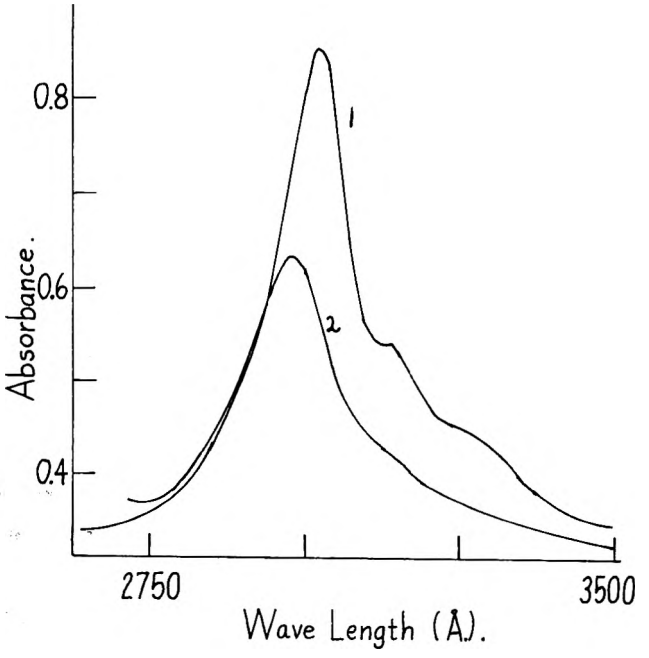

Fig. 1.—Absorption spectra of rubrene in EPA (5.2×10^{-6} *M*): (1) at −195°; (2) at 25°.

The purpose of this investigation was to examine the temperature dependence of the spectra of solutions of thermochromic compounds which can be classed as "overcrowded" molecules.

Experimental

Spectra were run on a Cary Model 14 spectrophotometer, using a specially made 1-cm. quartz cell mounted in a quartz dewar with optical windows (American Instrument Co.). Temperatures were regulated by filling the dewar with liquid nitrogen, with Dry Ice–acetone, or ice–salt. Higher temperatures were achieved with steam-heated thermal spacers in the cell compartment. Some of the spectra were also run on a Beckman D.U. spectrophotometer.

The EPA solvent and the methylcyclohexane were Spectrograde quality (Matheson Coleman and Bell). Solutions were accurately made up at room temperature, and concentrations at other temperatures were corrected for thermal expansion from the following data; each solvent was used in a half-filled tube 3.5 mm. in diameter and 35 cm. long, the meniscus marked at room temperature, and again at liquid nitrogen temperature. The difference in volume for EPA solvent was 22.5%. Data in the tables is for concentrations corrected for thermal expansion or contraction.

Several different samples of rubrene were used, some obtained from K and K Laboratories, some made in this laboratory by the method of Wittig and Waldi.[4] Tetracyclone used was the product of K and K Laboratories. Dimethylfulvene was made in this laboratory.

Results

Rubrene.—Rubrene has been noted as thermochromic.[5] Crystals of rubrene (5,6,11,12-tetraphenylnaphthacene) appear brick red; powdered rubrene is bright orange. It darkens on heating and finally provides a ruby red melt which reverts to its normal color on cooling. Solutions, which are notably fluorescent, become more pink on heating, lighter and more yellow at low temperature.

Figures 1 and 2 show the spectrum of rubrene in EPA at various temperatures; the data appear in Table I.

Notable features are the increase in absorption intensity with decreasing temperature, as well as the regular shift of the whole absorption curve toward the red. The increase in absorption at low temperature remains considerable even when corrected for volume change of the solvent. Beer's law is followed in all the solvents used.

Tetracyclone.—Tetracyclone (tetraphenylcyclopentadienone) is a shiny black solid which melts to a deep purple. When a thin film of melt is allowed to cool between cover glasses to which pressure is applied at a point, it crystallizes in long needles radiating from the

(1) This investigation was supported in part by the National Science Foundation, grant 7307, and in part by the National Science Foundation undergraduate research participation program.

(2) The data presented are abstracted from the M.S. theses of K. H. Kim and L. Smith, and an undergraduate honors project of T. Beinecke.

(3) J. H. Day, *Chem. Rev.*, **63**, 65 (1963).

(4) G. Wittig and D. Waldi, *J. prakt. Chem.*, **160**, 242 (1942).

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TABLE I

THE SPECTRA OF RUBRENE

Solvent	Temp., °C.	Absorption maxima (log extinction coefficient)			
EPA	−195	3025 (5.01)	4650 (3.74)	4970 (4.05)	5330 (4.10)
	−75	2995 (4.98)	4600 (3.65)	4960 (3.94)	5260 (3.97)
	−5	2985 (4.96)	4990 (3.62)	4885 (3.90)	5230 (3.91)
	26	2975 (4.95)	4585 (3.60)	4875 (3.87)	5220 (3.89)
Absolute ethanol	−75	2980 (4.98)	4600 (3.63)	4900 (3.92)	5250 (3.95)
	−5	2975 (4.96)	4580 (3.60)	4885 (3.88)	5225 (3.91)
	26	2970 (4.96)	4575 (3.59)	4875 (3.86)	5220 (3.88)
Methylcyclohexane	26	3000 (4.98)	4600 (3.63)	4910 (3.91)	5220 (3.93)
	95	2980 (4.93)	4600 (3.60)	4890 (3.87)	5225 (3.88)
Dimethyl phthalate	23	[a]	4650 (3.61)	4940 (3.93)	5280 (3.95)
	83	[a]	4680 (3.60)	4940 (3.90)	5260 (3.93)
Benzene[b]	Room	3030 (5.07)	4650 (3.79)	4950 (4.07)	5300 (4.08)

[a] Not measured. [b] From G. M. Badger, R. S. Pearce, H. J. Rodda, and I. S. Walker, *J. Chem. Soc.*, 3151 (1954). See also ref. 10.

pressure point. These crystals are deep purple when observed by transmitted light looking along the long axis of the needles. Observed normal to the long axis, the crystals are transparent and colorless gray. Solutions of tetracyclone become brownish on heating, and more purple on cooling; color changes are definite without being striking. Figure 3 shows representative spectra; the data appear in Table II.

TABLE II

THE SPECTRA OF TETRACYCLONE

Solvent	Temp., °C.	Absorption maxima (log extinction coefficient)		
EPA	−195	2660 (4.36)	[a]	5200 (3.03)
	−75	2630 (4.40)	3460 (3.84)	5100 (3.10)
	−5	2620 (4.37)	3370 (3.82)	5020 (3.12)
	26	2620 (4.35)	3340 (3.81)	5020 (3.12)
Absolute alcohol	26	2620 (4.36)	3400 (3.81)	[a]
Benzene	26	[a]	3420 (3.83)	5120 (3.12)
Benzene[b]	Room	[a]	3420 (3.83)	5120 (3.12)

[a] Not measured. [b] S. B. Coan, D. E. Trucker, and E. I. Becker, *J. Am. Chem. Soc.*, **75**, 900 (1953). For spectra in other solvents, see also p. 1057, Vol. I, Organic Electronic Spectral Data, Interscience Publishing Co., 1960.

The longest wave length band near 5100 Å. shows a regular shift toward the red as temperature is lowered, but there is no apparent change in intensity with temperature. The peak at 3400 Å. shifts to the red as expected, with little or no increase in intensity other than that caused by increased concentration due to solvent contraction.

Dimethylfulvene.—Dimethylfulvene when freshly prepared is a light yellow golden liquid which becomes much lighter in color at low temperature, and becomes a deep red near the boiling point. In dilute solution the color changes are similar but not as marked. Typical spectra are recorded in Fig. 4 and Table III.

TABLE III

THE SPECTRA OF DIMETHYLFULVENE

Solvent	Temp., °C.	Absorption maxima (log extinction coefficient)	
EPA	−195	2680 (4.24)	3500 (2.20)
	−75	2640 (4.21)	3500 (2.16)
	−5	2630 (4.19)	3500 (2.14)
	25	2630 (4.15)	3500 (2.12)
Benzene	25	[a]	3600 (2.06)
Absolute alcohol	25	[a]	3550 (2.06)

[a] Not measured.

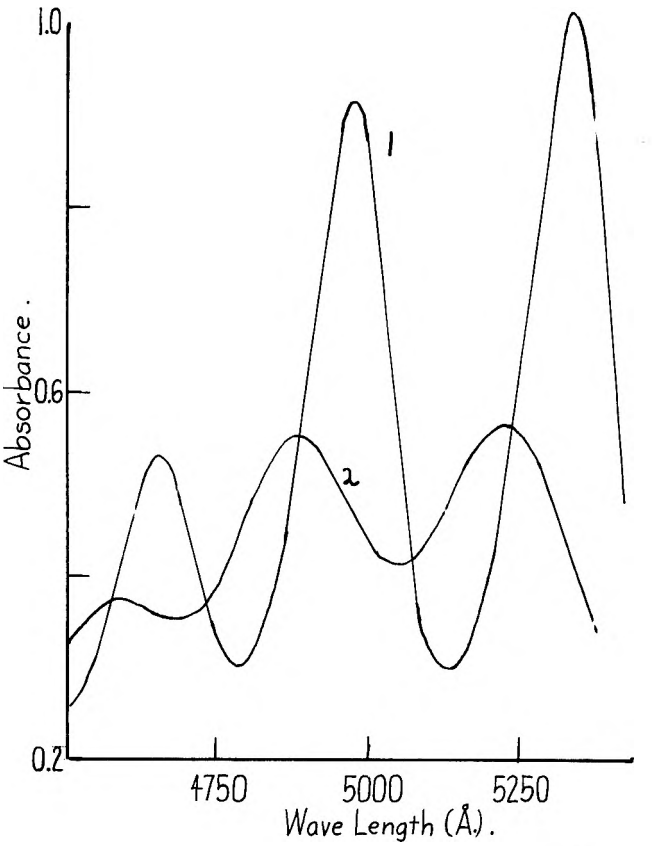

Fig. 2.—Absorption spectra of rubrene in EPA (5.2×10^{-5} *M*): (1) at −195°; (2) at 25°.

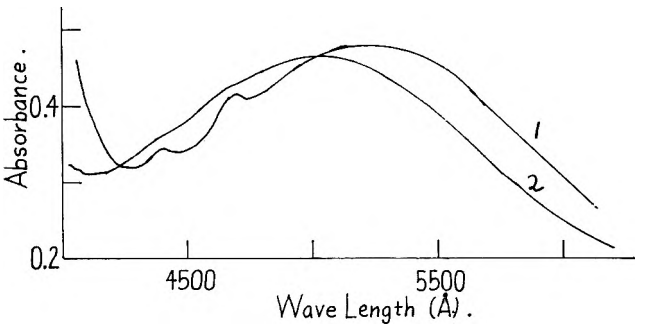

Fig. 3.—Absorption spectra of tetracyclone in EPA (2.30×10^{-4} *M*): (1) at −195°; (2) at 26°.

Discussion

In seeking an explanation for the thermochromism of rubrene, it is first necessary to decide whether there is a temperature-dependent equilibrium between two chemical species. The fact that Beer's law is obeyed over a range of concentrations rules out association equilibria, and e.p.r. spectra could detect no free radical formation.[6] Rubrene is diamagnetic, which probably rules out an easily reached triplet state.[7] The fact that no new peaks appear in the spectrum, and no old peaks disappear, makes the thermal generation of any new species of molecule unlikely as an explanation. Further evidence in this direction is the fact that a "heat of transformation" calculated from the usual plot of log ϵ_{max} *vs.* $1/T$ is so small as to be within experimental error, whereas a similar calculation for the thermochromic spiropyrans gives a value of 6 to 7 kcal./mole. The simultaneous shift in absorption maxima and in

(6) Courtesy of Schlumberger Corp.

(7) E. Muller and I. Muller-Rodloff, *Ann.*, **517**, 134 (1935).

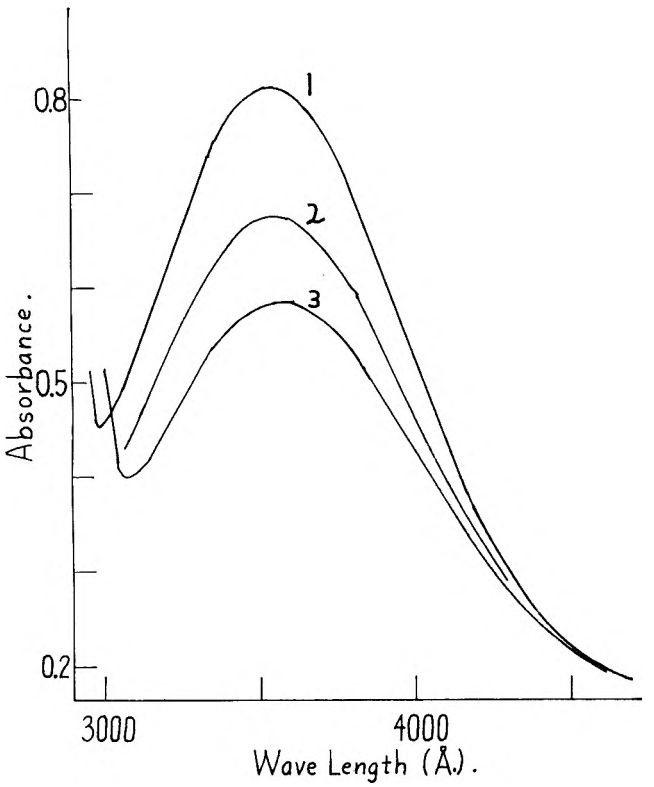

Fig. 4.—Absorption spectra of dimethylfulvene in EPA (3.2 10^{-3} *M*): (1) at −195°; (2) at −75°; (3) at 25°.

intensity as temperature is changed results in several isosbestic points, whose existence is further argument for the existence of a single chemical species.[8]

Since the eye looks *at* a sample, while the spectrophotometer looks *through* a sample, a room temperature solution of rubrene in dimethyl phthalate was compared visually with a sample heated to 200°. Viewed by reflected light the cool solution was brilliant orange-red with a noticeable yellow fluorescence, while the hot solution was a warm red with no trace of yellow. When viewed by transmitted light, both the hot and the cold solutions appeared orange, with little noticeable difference.

The shift of absorption peaks toward the red can be accounted for by the increase in refractive index of solvent as temperature is lowered.[9] Badger and Pearce[10] measured the spectrum of rubrene in nineteen different solvents and found a linear relationship between red shift and a function of the refractive index of the solvent. From this data they estimate that cooling to liquid nitrogen temperatures should cause a shift to the red of about 30 to 80 Å., which estimate is supported by the present data. However, they found that a slight decrease in absorption intensity accompanied the red shift caused by change of refractive index at room temperature, the reverse of what happens when the red shift is caused by temperature lowering.

Clar[11] measured spectra of several polynuclear hydrocarbons at room temperature and liquid nitrogen temperature. He also found a red shift of the order of 20 to 30 Å., and noted that the difference in intensities between maxima and minima more than doubled in going to the lower temperature. Similar results have been reported for naphthalene.[12] The increase in absorption intensity remains to be accounted for.

Tetracyclone and Dimethylfulvene.—The visible color change in tetracyclone may be ascribed to the considerable red shift together with the apparent increase in intensity of the 3500 Å. portion of the curve. The dimethylfulvene spectrum consists of a strong band in the ultraviolet and a weak broad band extending from 3000 Å. to beyond 4500 Å. The only change of visible spectrum is that of apparent increase in absorption intensity with decreasing temperature, which is almost entirely a solvent contraction effect; there is no red shift. It seems remarkable that the eye should perceive so definite a color change due to a simple thermal expansion.

Examination of the spectra will show that they behave differently as the temperature is lowered. The minima between peaks for rubrene have about the same red shift as do the peaks, and the minima lie lower as the peaks rise higher. For tetracyclone the minima have a smaller red shift than do the peaks; the order of intensity of the minima at 3100 Å. are in the same order as the peaks at 3500 Å., while the minima at about 4200 Å. have almost equal intensity. In dimethylfulvene the minima at 3000 Å. follow the order of the peaks.

The red shifts of rubrene and tetracyclone correspond to increase in solvent refractive index; the lack of any shift in the dimethylfulvene 3500 Å. peak seems remarkable from this standpoint, unless the phenyl groups on the first two compounds are somehow involved in the red shift.

Summary

The spectrum of rubrene undergoes a red shift with decreasing temperature which can be accounted for by increase in refractive index of solvent; the absorption intensity is approximately doubled at each absorption maximum as the temperature is lowered from room temperature to −195°. The observable thermochromism is believed due to the real spectral changes plus a temperature-dependent fluorescence. The apparent thermochromism of tetracyclone is probably due primarily to the red shift with lowering temperature. The apparent thermochromism of dimethylfulvene may be due to thermal expansion alone.

(8) J. R. Morrey, *J. Phys. Chem.*, **66**, 2169 (1962).
(9) W. J. Potts, Jr., *J. Chem. Phys.*, **23**, 65 (1955).
(10) G. M. Badger and R. S. Pearce, *Spectrochim. Acta*, **4**, 280 (1951).
(11) E. Clar, *ibid.*, **4**, 116 (1950).
(12) A. N. Terenin and V. L. Ermalaev, *Dokl. Akad. Nauk, SSSR*, 547 (1952).

The Effect of Structure on the Thermal Stability of Hydroperoxides

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1-Phenyl-2-methylpropyl 2-hydroperoxide and 1-phenyl-2-methylpropyl 1-hydroperoxide have been prepared and subjected to thermal decomposition. From an examination of the rates and products it is concluded that they do not give concerted decomposition.

Investigations of peresters have shown that their thermal stability can be greatly modified by variations in the structure of the acyl radical.[1,2] This has been a strong argument for, in the degradation of some peresters, the simultaneous cleavage of both carbon–carbon and oxygen–oxygen bonds which has been called a concerted decomposition.

The thermal stability of hydroperoxides, on the other hand, seems to be unresponsive to structural changes.[3] This is not surprising if the primary rupture is confined to the oxygen–oxygen bond.

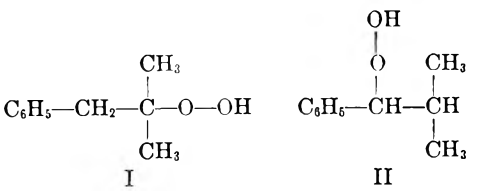
$$R_3C{-}O{-}O{-}H \longrightarrow R_3C{-}O\cdot + \cdot OH \qquad (1)$$

Conceivably the thermal decomposition could be analogous to those peresters which break in three, but for no hydroperoxides so far investigated has this been suggested. Product studies, where they have been done, have indicated the initial formation of an alkoxy

$$R_3C{-}O{-}O{-}H \longrightarrow R\cdot + R_2C{=}O + \cdot OH \qquad (2)$$

radical[4,5] as in equation 1.

Nevertheless concerted decomposition remained an attractive possibility for a hydroperoxide suitably constructed; that is, where one of the R groups would make a particularly stable, free radical and where all of the groups were sufficiently bulky to cause some crowding. The following is an account of the preparation and thermal degradation of two closely related hydroperoxides, 1-phenyl-2-methylpropyl 2-hydroperoxide (I), where these conditions obtain, and 1-phenyl-2-methylpropyl 1-hydroperoxide (II), where they do not.



I

II

Experimental

1-Phenyl-2-methylpropyl 2-Hydroperoxide.—A 0.2-mole sample of 1-phenyl-2-methylpropanol-2 was mixed with 0.5 mole of 100% hydrogen peroxide and the temperature raised to 75°. A 0.07-ml. sample of 70% sulfuric acid was added with stirring over 10 to 15 min.[6] After 1 hr. the mixture was cooled and extracted with ether. Distillation gave an oil, b.p. 80–81° (0.01 mm.), which slowly crystallized. Recrystallization from pentane gave white needles, m.p. 44–44.6°, which on refluxing with acidified potassium iodide released 98% of the theoretical amount of iodine.

The infrared spectrum of the hydroperoxide differed from that of the alcohol only in the regions of 2.8–3 and 11–12 μ, indicating that no skeletonal rearrangement had occurred during the reaction. Reduction of the product with lithium aluminum hydride gave 1-phenyl-2-methylpropanol-2. The n.m.r. spectrum was consistent only with the expected structure on one other, 2-phenyl-2-methylpropyl 1-hydroperoxide, a possibility that was excluded by the foregoing observations and by the pattern of products from the thermal decomposition.

1-Phenyl-2-methylpropyl 1-hydroperoxide was prepared by a similar procedure from 1-phenyl-2-methylpropanol-1, except that the reaction was carried out at room temperature. The product was an oil, b.p. 50–51° (0.01 mm.), which liberated 99% of the theoretical amount of iodine. Its infrared spectrum was very similar to that of the starting alcohol.

***t*-Butyl hydroperoxide** was obtained from Lucidol Corp. It was separated from water and distilled, taking the fraction boiling at 33° (18 mm.).

Benzene used was Fisher reagent grade, dried over sodium, and distilled.

Kinetic Runs.—Dilute solutions of hydroperoxide in benzene were placed in sealed tubes and heated in a constant-temperature bath. The remaining amount of hyperoperoxide was determined iodometrically. The presence or absence of oxygen was found to have negligible effect on the rates of decomposition and no effort was subsequently made to remove it. Plots of the log of hydroperoxide concentration *vs.* time gave straight lines.

Product Studies.—Solutions of hydroperoxide, 0.9 *M* in benzene, were heated at 165° for at least ten half-lives. The resulting solution in benzene was analyzed with the Beckman GC-2 gas chromatograph.

Results and Discussion

In Table I are the first-order rate constants for the thermal decomposition in benzene of the two hydroperoxides as well as those of *t*-butyl hydroperoxide done under the same conditions for comparison. Table II

TABLE I

RATE CONSTANTS FOR THE THERMAL DECOMPOSITION IN BENZENE

Hydroperoxide I		Hydroperoxide II		*t*-Butyl hydroperoxide	
Temp., °C.	$k \times 10^6$ sec.$^{-1}$	Temp., °C.	$k \times 10^6$ sec.$^{-1}$	Temp., °C.	$k \times 10^6$ sec.$^{-1}$
144.2	5.04	133.8	3.18	154.5	4.29
154.5	12.1	143.9	8.95	161.7	9.27
165.5	29.2	153.9	20	169.3	20
176.0	69.7	163.7	40.3	174.6	40
		174	97.7		
ΔH^* 30 kcal.		29.2 kcal.		40.8 kcal.	
ΔS^* −11.5 e.u.		−12.5 e.u.		+12.2 e.u.	

(1) P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.*, **80**, 1398 (1958).

(2) P. D. Bartlett and R. E. Pincock, *ibid.*, **82**, 1769 (1960).

(3) J. R. Thomas, *ibid.*, **77**, 246 (1955).

(4) E. R. Bell, J. H. Raley, F. F. Rust, F. H. Seubold, and W. E. Vaughan, *Discussions Faraday Soc.*, **10**, 242 (1951).

(5) M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **16**, 113 (1951).

(6) This preparation was attended by some hazard and was always carried out behind a safety screen. Occasionally a weird light was seen to flicker over the surface of the mixture during the addition and this was sometimes, but not always, followed by explosion. Subsequent findings indicate that the danger lies in addition of sulfuric acid to an alcohol–hydrogen peroxide mixture. Acidification of the concentrated hydroperoxide prior to its addition to the alcohol has eliminated the occurrence of explosions in preparation of other hydroperoxides. However, this does not obviate the need for all normal precautions in the use of concentrated hydrogen peroxide. We are grateful to a referee for indicating that this hydroperoxide may be prepared in 40–60% yields, using 30–50% hydroperoxide.

TABLE II
PRODUCTS OF THE THERMAL DECOMPOSITION IN BENZENE

Hydroperoxide I		Hydroperoxide II	
Product	Mol. %	Product	Mol. %
Acetone	81	*i*-Butyraldehyde	2
Toluene	28	Acetone	65
Benzyl alcohol	6	*i*-Propyl alcohol	3
Benzaldehyde	9	Benzaldehyde	44
1-Phenyl-2-methyl-propanol-2	4	Benzoic acid	28
Benzoic acid	8	Methanol	Trace
Methanol	Trace		

shows the major products of these decompositions determined by gas chromatography.

Measurement of the rates of homolysis of hydroperoxides has always been complicated by their tendency to exhibit induced decomposition. The difficulty has been usually overcome by extrapolation to zero of rate measurements at several initial concentrations,[4] or by the inclusion of radical traps in the solution.[3] The rates reported here were done with initial concentrations of hydroperoxide of 0.05 and 0.033 M, considerably lower than those generally used. Initial concentrations lower than these did not affect the rate constants obtained appreciably and it was concluded that induced decomposition was negligible at these concentrations.

If, as expected, 1-phenyl-2-methylpropyl 2-hydroperoxide were to decompose in a concerted manner, it should show a marked decrease in thermal stability relative to other hydroperoxides. Instead, the rates of decomposition of the three hydroperoxides are remarkably similar. Both hydroperoxides I and II have activation enthalpies considerably lower than *t*-butyl hydroperoxide, but this is balanced almost completely by the large decrease in activation entropy. In fact a ΔH^* of about 30 kcal. is usual for the homolytic cleavage of hydroperoxides,[3] and it is *t*-butyl hydroperoxide that is the anomalous one.

The presence of 1-phenyl-2-methylpropanol-2 in the products from hydroperoxide I seems to prove that it cannot be undergoing a concerted decomposition. The benzyldimethylmethoxy radical survives long enough to abstract a hydrogen atom from the surrounding medium.[7] The other products are as expected and easily explicable in terms of hydrogen abstraction radical fragmentation and recombination, and induced decomposition which undoubtedly occurs in the concentrated solutions used for the product study. The large amount of acetone from hydroperoxide II is a bit surprising. Apparently cleavage of the initially formed radical to benzaldehyde and isopropyl radical is very facile. Decomposition of this radical to give isobutyraldehyde was also noted, but no isobutyrophenone could be found.

Do these hydroperoxides, then, give a concerted decomposition? Generally speaking, the arguments in support of this mechanism fall into three categories: the rate of decomposition relative to that for similar compounds, entropies and energies of activation relative to these same standards, and the products of reaction. Comparing only hydroperoxide I with *t*-butyl hydroperoxide, it would appear that concerted decomposition was quite possible. However, then one would have to admit hydroperoxide II to the ranks of concerted decomposers, as well as a number of other hydroperoxides which from structural considerations seem unlikely to homolyze in this manner.[3] Convincing evidence for a concerted mechanism is, therefore, lacking.

While 1-phenyl-2-methylpropyl 2-hydroperoxide may or may not undergo induced decomposition, the analogous perester, *t*-butyl phenylperacetate, does. The difference may be explained by referring to the gain in energy from producing carbon dioxide by the perester, relative to that from producing acetone by the hydroperoxide. In a simpler case where direct comparison is possible, this difference amounts to 20 kcal.

$$CH_3—CO_2\cdot \longrightarrow CH_3\cdot + CO_2 + 17 \text{ kcal.}^8$$

$$(CH_3)_3CO\cdot \longrightarrow CH_3\cdot + (CH_3)_3CO - 3 \text{ kcal.}^9$$

Probably the fragmentation of benzyldimethylmethoxy radical is exothermic, but not enough to provide the kick necessary for the concerted decomposition.

Acknowledgment.—The authors wish to thank Professor Robert R. Fraser of the University of Ottawa for the n.m.r. spectra and interpretations. They are also grateful to the National Research Council for the grant under which these studies were carried out.

(7) However, it is possible that the small amount of alcohol arises from some α,α-dimethylphenethyl radical produced not by homolytic cleavage of the hydroperoxide, but by induced decomposition. The results of Kochi [J. K. Kochi, *J. Am. Chem. Soc.*, **84**, 1193 (1962)] on the metal ion-catalyzed decomposition of this hydroperoxide showed equivalent amounts of the parent alcohol in the products. This did not prevent speculation on a metal ion assisted, concerted mechanism for decomposition.

(8) I. Jaffe, E. J. Prosen, and M. Szwarc, *J. Chem. Phys.*, **27**, 416 (1957).

(9) P. Gray, *Trans. Faraday Soc.*, **52**, 344 (1956).

Notes

Structure of the Hemihydrates of Phenylglyoxals[1,2]

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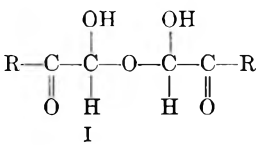
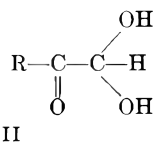
Received January 4, 1963

The literature contains a reference to hemihydrates of phenylglyoxals for which structure I has been presumed.[4] Prior to this publication the hemihydrates (I) and the normal hydrates (II) had often been confused. Evidence for structure I was based mainly on elemental analysis.[4] We have prepared the hemihydrate of *p*-methoxyphenylglyoxal and obtained proof for structure Ia.



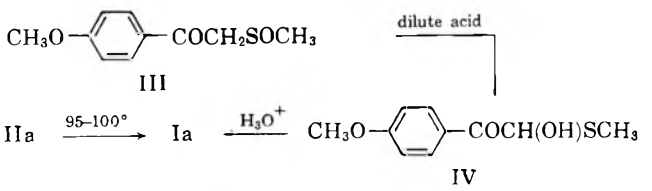
I



II

Ia, R = *p*-$CH_3OC_6H_4$– IIa, R = *p*-$CH_3OC_6H_4$–

In connection with a study of the formation of β-keto sulfoxides and their acid-catalyzed rearrangement into the hemimercaptals of α-ketoaldehydes,[5] we have found that, while treatment of the condensation product (III) of dimethyl sulfoxide and methyl *p*-anisate with dilute hydrochloric acid gives the hemimercaptal (IV), the use of more concentrated acid leads to a sulfur-free compound proved to be Ia. In separate experiments Ia was also formed from IV in the presence of strong acid or by heating of the glyoxal hydrate (IIa).



On the basis of elemental analysis, molecular weight determination, and infrared and integrated n.m.r. spectra we have been able to verify the bis(*p*-anisoylhydroxymethyl) ether structure for Ia. The n.m.r. spectrum of Ia is particularly instructive and conclusively supports structure Ia. In addition to the singlet for the methoxy group (τ = 6.15, area = 6.0 units) and the a_2b_2 system of the benzene ring protons at τ = 1.85, area = 4, and τ = 3.06, area = 4, J = 8.95 c.p.s., the spectrum contains a pair of doublets representing the H_a–C–OH_b group in Ia.[6] Deuterium exchange with deuterium oxide proved H_a absorbs at τ = 3.68, area = 2 and H_b absorbs at τ = 4.88, area = 2 with a coupling constant J_{ab} of 10.3 c.p.s. Similar absorption has been found for the H–C–OH group in the hemimercaptals of phenylglyoxals.

The hydrate of *p*-methoxyphenylglyoxal had been prepared by Karrer and v. Segesser[7a] as well as by Sisido and Nozaki.[7b] The melting point as given by Sisido and Nozaki (110–114°) is close to the melting point we observed for the hemihydrate (107–109°). We, therefore, prepared *p*-methoxyphenylglyoxal hydrate by the literature method.[7b] Its infrared spectrum was entirely different from that of Ia. Moreover, as reported,[7b] the hydrate (IIa) melted at about 70°, resolidified at about 75°, and melted again at 107–108°. The resolidified product did not depress the melting point of Ia.[8] When IIa was kept at 95–100° for four hours it was converted into Ia in good yield. It can, therefore, be stated that the melting point reported for IIa is actually that of its dehydration product, Ia.

Experimental

Preparation of Ia from III.—A few minutes after dissolving 250 mg. of III (1.18 mmoles), m.p. 101°, in 2.5 ml. of 18% hydrochloric acid, the initially clear solution turned cloudy and an oil separated. The mixture was kept in an open beaker at room temperature for 6 days during which time the aqueous phase evaporated to leave a crystalline residue. Washing with ether gave 89 mg. (43%) of Ia as colorless, ether-insoluble crystals, m.p. 107–109°, with a strong infrared absorption at 2.93 and 5.98 μ.

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24; mol. wt., 346. Found: C, 62.55; H, 5.24; mol. wt., 301 (dioxane).[9]

Preparation of Ia from IV.—A solution of 85 mg. of IV (0.4 mmole), m.p. 89–92°, in a mixture of 3 ml. of ethanol and 1.2 ml. of 18% hydrochloric acid was kept on a steam bath for 1 hr. Evaporation of solvent during this period left an oily substance which was kept in an open beaker for 4 days. Upon washing with ether 47 mg. (67%) of Ia was obtained as insoluble crystals, m.p. 107–109°. The infrared absorption spectrum was identical with that of Ia prepared from III.

Preparation of Ia from IIa.—Heating of 200 mg. of IIa (m.p., *ca.* 70°), prepared according to the directions of Sisido and Nozaki,[7b] at 95–100° for 4 hr. in a test tube gave a solid mass which, when treated with a few drops of ethanol at room temperature, yielded a yellowish crystalline substance. Washing with ether gave 180 mg. (95%) of insoluble Ia, m.p. 107–109°, which did not depress the melting point of Ia from III or IV and had an infrared absorption spectrum identical with that of Ia from III or IV.

Phenylosazone of *p*-Methoxyphenylglyoxal from Ia.—The hemihydrate Ia (25 mg.) was dissolved by heating in a solution of 0.5 ml. of ethanol, 0.2 ml. of water, and 1 drop of concentrated hydrochloric acid. After addition of 0.1 ml. of phenylhydrazine the reaction mixture was kept on a steam bath for 2 hr. A yellow solid was filtered off to yield the osazone of *p*-methoxyphenylglyoxal; m.p. 190° (lit.[10] m.p. 190°).

(1) Reactions of Resonance Stabilized Carbanions, part VI. For part V see G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, **84**, 4155 (1962).

(2) Supported in part by a grant from the Alfred P. Sloan Foundation.

(3) Alfred P. Sloan Foundation Fellow, 1959–1963.

(4) R. B. Moffett, B. D. Tiffany, B. D. Aspergren, and R. V. Heinzelman, *J. Am. Chem. Soc.*, **79**, 1687 (1957).

(5) G. A. Russell and H.-D. Becker, Abstracts of Papers, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 3Q.

(6) The spectrum was measured for a saturated solution of Ia in chloroform-*d* at 60 Mc./sec.

(7) (a) P. Karrer and A. v. Segesser, *Helv. Chim. Acta*, **18**, 273 (1935); (b) K. Sisido and H. Nozaki, *J. Am. Chem. Soc.*, **70**, 3326 (1948).

(8) Melting points are uncorrected and were obtained using a Fisher-Johns melting point block.

(9) Determined by a thermoelectric osmometric measurement, Schwarzkof Microanalytical Laboratories, Woodside, N. Y.

(10) C. Weygand, *Ann.*, **459**, 99 (1927).

Synthesis of Ninhydrin[1,2]

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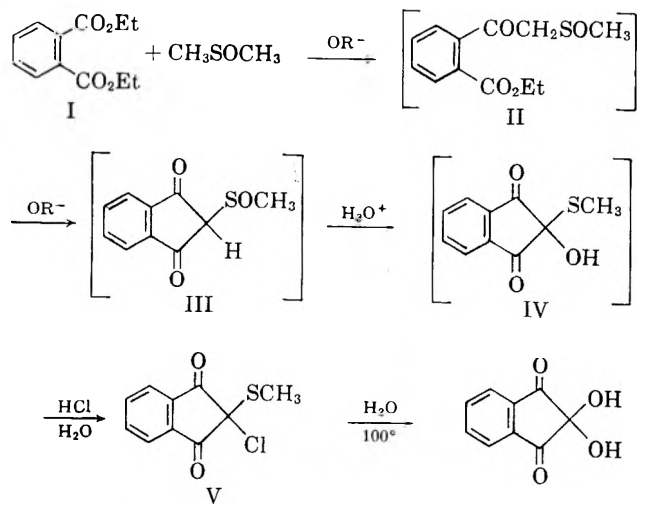
We have found that ninhydrin readily can be synthesized in two steps from ethyl phthalate. Ninhydrin is usually prepared by a six-step synthesis starting from esters of phthalic acid.[4] Other methods of preparation starting from 1,3-indandione or *p*-naphthoquinone give low yields of ninhydrin.[5]

We have reported recently that the condensation of esters with dimethyl sulfoxide in the presence of alkali metal alkoxides leads to β-keto sulfoxides which in the presence of mineral acids undergo the Pummerer rearrangement to give hemimercaptals of α-ketoaldehydes.[6]

$$RCO_2R' + CH_3SOCH_3 \xrightarrow{OR^-} RCOCH_2SOCH_3 \xrightarrow{H_3O^+} RCOCH(OH)SCH_3$$

When diethyl phthalate is used in this reaction, an intramolecular ester condensation leads to the formation of the 1,3-indandione system. The reaction product isolated upon acidification with hydrochloric acid proved to be the α-chloro thioether (V). The formation of V from I probably involves the as yet unisolated intermediates II–IV.



The condensation occurs upon the addition of diethyl phthalate to a solution (or suspension) of an alkali metal alkoxide in anhydrous dimethyl sulfoxide under an atmosphere of dry, oxygen-free nitrogen. Removal of the solvent by vacuum distillation leaves a salt (presumably the alkali metal salt of III) which is soluble in water. When the aqueous solution of this salt is added to 5 *M* hydrochloric acid V rapidly precipitates in a high state of purity.

(1) Reactions of Resonance Stabilized Anions, part VII. For part VI see H.-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1895 (1963).

(2) This work was supported by a grant from the Alfred P. Sloan Foundation.

(3) Alfred P. Sloan Foundation Fellow, 1959–1963.

(4) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 472.

(5) See D. J. McCaldin, *Chem. Rev.*, **60**, 39 (1960).

(6) G. A. Russell and H.-D. Becker, Abstracts of Papers, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 3Q.

When V is hydrolyzed in boiling water ninhydrin can be isolated in nearly quantitative yields. Because of the ease of hydrolysis V cannot be recrystallized from hydroxylic solvents. A color reaction typical of ninhydrin was obtained when V (absorbed on filter paper) was treated with a solution of glycine and heated to 80°.

Experimental[7]

Reagents.—Dimethyl sulfoxide (Crown Zellerbach Corp.) was distilled from calcium hydride at a pressure of about 1 mm. Sodium methoxide (Matheson Coleman and Bell) was used without purification. Diethyl phthalate was distilled under vacuum. In the condensation reaction described later it is important to use only anhydrous reagents since water has a deleterious effect due to the hydrolysis of the phthalate ester to phthalic acid.

2-Chloro-2-methylmercapto-1,3-indandione (V).—Sodium methoxide (5.4 g., 0.1 mole) was suspended in 75 ml. of anhydrous dimethyl sulfoxide in a 250-ml. round-bottomed flask under an atmosphere of nitrogen. The suspension was stirred by a stream of nitrogen introduced by a gas inlet tube extending to the bottom of the flask. Diethyl phthalate (5.5 g., 0.025 mole) was added dropwise to this suspension. The reaction mixture, which turned yellow after about 5 min., was kept under nitrogen for 4 hr. at room temperature after which it was subjected to vacuum distillation at 1-mm. pressure (bath temperature 65–70°) for 50 min. To the resulting sticky yellow residue 50 ml. of ether and 50 ml. of ice–water were added. The yellow aqueous layer was separated and added dropwise with stirring to a mixture of 60 ml. of water and 40 ml. of concentrated hydrochloric acid. The colorless precipitate which formed rapidly was removed by filtration and dried under vacuum to give V, 4.55 g. (80%), m.p. 63°. A sample recrystallized from ether containing a trace of ethanol had m.p. 63–64°.

Anal. Calcd. for $C_{10}H_7ClO_2$; C, 52.90; H, 3.25; Cl, 15.44; S, 14.38; mol. wt., 226.6. Found: C, 53.0; H, 3.10; Cl, 15.61; S, 14.13; mol. wt., 226 (dioxane).[8]

The infrared absorption of V gave the characteristic indandione absorption at 5.70 and 5.85 μ as well as absorption due to the carbon sulfur bond at 8.05 μ. Absorption characteristic of a sulfoxide at 9.8 μ was absent. The integrated n.m.r. (60 Mc./sec.) spectrum gave aromatic hydrogen (unresolved), intensity 4.0, at 481 cycles relative to tetramethylsilane and methyl hydrogens, (singlet) at $\tau = 7.52$, intensity 3.

Ninhydrin from V.—One gram of V was added slowly to 50 ml. of boiling water in a 100-ml. erlenmeyer flask. The slightly yellow solution was kept on a steam bath for 12 hr. during which most of the water evaporated. The concentrated aqueous solution was transferred to a 50-ml. beaker and evaporated on a steam bath for another hour to yield a crystalline residue which was dried under vacuum. The material thus prepared (775 mg., 99%) had m.p. 239–240° and an infrared spectrum identical with that of commercial ninhydrin.

(7) All melting points are uncorrected and were obtained using a Fisher-Johns melting point block.

(8) Determined by the thermoelectric osmometric method, Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

Preparation of β-Keto Sulfones by Condensation of Aromatic Esters with Dimethyl Sulfone[1,2]

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We have reported previously that in dimethyl sulfoxide (DMSO) solution aromatic esters undergo a con-

(1) Reactions of Resonance Stabilized Anions, part VIII. For part VII see *J. Org. Chem.*, **28**, 1896 (1963).

(2) This work was supported by a grant from the Alfred P. Sloan Foundation.

(3) Alfred P. Sloan Foundation Fellow, 1959–1963.

densation reaction with dimethyl sulfoxide in the presence of alkali metal alkoxides to form β-keto sulfoxides.[4] This suggested that other weak acids, such as dimethyl sulfone, should react with esters in dimethyl sulfoxide solution in the presence of alkoxide ions.

It is known that methyl ketones and esters readily undergo condensation in dimethyl sulfoxide containing sodium hydride to form β-diketones.[5] Moreover, reaction of dimethyl sulfone with ethyl benzoate in the presence of a sodium dispersion in benzene solution has been reported to give a 44% yield of the β-keto sulfone[6a] while numerous cyclizations of ω-methylsulfonyl esters (using sodium ethoxide in toluene) and ω-methylsulfonylnitriles (using sodium amide in refluxing benzene) are reported.[6]

We have found that dimethyl sulfone in dimethyl sulfoxide solution containing potassium *t*-butoxide reacts with ethyl benzoate at 50–60° to form ω-(methylsulfonyl)acetophenone (Ia) in 90% yield. In a similar

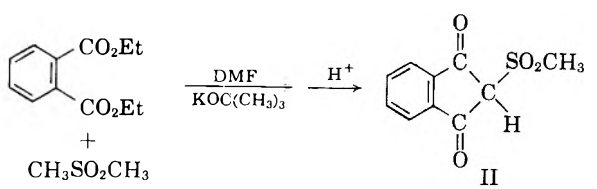
$$RCOOR' + CH_3SO_2CH_3 \xrightarrow[KOC(CH_3)_3]{DMSO} RCOCH_2SO_2CH_3$$

I

Ia, R = phenyl
Ib, R = *p*-methoxyphenyl

manner we have prepared ω-(methylsulfonyl)-*p*-methoxyacetophenone (Ib) in good yield. Thus, the condensation reaction using dimethyl sulfoxide as the solvent appears to be the preferred method of synthesis.

We have also studied the condensation reaction of dimethyl sulfone with diethyl phthalate. This reaction had been attempted earlier with negative results in hope of preparing a benzothiepin derivative.[7] In dimethyl sulfoxide solution the condensation also failed to yield identifiable products, although in the absence of dimethyl sulfone we have found that dimethyl sulfoxide condenses readily with diethyl phthalate to give an intermediate sulfoxide analogous to II.[1] When the condensation reaction was performed in dimethylformamide (DMF) solution, II was isolated in the form of a crystalline potassium salt which upon acidification with hydrochloric acid yielded colorless crystalline II in an over-all yield of 18%. The titration curve of II in aqueous solution resembles that of hydrochloric acid. In aqueous solution a 0.04 *M* solution of II gave a pH of 1.5 as measured by a calibrated glass electrode. This pH is approximately the same as found for 0.04 *M* solutions of hydrochloric acid. The pK_a value of II obviously is smaller than 2 but it can not be determined with any accuracy from the potentiometric titration curve.[8]



The structures of the β-keto sulfones prepared are supported by integrated n.m.r. spectra.[9] In addition to the absorption of the aromatic protons (intensity 5) the spectrum of Ia exhibits a singlet at $\tau = 5.37$ (intensity 2) for the methylene group and a singlet at $\tau = 6.89$ (intensity 3) for the methyl group. The spectrum of Ib has the following absorptions: protons (a_2b_2) at $\tau = 2.04$ and $\tau = 3.07$ ($J_{ab} = 9.05$ c.p.s.), total intensity 4; a singlet at $\tau = 5.47$ (intensity 2) for the methylene group; a singlet at $\tau = 6.12$ (intensity 3) for the methoxy group; and a singlet at $\tau = 6.89$ (intensity 3) for the methyl group. The n.m.r. spectrum of II shows four aromatic protons, a singlet at $\tau = 5.4$ (intensity 1) for the methine group, and a singlet at $\tau = 6.7$ (intensity 3) for the methyl group.

Experimental[10]

Reagents.—Dimethyl sulfoxide (Crown Zellerbach Corp.) was dried over calcium hydride and distilled under vacuum with a bath temperature of 60°. Dimethyl sulfone was recrystallized from chloroform. Potassium *t*-butoxide was sublimed under vacuum.

ω-(Methylsulfonyl)-acetophenone (Ia).—Potassium *t*-butoxide (2.44 g.) was suspended in a solution of 1.882 g. (20 mmoles) of dimethyl sulfone in 15 cc. of dimethyl sulfoxide under dry, oxygen-free nitrogen. To this solution 1.5 g. of ethyl benzoate (10 mmoles) was added dropwise. The mixture was maintained at 50–60° for 90 min. with agitation from a stream of nitrogen introduced at the bottom of the flask. Addition of 100 cc. of ice–water and 10 cc. of 5 *N* hydrochloric acid yielded 1.63 g. of a colorless crystalline precipitate, m.p. 105°. The filtrate was twice extracted with 100 cc. of ether to yield an additional 175 mg. of colorless product. The total crude yield of Ia was 1.8 g. (91%). Recrystallization from a chloroform–ethanol mixture raised the m.p. to 106–107° (lit.[6a] m.p. 107.5–108°).

Anal. Calcd. for $C_9H_{10}O_3S$ (198.17): C, 54.54; H, 5.09; S, 16.12. Found: C, 54.54; H, 5.32; S, 16.23.

ω-(Methylsulfonyl)-*p*-methoxyacetophenone (Ib).—Condensation of methyl *p*-anisate (1.66 g., 10 mmoles) with 1.882 g. (20 mmoles) of dimethyl sulfone in a manner similar to that employed in the preparation of Ia, yielded 1.92 g. (89%) of crude Ib, m.p. 135–136°. Recrystallization from chloroform, containing a little ethanol, gave colorless needles, m.p. 137–138°.

Anal. Calcd. for $C_{10}H_{12}O_4S$(228.20): C, 52.63; H, 5.30; S, 14.03. Found: C, 52.36; H, 5.25; S, 13.75.

2-(Methylsulfonyl)-1,3-indandione.—Dimethyl sulfone (471 mg., 5 mmoles) and 600 mg. of potassium *t*-butoxide were dissolved in 10 cc. of dimethylformamide with agitation from a stream of dry, oxygen-free nitrogen. Diethyl phthalate (1.1 g., 5 mmoles) was added dropwise to the solution at 50°. The mixture was agitated under nitrogen for an additional 30-min. period at 50°. After this time 10 cc. of water and 30 cc. of ether were added to the dark yellow reaction mixture. The yellow aqueous layer was separated and kept in an open Petri dish overnight. The resulting yellow oil was treated with 100 cc. of ethanol yielding a crystalline yellow potassium salt, which was separated by filtration, boiled briefly in 10 cc. of ethanol, filtered, and dried to give 250 mg. of product. This product when dissolved in 2 cc. of warm water followed by the addition of 0.5 cc. of 7.5 *N* hydrochloric acid yielded 210 mg. of colorless crystalline II (18.7%), m.p. 150–151°. Recrystallization from hot chloroform gave colorless prismatic needles, m.p. 150–151°. The substance turns yellow upon melting, forming colorless crystals on resolidification.

Anal. Calcd. for $C_{10}H_8O_4S$ (224.16): C, 53.58; H, 3.60; S, 14.28. Found: C, 53.71; H, 3.63; S, 14.46; neut. equiv., (potentiometrically), 226.

(4) G. A. Russell and H.-D. Becker, Abstracts of Papers, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 3Q.

(5) J. J. Bloomfield, *J. Org. Chem.*, **27**, 2742 (1962).

(6) (a) W. E. Truce and R. H. Knospe, *J. Am. Chem. Soc.*, **77**, 5063 (1955); (b) W. E. Truce, W. W. Bannister, and R. H. Knospe, *J. Org. Chem.*, **27**, 2821 (1962).

(7) W. E. Truce and F. J. Lotspeich, *J. Am. Chem. Soc.*, **78**, 848 (1956).

(8) Preliminary results of a spectrophotometric determination of the pK_a of this unusually strong acid in perchloric acid solution by G. J. Mikol indicates a pK_a of −0.23.

(9) Determined at 60 Mc./sec. in chloroform-*d* solution.

(10) Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

The infrared absorption of II in potassium bromide pellets did not indicate the presence of a hydroxyl group. The absence of an enolic structure was also consistent with the n.m.r. analysis.

Lithium Aluminum Hydride Reductions of Pyrazine Carboxylic Esters. Synthesis of Pyrazinealdehyde from Methyl Pyrazinoate

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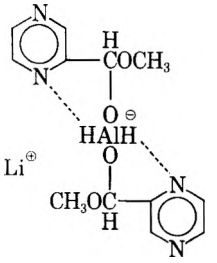
A search of the literature shows that only one pyrazinealdehyde, the 3-amino-2-pyrazinealdehyde,[1] has been described. It was obtained by the acid hydrolysis of the rather inaccessible pteridine. However, the existence of pyrazinealdehyde I, at least as a transitory species, was confirmed by the *in situ* preparations of the 2,4-dinitrophenylhydrazone and the thiosemicarbazone[2,3] *via* the McFadyen–Stevens reaction.

Kakemi, *et. al.*,[4] used the same reaction to prepare nicotinoyl- and isonicotinoylhydrazones of I. Behun and Levine synthesized[5] pyrazinealdehyde dimethyl acetal from sodium methoxide and dichloromethylpyrazine, but preliminary experiments to hydrolize the latter were unsuccessful. We have obtained I in 78% yield (as the 2,4-dinitrophenylhydrazone) by a novel, selective reduction of methyl pyrazinoate with lithium aluminum hydride. The reaction was carried out in tetrahydrofuran at −70° by "inverse" addition of 0.5 mole of lithium aluminum hydride per mole of ester. After standing at −70° for fifteen minutes, the reaction was stopped by adding glacial acetic acid.

A preliminary investigation of the reaction mechanism suggests the formation of a soluble hemiacetal complex. Aldehyde is then liberated upon the addition of acid.



In a series of experiments, increasing amounts of lithium aluminum hydride were used and the corresponding yields of aldehyde were determined. An optimum yield of pyrazinealdehyde was obtained when 0.5 mole of lithium aluminum hydride was allowed to react with one mole of methyl pyrazinoate while excess of the reductant had only a negligible effect. In a number of experiments, pyrazinealdehyde was substituted for methyl pyrazinoate and subjected to the stated lithium aluminum hydride reduction conditions. We were able to recover only small amounts of unchanged aldehyde, the remainder having undergone further reduction.

Pyrazinealdehyde is a light-sensitive, low melting solid (m.p. 31–33°, b.p. at 6 mm., 57–58°). It was characterized by conversion to the octahydroxanthene derivative as well as to the known 2,4-dinitrophenylhydrazone,[2] nicotinoylhydrazone, and isonicotinoylhydrazone.[4] I dissolves in a saturated sodium bisulfite solution with the formation of a soluble addition product. Like pyridine-2-aldehyde, which yields α-pyridyl-α-hydroxymethanesulfonic acid[6] when treated with aqueous sulfurous acid, I forms an analogous reaction product. The aldehyde undergoes a Cannizzaro reaction, yielding pyrazinoic acid and pyrazylmethanol. Since the latter compound is as yet unrecorded in the literature, it was characterized by ultraviolet and infrared spectra and the preparation of its α-naphthylcarbamate derivative.

Benzoin condensation of I affords pyrazoin in 85% yield. The absence of carbonyl absorption in its infrared spectrum as well as its behavior towards Tillmann's reagent[7] suggests an enediolic structure analogous to α-pyridoin.[8] Prior to the described reduction procedure we attempted to obtain pyrazinealdehyde by the reduction of pyrazinoyl chloride with lithium tri-*t*-butoxyaluminohydride.[9] The yield of I, however, never exceeded 20% (as the 2,4-dinitrophenylhydrazone). The major product of this reaction was pyrazylmethyl pyrazinoate, which was isolated in a 55% yield.

It was of interest to ascertain whether the low temperature reduction with lithium aluminum hydride could be extended to esters belonging to other series. Consequently, we initiated a series of experiments in which a number of esters were subjected to standardized reaction conditions. To simplify the experiments, only such esters were selected for which the corresponding aldehydes and their 2,4-dinitrophenylhydrazones were known, and the yields were determined by isolating the 2,4-dinitrophenylhydrazones. We found that while the reaction is not confined to methyl pyrazinoate it appears, however, to be limited to π-electron deficient systems. Aldehyde formation also is favored when the carbomethoxy group is in an electron deficient position. Thus, the three isomeric carbomethoxypyridines gave 75%, 12%, and 50% yields of the corresponding 2-, 3-, and 4-aldehydes. Quinoline-2-aldehyde was formed in 92% yield from methyl quinaldate. Ethyl acetate, methyl benzoate, diethyl phthalate, and benzonitrile failed to give carbonyl positive materials. Methyl *o*-nitrobenzoate produced only 5% of the expected aldehyde (probably because of steric hindrance), while the *p*-nitro ester reacted to the extent of 36% (a yield comparable to that of 4-carbomethoxypyridine).

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(2) T. I. Fand, dissertation, Polytechnic Institute of Brooklyn, 1954.

(3) S. Kushner, H. Dalalian, J. L. Sanjuro, F. L. Bach, Jr., S. F. Safir, V. K. Smith, Jr., and J. H. Williams, *J. Am. Chem. Soc.*, **74**, 3617 (1952).

(4) K. Kakemi, T. Uno, T. Arita, H. Nakao, I. Shimada, Y. Ikegami, and S. Kitazawa, *Yakugaku Zasshi*, **81**, 1609 (1961); *Chem. Abstr.*, **56**, 10142e (1962).

(5) J. D. Behun and R. Levine, *J. Org. Chem.*, **23**, 406 (1958).

(6) W. Mathes and W. Sauermilch, *Ber.*, **84**, 648 (1951).

(7) Solution of sodium 2,6-dichlorophenol-indophenol.

(8) W. Mathes, W. Sauermilch, and T. Klein, *Ber.*, **84**, 452 (1951).

(9) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **80**, 5377 (1958).

Experimental

All the melting points are corrected. The methyl pyrazinoate was prepared from pyrazinoic acid using the procedure described by Hall and Spoerri.[10] Pyrazinoic acid was obtained by selenium dioxide oxidation[11] of 2-methylpyrazine.[12]

Yield determinations of aldehydes were made *via* the 2,4-dinitrophenylhydrazones according to the method of Iddles, *et al.*[13]

Pyrazinealdehyde I.—Methyl pyrazinoate (25.0 g., 0.181 mole) in 500 ml. of dry tetrahydrofuran was cooled to −70° under nitrogen. While maintaining the temperature at −68° to −73°, 268 ml. of 0.34 *M* lithium aluminum hydride in tetrahydrofuran[14] (0.091 mole) was added with stirring over a period of 30 min. After stirring for an additional 15 min. at −75°, the reaction was stopped by slow addition of 25 ml. of glacial acetic acid. The light brown reaction mixture containing 0.142 mole of I was evaporated *in vacuo*. The residue was dissolved in 170 ml. of 2.5 *N* hydrochloric acid and 100 ml. of chloroform. The aqueous layer was extracted eight times with 50-ml. portions of chloroform. The combined extracts were stirred with 50 ml. of water and 25 g. of sodium bicarbonate until neutral. After filtration, the chloroform layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. Fractional vacuum distillation with tetraethyleneglycol dimethyl ether (Ansul ether 181) as chaser yielded 9.04 g. (46%) of pyrazinealdehyde, b.p. 57–58° at 6 mm., as a light yellow liquid. Redistillation afforded 5.26 g. of pure I, b.p. 57.0–57.8° at 6 mm., m.p. 31–33°, b.p. (Emich) 174°. The infrared spectrum of I (as a film) revealed a prominent band at 5.90 μ (C=O). I, octahydroxanthene, had m.p. (benzene–hexane) 176–177°.

Anal. Calcd. for $C_{21}H_{24}N_2O_8$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.31; H, 7.08; N, 7.64.

I, 2,4-dinitrophenylhydrazone, had m.p. 239–240° (lit.[2] m.p. 239–240°).

I, nicotinoylhydrazone, had m.p. (ethyl acetate) 195–195.5° (lit.[4] m.p. 195°).

I, isonicotinoylhydrazone, had m.p. (ethyl acetate) 197–198° (lit.[4] m.p. 200°).

α-Pyrazyl-α-hydroxymethanesulfonic Acid (II).—Sulfur dioxide was bubbled into a cooled mixture of 0.35 g. of I in 17 ml. of chloroform and 5 ml. of water. Addition of 100 ml. of acetone and subsequent refrigeration yielded 0.46 g. (75%) of II as light yellow crystals. Recrystallized from water–acetone, II melts at 159–159.5° (partial dec., sealed capillary); neut. equiv., 192.2 (theory, 190.1).

Pyrazoin(1,2-dipyrazyl-1,2-ethenediol) (III).—Potassium cyanide (0.2 g.) was added to 0.27 g. of I in 19 ml. of water. The solution darkens quickly with formation of yellow-brown crystals. The crystal slurry was stirred at room temperature for 1 hr., acidified with 0.2 ml. of glacial acetic acid, and filtered. Yield: 0.23 g. of III (85%), bronze colored crystals, m.p. (ethyl acetate) 218–219° dec.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.75; H, 3.86; N, 25.78.

Pyrazoin gives a positive Fehling test and decolorizes Tillmann's reagent. The infrared spectrum of III (in potassium bromide) shows no significant absorption bands between 5.5 and 6.2 μ.

Pyrazylmethanol (IV).—Pyrazinealdehyde (2.0 g.) and 3 ml. of 40% aqueous sodium hydroxide were mixed in a test tube cooled in ice–water. The resultant white paste was stirred for 10 min., then diluted with 12 ml. of water. Carbon dioxide was bubbled into the clear solution until the pH was 8–9. Evaporation to dryness *in vacuo*, extraction of the residue with chloroform, and distillation yielded 0.60 g. (59%) of pyrazylmethanol as a colorless, hydroscopic oil; b.p. 59–62° at 0.1 mm., m.p. 35–36°. Infrared spectrum (film): 3.0 μ (–OH), 9.40 μ (–C–OH). Ultraviolet spectrum (in 95% ethanol): maxima at 266 mμ, ε 6700; 309 mμ, ε 800. For analysis, the α-naphthylcarbamate of IV was prepared; m.p. (benzene–hexane) 110–110.5°.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.04. Found: C, 68.65; H, 4.81; N, 14.99.

The residue from the chloroform extraction was dissolved in water and acidified with hydrochloric acid to liberate the pyrazinoic acid. Yield: 1.02 g. (89%) white crystals, m.p. 224.5° dec., m.m.p. 224.5 dec.

Pyrazylmethyl Pyrazinoate.—This ester was formed in the reduction of pyrazinoyl chloride with lithium tri-*t*-butoxyaluminohydride in tetrahydrofuran by the method of Brown and Subba Rao.[9] With slow addition of the reductant over a 2-hr. period, a yield of 55% of pyrazylmethyl pyrazinoate was obtained as colorless needles, m.p. (benzene–hexane) 115–115.5°.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.64; H, 3.82; N, 25.83.

Saponification of the ester with 0.1 *N* sodium hydroxide at room temperature for 1 and 2 days gave a saponification equivalent of 211 and 214, respectively (theory 216.2). The distillation residue yielded pyrazinoic acid, m.p. 224.5° dec., undepressed on admixture with authentic pyrazinoic acid.

Lithium Aluminum Hydride Reduction Procedure on Esters Other than Methyl Pyrazinoate.—All reductions were conducted on a 1-mmole scale. The compound dissolved in 4 ml. of tetrahydrofuran was stirred magnetically while cooling to −70° to −75° in a methanol–Dry Ice bath. The lithium aluminum hydride solution (0.43 *M*) was added from a 10-ml. buret (protected from the atmosphere by a nitrogen-filled balloon) over a period of 5–7 min. After an additional 15 min. at −70°, the reaction was stopped by adding 0.25 ml. of glacial acetic acid. On warming to room temperature the reaction mixture was poured into 55 ml. (1.1 mmoles) of saturated 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid and allowed to stand for 48 hr. The 2,4-dinitrophenylhydrazone derivatives were filtered, washed with 5% hydrochloric acid, then water, and dried at 120° for 1 hr. before weighing. As a control, the yield of pyrazinealdehyde 2,4-dinitrophenylhydrazone from methyl pyrazinoate was reproducible within 0.5% in four reductions performed on three different days.

(10) S. A. Hall and P. E. Spoerri, *J. Am. Chem. Soc.* **62**, 664 (1940).

(11) H. Gainer, *J. Org. Chem.*, **24**, 691 (1959).

(12) The 2-methylpyrazine used in this study was generously supplied by Wyandotte Chemicals Corp.

(13) H. A. Iddles, A. W. Low, B. D. Rosen, and R. T. Hart, *Anal. Chem.*, **11**, 102 (1939).

(14) The concentration of LAH was determined by gravimetric analysis of the aluminum with oxine.

Participation of a Neighboring Amide Group in the Decomposition of Esters and Amides of Substituted Phthalamic Acids[1]

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The labilization of amide groups by a second neighboring amide function has been described recently for succinamide[2] and for phthalamide.[3] A similar labilization of benzyl esters has been reported also.[4] Because of the predominance of amide groups in proteins, the possibility arises that these groups may also, in some cases, be involved in the mode of action of hydrolytic enzymes. This possibility seemed to justify a further study of activation by neighboring amide groups.

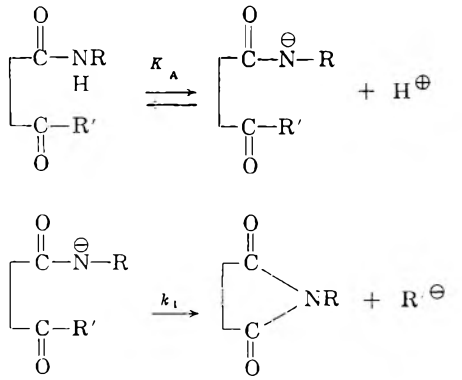
The attack of neighboring amide on amide or ester groups to form an imide intermediate proceeds at a rate inversely proportional to hydrogen ion concentration, suggesting the following mechanism.

(1) Financial support of this research by the National Institute of Health is gratefully acknowledged.

(2) B. Vigneron, P. Crooy, F. Kezdy, and A. Bruylants, *Bull. soc. chim. Belges*, **69**, 616 (1960).

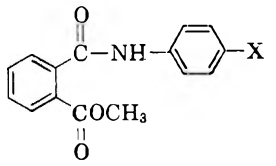
(3) P. Crooy, doctoral dissertation, Catholic University, Louvain, 1961.

(4) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962).



This is assuming that $K_A/(H^+) \ll 1$.

It would be expected that an increase in the acidity of the neighboring amide function would increase the concentration of the amidate nucleophile but at the same time reduce its reactivity. Kinetic investigation of a series of compounds in which each R is a *para* substituted phenyl group would then offer a convenient method for assessing the relative importance of these two factors[5] and such a study was carried out on compounds of type I with X = H, CN, NO_2, and CH_3.

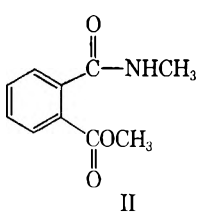


I

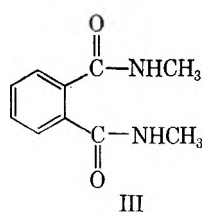
Applying the classical Hammett treatment to the effect of X on the reaction rate we obtain

$$\log (k/k^\circ) = (\rho_A + \rho_1)\sigma^* \qquad (1$$

where ρ_A and ρ_1 describe the sensitivity of K_A and k_1 to substituent effects. Applying equation 1 to data for compounds with electron-withdrawing substituents in Table I and using σ^* values recommended by Jaffe,[6] we obtain for $\rho_A + \rho_1$ a small negative value between -0.1 and -0.2. (With this small substituent sensitivity, the effect of *p*-methyl substitution would be expected to be negligible and the slight deactivation observed is not considered significant.) It may, therefore, be concluded that the increased concentration of the amidate ions resulting from increasingly electronegative substituents is insufficient to compensate for their reduced nucleophilic reactivity. The fact that methyl N-methylphthalamate (II) is four times more reactive than methyl phthalamate is qualitatively in the direction to be expected from the results discussed earlier, although the magnitude of the effect is surprising since unsubstituted amides and N-methylamides would be expected to differ in acidity less than anilides and *p*-nitroanilides. The observation that there is a smaller



II



III

(5) We are indebted to C. H. W. Hirs for suggesting this approach.

(6) H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

TABLE I

RATES OF IMIDE FORMATION FROM *para* SUBSTITUTED METHYL N-(PHENYL)PHTHALAMATES[a]

X	$10^4 k_1$ sec.$^{-1}$
H	3.9
CH_3	3.8
NO_2	2.8
CN	2.5

[a] Temp. = 25.3°, 40/60 v./v. dioxane-water, μ = 0.12, apparent pH = 7.8. Initial ester concentration 1.7×10^{-2} to 2.7×10^{-2} mg./ml.

TABLE II

RATES OF IMIDE FORMATION FOR SOME PHTHALAMIC ACID DERIVATIVES[a]

	k_2 (l. mole^{-1} sec.$^{-1}$)
Methyl N-methylphthalamate[b]	12,400
Methyl phthalamate[c]	3,100
N,N′-Dimethylphthalamide[d]	7.6
Phthalamide[e]	4.9

[a] In aqueous solution, temp. = 25.9°, μ = 0.1. [b] 6×10^{-3} mg./ml. [c] 6×10^{-3} mg./ml. [d] 5.9×10^{-2} mg./ml. [e] 3.2×10^{-1} mg./ml.

difference between the reactivities of N-N′-dimethyl phthalamide (III) and phthalamide is not surprising, since the nucleophilicity of the attacking and leaving groups is being changed by similar factors.

It may be pointed out that methanol is eliminated from the methyl esters of phthalamic acid and N-methylphthalamic acid more rapidly than from methyl *o*-formylbenzoate, which has been described recently[7] as the most reactive known methyl ester. This comparison is of interest since the release of methanol is the primary process reflecting the efficiency of neighboring group attack on the ester function. On the other hand, since the imide intermediate formed from II is relatively stable (200–300 times less reactive than the parent ester), methyl *o*-formylbenzoate is converted faster to the corresponding acid. The stability of the imide intermediate has to be taken into account also in considering the possibility that an amide group might form part of the active site of an esteratic enzyme. This difficulty does not arise when the neighboring amide serves to activate another amide; the reactivity of the imide intermediate is then comparable to that of the parent amide.

Experimental

Materials.—Substituted N-phenylphthalamic acids were prepared according to a method previously described.[8] The corresponding silver salts were made by neutralizing the acid with 1 *N* ammonia and mixing the resulting solution with an equivalent of concentrated silver nitrate solution.

Methyl esters of substituted N-phenylphthalamic acids were prepared by treating overnight with vigorous stirring the dry silver salt with excess methyl iodide in dry benzene or acetone at room temperature. These methods are reported elsewhere.[9,10] The benzene or acetone was evaporated and the residue was taken up in chloroform. The resulting products were then precipitated with hexane. The esters were crystallized three times

(7) M. L. Bender and M. S. Silver, *J. Am. Chem. Soc.*, **84**, 4589 (1962).

(8) M. L. Sherrill, F. L. Schaeffer, and E. P. Shoyer, *ibid.*, **50**, 474 (1928).

(9) M. M. S. Hoogewerff and W. A. Van Dorp, *Rec. trav. chem.*, **18**, 358 (1899).

(10) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd Ed., Longmans, London, 1959, pp. 388–389.

TABLE III
ANALYSES OF ESTERS STUDIED

Compound		Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Dec., °C.	Rep. dec., °C.
Methylphthalamate	$C_9H_9NO_3$	60.33	5.06	7.82	60.20	5.12	7.90	98-102	98-102[a]
Methyl N-methylphthalamate	$C_{10}H_{11}NO_3$	62.17	5.74	7.25	62.17	5.90	7.50	112-114	
Methyl N-phenylphthalamate	$C_{15}H_{13}NO_3$	70.58	5.13	5.49	70.81	5.28	5.67	111-112	
Methyl N-(*p*-methylphenyl)-phthalamate	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	71.09	5.63	5.22	145-146	
Methyl N-(*p*-nitrophenyl)-phthalamate	$C_{15}H_{12}N_2O_5$	60.00	4.03	9.33	60.06	4.14	9.24	158-159	
Methyl N-(*p*-cyanophenyl)-phthalamate	$C_{16}H_{12}N_2O_3$	68.56	4.32	10.00	68.81	4.48	9.87	157-158	

[a] See ref. 9.

from chloroform–hexane at room temperature, and gave acceptable elemental analyses (Table III).

Substituted N-phenylphthalimides were prepared by heating the corresponding substituted anilines in refluxing glacial acetic acid for half an hour with phthalic anhydride.[11] These imides have been reported previously and their melting points checked with those reported in the literature.

Ammonium phthalamate and ammonium N-methylphthalamate were prepared by adding phthalic anhydride to concentrated ammonia or 25% aqueous methylamine according to a method described by Chapman and Stephen.[12] The corresponding silver salts were prepared by dissolving the ammonium salts in water and adding an equivalent of concentrated silver nitrate solution.

Methyl N-methylphthalamate and methylphthalamate were prepared from their silver salts by methods described earlier.

All materials whose origin is not specified were obtained commercially in the highest purity available and purified when necessary, until their melting points corresponded to those previously reported.

Solutions.—Dioxane–water buffer was 40/60 v./v. The solution formally contained 0.0112 *M* Na_2HPO_4, 0.0128 *M* NaH_2PO_4, and enough sodium chloride to make the ionic strength 0.12. The apparent pH was 7.8. In all other buffers water was the only solvent and the ionic strength was 0.10 with the concentration of ionized acid less than 0.02 *M*.

Measurements of pH were made with a Cambridge Research Model pH meter.

Kinetics.—The rate of disappearance of reactant or the appearance of product was followed with a Beckman DU spectrophotometer by observing the change in optical density (D) with time in a thermostated cell. The following wave lengths were employed to study the various decompositions: phthalimide, N-methylphthalimide, N,N′-dimethylphthalamide, phthalamide, methyl phthalamate, and methyl N-methylphthalamate, 299 mμ; methyl N-phenylphthalamate, 275 mμ; methyl N-(*p*-methylphenyl) phthalamate, 281 mμ; methyl N-(*p*-nitrophenyl)phthalamate, 320 mμ; methyl N-(*p*-cyanophenyl)phthalamate, 294 mμ. For the esters plots of $-\ln (D - D_\infty)$ or $-\ln (D_\infty - D)$ were linear in time, and their slopes gave the pseudo first-order rate constants. In the case of the decomposition of phthalamide and N,N′-dimethylphthalamide, consecutive first-order reaction theory was used to obtain the rate of imide formation and decomposition. The formation of the imide intermediates was verified by the similarity between the rate constants assigned to the hydrolysis of the imides from the decomposition of the amides and to the rate constants observed from the separate hydrolyses of the imides.

Where the products were stable, they were identified by the similarity between their ultraviolet spectra and those of the expected products.

In the case of the methyl esters of the substituted phthalamic acids, the fact that the ultraviolet spectra of the esters approached that of the corresponding imide was taken as verification of the postulated reaction path. However, here the true infinity reading had to be calculated from the extinction coefficients of the imide and the concentration of the reactant, since in a time corresponding to ten half-lives of imide formation, the imide hydrolysis could not be neglected. Imide hydrolysis could be neglected during the first half-life of imide formation.

(11) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd Ed., Longmans, London, 1959, p. 423.

(12) E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1791 (1925).

Derivatives of Sulfenic Acids. XLII. 3-Chloroformylpropanesulfenyl Chloride and 1,2-Thiazan-3-one[1]

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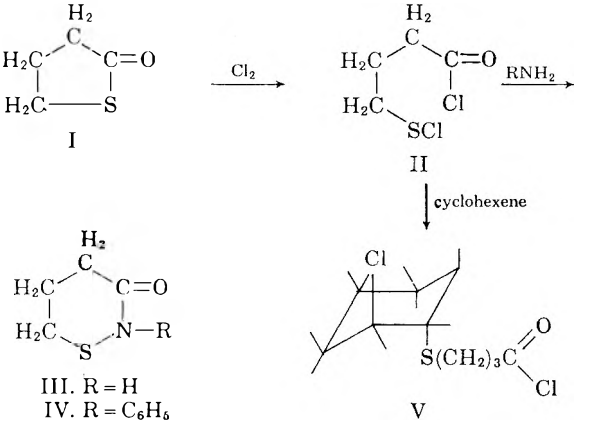
While aromatic sulfenyl chlorides have been studied in considerable detail,[2] less attention has been given to aliphatic examples, although the works of Douglass and co-workers, and of Brintzinger and others are notable.[3] Aliphatic polyfunctional sulfenyl chlorides have been mentioned in only a few cases, and even those recorded are very little known.[4]

We now report the synthesis of 3-chloroformylpropanesulfenyl chloride (II), by chlorinolysis of γ-thiobutyrolactone (I), and describe the properties of the former compound. For laboratory scale, the preparation of I is carried out conveniently by pyrolysis of γ-mercaptobutyric acid,[5] which is obtained, in turn, from γ-butyrolactone *via* the isothiuronium bromide.[6] Treatment of I with chlorine, or with sulfuryl chloride, in anhydrous chlorinated solvents at −20° leads



(1) This study was supported by a grant from the Stauffer Chemical Co., and contract DA-04-495-Ord 901 with the Army Research Office (Durham).

(2) Earlier papers in this series; *cf.* also N. Kharasch, Chap. 32, "Organic Sulfur Compounds," Vol. 1, Pergamon Press, 1961, pp. 375–396.

(3) I. B. Douglass, *ibid.*, pp. 350–360.

(4) H. Brintzinger, M. Langheck, and H. Ellwanger, *Ber.*, **87**, 320 (1954); H. Brintzinger, H. Schmahl, and H. Witte, *ibid.*, **85**, 338 (1952); *cf.* also ref. 3.

(5) B. Holmberg and E. Schjanberg, *Arkiv Kemi, Mineral. Geol.*, **14A**, No. 7 (1940); *Chem. Abstr.*, **35**, 2113 (1941).

(6) L. Schotte, *Arkiv Kemi*, **8**, 457 (1955).

smoothly to high yields of 3-chloroformylpropanesulfenyl chloride (II), a fuming, orange liquid.

Compound II was characterized by its ready reaction with cyclohexene to form 2-chlorocyclohexyl 3-chloroformylpropyl sulfide (V), assumed to be the *trans* adduct. By reaction of anhydrous ammonia and II, a first example of a new type of heterocyclic system, 1,2-thiazan-3-one (III), was obtained as the principal product. The substitution of aniline for ammonia in this reaction leads to 2-phenyl-1,2-thiazane-3-one (IV). The course of reactions of II, followed by disappearance of the color associated with the –SCl function, with cyclohexene, ammonia, and aniline clearly show the greater reactivity of the sulfenyl chloride function in comparison with the acyl chloride group.

Earlier examples of the chlorinolyses of thiol esters include the first preparation of 2,4-dinitrobenzenesulfenyl chloride from 2,4-dinitrophenyl thiolbenzoate[7] and the studies of Douglass and Osborne,[8] leading to alkyl sulfur trichlorides from methyl and ethyl thiolesters. The formation of II from I is thus in agreement with the earlier examples.

The observed infrared absorption spectra of the compounds described are in agreement with the proposed structures. In particular, the absorption peak attributed to the acidic carbonyl group shifted to the anticipated frequency for the derivative in every case. Although it was not possible to obtain analytical results of highest accuracy for II, due to its instability, the values obtained are not far off and are in line with decompositions involving loss of chlorine.

Experimental

γ-Mercaptobutyric Acid.—A mixture of 430 g. of γ-butyrolactone (5.0 moles), 380 g. of thiourea (5.0 moles), and 1000 g. of hydrobromic acid (48%) was refluxed with stirring, for 6 hr. After cooling, 625 g. of sodium hydroxide in 625 ml. of water was added gradually with good stirring. (Caution! As the neutral point was approached, the mixture began to foam quite suddenly. Considerable care was required to prevent overflow.) After all the base had been added, the mixture was heated to reflux for 2 hr. with stirring, cooled, and extracted with ether. The ether was discarded and the aqueous layer was acidified to pH 1 with concentrated hydrochloric acid. After cooling again it was extracted several times with ether. The combined ether extracts were dried over calcium chloride. After removal of the ether on a water bath, under aspirator vacuum, the residual oil was distilled under reduced pressure. To avoid pyrolysis, care was taken to keep the pot temperature below 100°. B.p. 85–90° (2 mm.). Yield: 437 g. or 73%. The infrared spectrum shows a strong peak at *ca.* 1710 cm.$^{-1}$, typical of carboxylic acids, and a weak mercapto peak at *ca.* 2600 cm.$^{-1}$

3-Carboxypropyl 2,4-dinitrophenyl sulfide, a derivative, was prepared from γ-mercaptobutyric acid by reaction with an equivalent of 2,4-dinitrobenzenesulfenyl chloride; m.p. 128–129°, after recrystallizing from aqueous methanol.

Anal. Calcd. for $C_{10}H_9O_6N_2S_2$: S, 20.0. Found: S, 20.15.

Pyrolysis of γ-Mercaptobutyric Acid to γ-Thiobutyrolactone.—A 240-g. sample of γ-mercaptobutyric acid was heated slowly in a distilling apparatus, at atmospheric pressure. Removal of water was complete at 105°. The temperature then rose to 185°, at which point a second colorless liquid began to distil. The temperature stabilized at 197°, with no sign of any more water separating. At this point the residue was allowed to cool, and the distillate was separated from the water, dried over sodium sulfate, and returned to the pot. After drying the apparatus, distillation was continued under reduced pressure. B.p. 40–45° (1–2 mm.). Yield: 160 g. or 78%. The infrared spectrum showed a strong peak at *ca.* 1670 cm.$^{-1}$, indicative of the carbonyl group, but the peak at 2600 cm.$^{-1}$ found in the mercapto acid had disappeared.

4-Mercaptobutyranilide, prepared as a derivative, was obtained by heating a sample of the thiolactone with aniline, giving a white solid, m.p. 88–89°, after recrystallization from benzene-ligroin mixture.

Anal. Calcd. for $C_{10}H_{13}NOS$: N, 7.17. Found: N, 7.32.

Chlorinolysis of γ-Thiobutyrolactone to 3-Chloroformylpropanesulfenyl Chloride.—To a solution of 20.4 g. (0.2 mole) of γ-thiobutyrolactone in 100 ml. of dry carbon tetrachloride, kept at −20° to −30°, was added, in small portions with good stirring, a solution of 14 g. (0.2 mole) of chlorine in 100 ml. of dry carbon tetrachloride, at the same temperature. The addition rate was regulated to prevent the exothermic reaction from causing the temperature to rise above −20°. A transient white precipitate, possibly the alkyl sulfur trichloride, formed with each addition of chlorine, but dissolved within several seconds into the stirred reaction mixture. An orange solution formed, becoming more colored as chlorine addition progressed. After chlorine addition was complete the reaction mixture was removed from the cooling bath and allowed to stand for a few minutes. The solvent was then removed under aspirator vacuum on a 40° water bath. A viscous orange liquid remained; crude yield: 35 g., theoretical, 34.4 g.

The crude material was immediately distilled under reduced pressure. B.p. 64–69° (1 mm.). Yield: 23.5 g. or 67%. This distillate was redistilled, b.p. 66–68° (1 mm.). Yield: 14.5 g. or 61% of the first distillate.

The product was an orange colored, oily liquid which fumed in air, and had a sharp odor like the aliphatic carboxyl chlorides. When stored at room temperature in a sealed bottle, considerable pressure (HCl) formed within a day. An analytical sample which stood 3 days at room temperature showed a loss of about 12% of its chlorine. To obtain a satisfactory elemental analysis, a freshly prepared and twice distilled sample was stored in Dry Ice and analyzed within 16 hr.

Anal. Calcd. for $C_4H_6Cl_2OS$: C, 27.76; H, 3.49; Cl, 40.98. Found: C, 28.39; H, 3.49; Cl, 40.06.

The infrared spectrum had a strong peak at 1790 cm.$^{-1}$, typical of acid chlorides; $n^{20}D$ 1.6174.

2-Chlorocyclohexyl 3-Chloroformylpropyl Sulfide.—To a solution of 6 g. of freshly prepared 3-chloroformylpropanesulfenyl chloride in 25 ml. of dry carbon tetrachloride at −10° was added a solution of 3 g. of cyclohexene in 25 ml. of dry carbon tetrachloride. This was added portionwise, with stirring, at a rate which did not let the exothermic reaction cause the temperature to rise above 0°. Almost all of the orange color of the sulfenyl chloride had disappeared within 1 min. after addition of the cyclohexene was complete. Removal of the solvent under reduced pressure left a yellow colored liquid; crude yield: 9 g. The product was distilled under reduced pressure. B.p. 136–137° (1 mm.). Yield: 6.5 g. or 78%. When redistilled, b.p. was 128–129° (1 mm.). The product had a trace of yellow color, which was probably due to impurities.

Anal. Calcd. for $C_{10}H_{16}Cl_2OS$: C, 46.63; H, 6.28; Cl, 27.39. Found: C, 47.24; H, 6.71; Cl, 27.92.

The infrared spectrum shows a sharp peak at 1790 cm.$^{-1}$, typical of acid chlorides; $n^{20}D$ 1.5276.

1,2-Thiazan-3-one.—To 20 g. of anhydrous ammonia in 300 ml. of dry carbon tetrachloride at −20° was added, in small portions with good stirring, a solution of 17 g. of 3-chloroformylpropanesulfenyl chloride[9] in 100 ml. of dry carbon tetrachloride, also at −20°. There was a strong exothermic reaction and a large amount of white solid formed. The mixture was allowed to stand overnight, then warmed to room temperature, and filtered. After drying, the solid weighed 19 g. This material was stirred with 200 ml. of water at room temperature to remove ammonium chloride, collected, and dried. Yield: 12 g., theoretical, 11.7 g. A sample was recrystallized from water four times to obtain a constant melting point; m.p. 160° (uncor.).

Anal. Calcd. for C_4H_7NOS: C, 41.00; H, 6.02; N, 11.96; S, 27.36. Found: C, 41.35; H, 6.08; N, 12.06; S, 27.15.

The infrared spectrum shows a sharp peak at 1650 cm.$^{-1}$, typical of amides. In the ultraviolet, a maximum was noted at 2510 Å.

(7) K. Fries and W. Buchler, *Ann.*, **454**, 258 (1927).

(8) I. B. Douglass and C. E. Osborne, *J. Am. Chem. Soc.*, **75**, 4582 (1953).

(9) Crude 3-chloroformylpropanesulfenyl chloride appears to be as satisfactory as redistilled material for synthetic purposes. Comparison of the infrared spectra of the crude and redistilled material also indicated that the product was of high purity before distillation. Because of its rapid decomposition, however, II was prepared only as required for immediate use.

2-Phenyl-1,2-thiazan-3-one.—To a solution of 17.3 g. (0.1 mole) of 3-chloroformylpropanesulfenyl chloride in 100 ml. of dry carbon tetrachloride was added, dropwise with good stirring, at −20°, a solution of 9.1 g. (0.1 mole) of aniline and 16 g. (0.2 mole) of pyridine, in 100 ml. of dry carbon tetrachloride. A white precipitate formed during the addition, but when the mixture was allowed to warm to room temperature over about 2 hr., the precipitate became nearly black and tarlike. The solvent was decanted and the residue was dissolved in 200 ml. of hot methanol. After repeated treatment with decolorizing carbon a light brown solution was obtained. Addition of 75 ml. of water to the boiling solution induced crystallization. On chilling a tan precipitate was obtained; m.p. 158–161°. Yield: 11 g. After recrystallizing three times from 95% ethanol the product was obtained as white needles; m.p. 169–170°.

Anal. Calcd. for $C_{10}H_{11}OHS$: C, 62.15; H, 5.74; N, 7.26. Found: C, 62.43; H, 5.93; N, 7.02.

The infrared spectrum showed a peak at *ca.* 1650 cm.$^{-1}$, typical of the carbonyl group in amides.[10]

(10) The infrared spectra of all liquids were made on the neat liquids pressed between sodium chloride plates. Solids were pressed in potassium bromide pellets.

Derivatives of Sulfenic Acids. XLIII. The Chlorinolysis of Certain Aryl Benzyl Sulfides as a Route to Sulfenyl Chlorides[1]

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The synthesis of 2,4-dinitrobenzenesulfenyl chloride (I) by catalytic chlorinolysis of bis(2,4-dinitrophenyl) disulfide has until now been the recommended method[2] for preparing this generally useful reagent.[3a,b] This procedure, however, has certain disadvantages which occasionally cause the synthesis to fail even in the hands of investigators who are thoroughly familiar with the preparation. The major difficulty has been in assuring the rigorously dry conditions or reagent purities needed for the effective action of the catalyst. The long reflux periods required at elevated temperatures and the very low solubility of bis(2,4-dinitrophenyl) disulfide in the solvents usually used, carbon tetrachloride or ethylene chloride, also present difficulties which led us to seek a more satisfactory synthesis of 2,4-dinitrobenzenesulfenyl chloride.

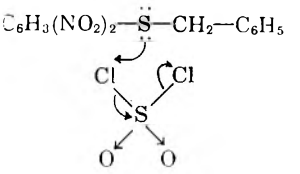
Other methods for preparing 2,4-dinitrobenzenesulfenyl chloride include the chlorinolysis of 2,4-dinitrophenyl thiolbenzoate,[4] 2,4-dinitrophenyl thiolacetate,[5] and the reaction of 2,4-dinitrobenzenethiol with chlorine.[6] The preparation of sulfenyl chlorides by chlorinolysis of benzyl aryl sulfides has been reported by Zincke,[7] and the formation, but not isolation of I by the cleavage of 2,4-dinitrophenyl benzyl sulfide (IV) was recorded.[8] In connection with a study of the scission of carbon–sulfur bonds, we have now developed the latter method into a convenient and fully reliable procedure for the preparation of 2,4-dinitrobenzenesulfenyl chloride.

2,4-Dinitrophenyl benzyl sulfide (IV) was prepared in 80–90% yields by reaction of 2,4-dinitrochlorobenzene with benzyl mercaptan, in the presence of pyridine. The resulting sulfide was readily cleaved to yield I, using either chlorine or sulfuryl chloride in chlorinated solvents. Because of the ease in handling, sulfuryl chloride was preferred for laboratory scale work. The reactions involved are shown.

$$2,4\text{-}(NO_2)_2C_6H_3Cl + C_6H_5CH_2SH + C_5H_5N \longrightarrow 2,4\text{-}(NO_2)_2C_6H_3SCH_2C_6H_5 + C_5H_5N{:}HCl$$

$$2,4\text{-}(NO_2)_2C_6H_3SCH_2C_6H_5 + SO_2Cl_2 \longrightarrow 2,4\text{-}(NO_2)_2C_6H_3SCl + C_6H_5CH_2Cl + SO_2$$

The rapid reaction of the sulfuryl chloride with the sulfide possibly involves a first step wherein positive chlorine, from sulfuryl chloride, transfers to the sulfur atom. The formation of benzyl chloride in near quantitative yield was observed, but the question of whether a cyclic mechanism, as inferred, actually occurs is not answered by the present work.



2,4-Dinitrobenzenesulfenyl bromide (III) was also obtained easily by the brominolysis of 2,4-dinitrophenyl benzyl sulfide. In the absence of catalysts, the reaction with bromine appears to be decidedly slower than that with chlorine, or sulfuryl chloride. However, in our experience with other methods for preparing this compound, the brominolysis of the benzyl sulfide is advantageous.

The reaction of bromine with 2,4-dinitrophenyl benzyl sulfide (IV), in cold chloroform, was reported by Fromm[9] to give an unidentified bromine-containing product, $C_{13}H_9BrN_2O_4S$. Our efforts to duplicate his work were unsuccessful, with no detectable amount of any such product being found. In all cases high yields of III were obtained. The sulfenyl bromide was identified by preparation of previously known derivatives and comparison of infrared spectra and melting points.

The synthesis of sulfenyl chlorides by chlorinolysis of aryl benzyl sulfides also succeeded in the case of 2-nitrobenzenesulfenyl chloride (V). This product was obtained in good quality and yield from 2-nitrophenyl benzyl sulfide. Although Zincke and Dahm[10] suggested this method for the synthesis of V they did not claim actually to have prepared the compound in this manner.

Efforts to obtain 4-nitrobenzenesulfenyl chloride by this method were not successful, however; in this case, bis(4-nitrophenyl) disulfide was obtained as the principal product. This difficulty in isolating 4-nitroben-

(1) This study was supported by grants from the Stauffer Chemical Company and the Petroleum Research Fund of the American Chemical Society.

(2) D. D. Lawson and N. Kharasch, *J. Org. Chem.*, **24**, 858 (1958).

(3) (a) N. Kharasch, *J. Chem. Educ.*, **33**, 585 (1956); (b) R. B. Langford and D. D. Lawson, *ibid.*, **34**, 510 (1957).

(4) K. Fries and W. Buchler, *Ann.*, **454**, 258 (1927).

(5) N. Kharasch and R. B. Langford, unpublished work.

(6) G. W. Perold and H. L. F. Snyman, *J. Am. Chem. Soc.*, **73**, 2379 (1951).

(7) T. Zincke, *Ber.*, **44**, 769 (1911).

(8) R. H. Baker, R. M. Dodson, and B. Riegel, *J. Am. Chem. Soc.*, **68**, 2636 (1946).

(9) E. Fromm, *Ann.*, **396**, 89 (1913).

(10) T. Zincke and A. Dahm, *Ber.*, **45**, 3457 (1912).

zenesulfenyl chloride is consistent with the results reported for other methods of preparing this compound.[11] A good preparation for this compound is still required.

The synthesis of 2,4,6-trinitrobenzenesulfenyl chloride by the chlorinolysis of 2,4,6-trinitrophenyl benzyl sulfide was also attempted, but the sulfide was recovered unchanged after long heating with sulfuryl chloride. Ultraviolet irradiation of solutions of 2,4,6-trinitrophenyl benzyl sulfide also failed to initiate its cleavage by chlorine.

1-Anthraquinonesulfenyl chloride (II) was also prepared conveniently by the cleavage of 1-anthraquinonyl benzyl sulfide with sulfuryl chloride. This sulfenyl chloride was first reported by Fries,[12] who treated bis(1-anthraquinonyl) disulfide with chlorine.

The intermediate 1-anthraquinonyl benzyl sulfide was obtained in good yield by the reaction of sodium benzyl mercaptide with 1-chloroanthraquinone.[13] 1-Anthraquinonyl benzyl sulfide has been reported by Gatterman,[14] who prepared it from 1-mercaptoanthraquinone and a benzyl halide, and by Hoffman and Reid[15] who used 1-anthraquinonesulfonic acid and benzyl mercaptan.

The synthesis of aromatic sulfenyl chlorides by chlorinolysis of aryl benzyl sulfides is undoubtedly capable of considerable extension. However, substituent effects, steric factors, and the stability of the product under the reaction conditions will have to be taken into account in each case.

Experimental

2,4-Dinitrophenyl Benzyl Sulfide (IV).—A mixture of 202 g. (1.0 mole) of 2,4-dinitrochlorobenzene (m.p. 50–52°), 400 ml. of methanol, 124 g. (1.0 mole) of benzyl mercaptan, and 87 g. (1.1 moles) of pyridine was stirred and heated at reflux for 16 hr., cooled to 0°, washed with cooled methanol, and dried at 60–80°. Yield: 250 g. or 86%, m.p. 128–129° (lit. m.p. 128°).[16]

2,4-Dinitrobenzenesulfenyl Chloride (I).—To a suspension of 232 g. (0.8 mole) of dry IV (material prepared previously gave good results without further purification) in 400 ml. of dry ethylene chloride was added, at room temperature, 119 g. (0.88 mole) of sulfuryl chloride. A mildly exothermic reaction raised the temperature 10–15°, and the solid dissolved within 1–2 min. The clear yellow solution which resulted was concentrated to an oil by heating on a steam bath under aspirator vacuum. After cooling to room temperature, four volumes of dry petroleum ether were added, with vigorous hand stirring. The oil quickly crystallized and the yellow, crystalline solid was collected, washed well with petroleum ether, and dried at 60–80°. The yield was 160 g. or 86% of a product melting at 95–96° (lit.[2] m.p. 96°). This material gave no melting point depression with samples of I which were prepared by the chlorinolysis of bis(2,4-dinitrophenyl) disulfide. Infrared spectra of the two materials were also identical. Derivatives with methanol, m.p. 125–126° (lit.[3b] m.p. 125°), and with cyclohexene, m.p. 118–120° (lit.[3b] m.p. 117–118°), were prepared.

By concentrating the petroleum ether solution from the previous preparation, a lachrymatory colorless liquid was obtained, b.p. 80–82° (25 mm.). Infrared spectra of this liquid and a known sample of benzyl chloride (J. T. Baker, purified grade) were identical. Yield: 85 g. or 95.5%.

2,4-Dinitrobenzenesulfenyl Bromide (III).—To a suspension of 2,4-dinitrophenyl benzyl sulfide in 150 ml. of carbon tetrachloride was added, in portions, 16 g. of bromine. As there was no apparent reaction the mixture was heated, at first gently and then at reflux, on a steam bath. After about 15 min. the solid had disappeared and the bromine color had become much less intense. On standing overnight at room temperature a crystalline precipitate had formed. This was collected by filtration, washed with carbon tetrachloride and then petroleum ether, and dried in an 80° oven to constant weight (only a few minutes were required). The orange colored crystals melted at 103° (uncor.) (lit.[17] m.p. 104.5–105.5°). Yield: 15.5 g. On heating further the color faded to pale yellow and the melt resolidified at about 140°. This solid decomposed at 270–280°. (Note: bis(2,4-dinitrophenyl) disulfide decomposed at 280°.) The adduct of III to cyclohexene corresponded to the known product.[17]

Concentration of the mother liquor on a 40° water bath under aspirator vacuum gave a residual oil which, on stirring with four volumes of petroleum ether, gave a second crop of III. Yield: 8.5 g. Combined yield: 24 g. or 86%.

On concentrating and distilling the wash liquids under reduced pressure a colorless, lachrymatory liquid was obtained, b.p. 45–50° (2–4 mm.). Its infrared spectrum was identical with that recorded[18] for benzyl bromide. Yield: 13.5 g. or 79%.

Identity of III was verified by preparation of its derivatives with cyclohexene, m.p. 120° (uncor.) (lit.[19] m.p. 123°). A comparison of the infrared spectra of I and II showed them to be nearly identical. No peaks which could be attributed to a benzyl group were present.

2-Nitrophenyl Benzyl Sulfide.—To a sodium methoxide solution prepared from 7.7 g. of sodium and 200 ml. of absolute methanol was added 41.3 g. of benzyl mercaptan in 100 ml. of methanol. To this was added, portionwise with swirling, a solution of 52.5 g. of 2-nitrochlorobenzene. There was no exothermic or apparent reaction. After heating for 1 hr. the mixture was allowed to stand at room temperature overnight. Beautiful large yellow crystals formed, m.p. 81–82°, on recrystallization from methanol, m.p. 83.5–84.5° (uncor.) (lit.[20] m.p. 82–83°). Yield: 64 g. or 78%. A second crop was obtained by chilling the mother liquor to −20°. Yield: 6.2 g.

2-Nitrobenzenesulfenyl Chloride.—To a suspension of 12.2 g. of 2-nitrophenyl benzyl sulfide in 80 ml. of carbon tetrachloride was added a solution of 6.8 g. of sulfuryl chloride in 25 ml. of carbon tetrachloride. The temperature rose about 5° and all but a few crystals of the sulfide had dissolved within a minute. These also disappeared on warming to 45°. After concentrating an oil, by heating on a steam bath under aspirator vacuum, 25 ml. of carbon tetrachloride was added. To the resulting solution was added, with good stirring, 100 ml. of petroleum ether. The product precipitated as yellow needles. After chilling to −20° the precipitate was collected, petroleum ether washed, and dried. Yield: 7.8 g. or 82%. M.p. 73–74° (lit.[21] m.p. 73–74.5°). From the mother liquor and washing benzyl chloride was isolated and identified as before. Yield: 3.2 g. or 51%.

2,4,6-Trinitrophenyl Benzyl Sulfide.—To 24.7 g. of picryl chloride in 100 ml. of methanol was added 12.4 g. of benzyl mercaptan and 8.7 g. of pyridine. The mixture turned red when the pyridine was added, the temperature rose to 52°, and color faded to orange within 5 min. (Note: in one run the reaction did not begin on addition of the pyridine, but on warming to about 50° on steam bath it was initiated. From that point on the reaction, and yield, appeared to be normal.) A yellow precipitate began to form within 5–10 min. After standing 30 min. the mixture was chilled and the precipitate collected and washed with cold methanol. The product was dried at 80°. Yield: 30.5 g. or 90%; m.p. 109–110°; 112–113° after recrystallization from methanol.

Anal. Calcd. for $C_{13}H_9O_6S$: C, 46.56; H, 2.71; S, 9.55. Found: C, 46.71; H, 2.90; S, 9.22.

Preparation of 1-Anthraquinonyl Benzyl Sulfide.—To a solution of sodium methoxide, made by dissolving 2.74 g. of sodium in 300 ml. of absolute methanol was added 14.75 g. of benzyl mercaptan. After refluxing this mixture 1 hr., 28.6 g. of 1-chloroanthraquinone[13] was added. Heating was continued for

(11) T. Zincke and S. Lenhart, *Ann.*, **400**, 1 (1913).
(12) K. Fries, *Ber.*, **45**, 2968 (1912).
(13) W. J. Scott and C. H. F. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 128.
(14) L. Gatterman, *Ann.*, **393**, 113 (1912).
(15) W. S. Hoffman and E. E. Reid, *J. Am. Chem. Soc.*, **45**, 1833 (1923).
(16) C. Willgerodt, *Ber.*, **18**, 331 (1885).
(17) N. Kharasch, C. M. Buess, and S. I. Strashun, *J. Am. Chem. Soc.*, **74**, 3422 (1952).
(18) Sadtler Standard Spectra, no. 2504, Sadtler Research Laboratories, Philadelphia, 1959.
(19) N. Kharasch, D. P. McQuarrie, and C. M. Buess, *J. Am. Chem. Soc.* **75**, 2658 (1953).
(20) A. Sieglitz and H. Koch, *Ber.*, **58**, 82 (1925).
(21) M. H. Hubacher, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 455.

15 hr. On cooling to room temperature the precipitate was collected and washed with three 100-ml. portions of hot methanol. The solid was then boiled with 500 ml. of methanol and filtered hot. Yield: 32 g. or 91%. M.p. 241–242°. Recrystallization from 6 l. of glacial acetic acid gave 31 g. of a product which had a melting point of 242°, in agreement with the literature value.

1-Anthraquinonesulfenyl Chloride.—To 21.75 g. of 1-anthraquinonyl benzyl sulfide in 800 ml. of dry benzene was added 8.9 g. of sulfuryl chloride. The mixture was warmed and shaken until a reaction occurred and a clear solution resulted. After filtering, the solution was allowed to cool to room temperature. The resulting crystalline precipitate was collected and the mother liquor was concentrated to obtain a second and a third crop. Yield: 17.9 g. or 99%. M.p. 220–223° (first crop), m.p. 216–220° (later crops) (lit. m.p. 224°). Recrystallization did not improve the melting point of the lower melting product.

Symmetrical Anhydrides of Hydroxy Acids[1]

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The symmetrical anhydrides of carboxylic acids containing unprotected hydroxyl functions apparently have not been prepared or described. This paper reports the synthesis and characterization of a series of these derivatives and establishes the symmetrical anhydrides of hydroxy acids as a known class of compounds.

In the course of amide syntheses using mixed carboxylic–carbonic anhydrides of the hydroxy fatty acids obtainable from castor oil,[2a,b] a series of experiments was performed to determine the reactivity of the secondary alcohol functions under the reaction conditions employed. The hydroxyl groups in these compounds were found to be unreactive at 0° toward ethyl chloroformate or toward the mixed carboxylic–carbonic anhydrides[3] formed from ethyl chloroformate and the triethylammonium salts of the carboxylic acids. Neither carbethoxylation nor esterification could be discounted *a priori* since both types of reaction are known to take place with secondary alcohols[4,5] under conditions suitable for the mixed anhydride reaction.

Since the alcohol functions in question were quite inert it seemed worth while to determine if the mixed anhydride method could be utilized for symmetrical anhydride formation with these hydroxy acids, as has been done in a few cases involving other carboxylic acids,[6,7] and if the products could be isolated despite the presence of both hydroxyl and anhydride functions in the same molecule.

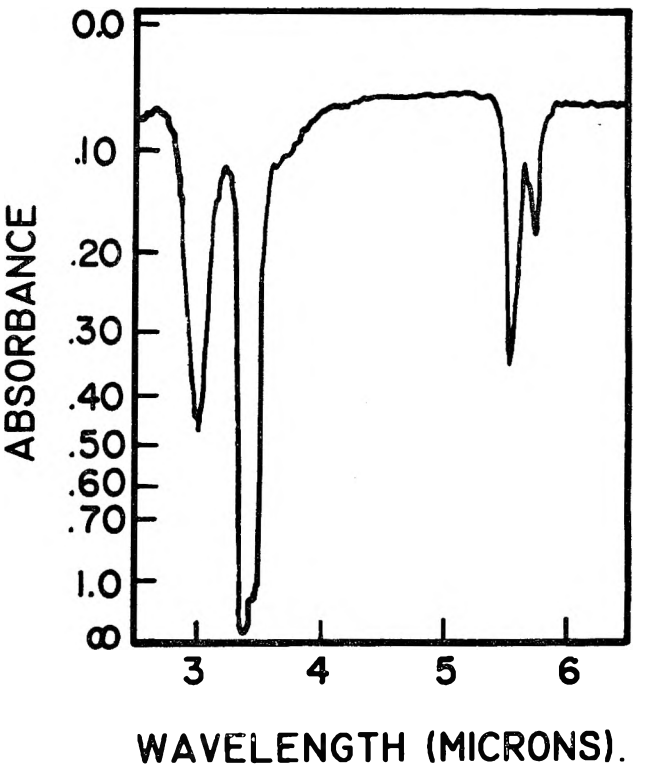
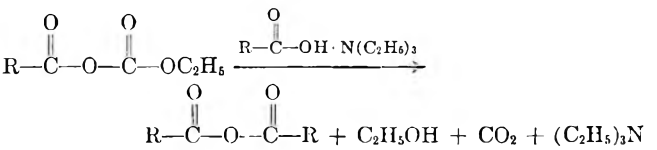


Fig. 1.—Infrared spectrum of 9,10-dihydroxyoctadecanoic anhydride: Nujol mull.

Reaction of the mixed carboxylic–carbonic anhydride of each hydroxy acid with one equivalent of the carboxylate anion of the same acid (present as the triethylammonium salt) in tetrahydrofuran at 0° gave a series of crystalline compounds, the symmetrical anhydrides, with melting points about 20° higher than those of the parent acids. These products (listed in Table I with yields and other pertinent data) have the expected infrared spectra for symmetrical hydroxy acid anhydrides. A typical example (Fig. 1) shows the hydroxyl band at 3.0 μ, and the paired carbonyl bands characteristic of carboxylic acid anhydrides.[8]

Though it has not been widely employed, this method of anhydride synthesis is a convenient, high yield procedure. Attack of the carboxylic acid anion on the carboxyl carbonyl of the mixed anhydride appears to be



rapid and straightforward. No detectable side reactions occurred in the cases reported here, and the yields were 95% or greater.

The hydroxy acid anhydrides are slowly decomposed at temperatures considerably above their melting points to give acidic material and polymeric esters. At ordinary temperatures, they apparently can be stored indefinitely. The 12-hydroxy-*cis*-9-octadecenoic symmetrical anhydride is best kept below 0°, but the other

(1) Presented before the American Chemical Society Meeting in Miniature, Berkeley, Calif., December 17, 1962.

(2) (a) 12-Hydroxy-*cis*-9-octadecenoic, 12-hydroxy-*trans*-9-octadecenoic, 12-hydroxyoctadecanoic, 9,10-dihydroxyoctadecanoic, and 9,10,12-trihydroxyoctadecanoic acids; (b) T. H. Applewhite, Jane S. Nelson, and L. A. Goldblatt, *J. Am. Oil Chemists' Soc.*, **40**, 101 (1963).

(3) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann. Chem.*, **572**, 190 (1951).

(4) N. F. Albertson, *Org. Reactions*, **12**, 157 (1962), has suggested such reactions as a possible cause of difficulties in mixed anhydride syntheses using hydroxy amino acids.

(5) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 318, describes the carbethoxylation of alcohols with ethyl chloroformate.

(6) L. N. Akimova and N. I. Gavrilov, *Zh. Obshch. Khim.*, **23**, 417 (1953); *Chem. Abstr.*, **48**, 3904 (1954).

(7) E. Schipper and J. Nichols, *J. Am. Chem. Soc.* **80**, 5714 (1958).

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen and Co. Ltd., London, 1958, p. 127.

TABLE I

HYDROXY ACID ANHYDRIDES

$(RC)_2O$ / R—	Yield,[a] % of theory	M.p., °C.	Infrared bands: Hydroxyl region, μ	Infrared bands: Carbonyl region, μ	% C: Calcd.	% C: Found	% H: Calcd.	% H: Found
$CH_3(CH_2)_5C(OH)(H)—CH_2CH=CH(CH_2)_7$- *cis*	95	35–35.5	2.90[c] 2.75[d]	5.56[c] 5.76[c] 5.50[d] 5.71[d]	74.7	74.5	11.5	11.4
$CH_3(CH_2)_5C(OH)(H)—CH_2CH=CH(CH_2)_7$- *trans*	96	64–64.5	3.0[c] 2.79[d]	5.52[c] 5.76[c] 5.51[d] 5.72[d]	74.7	74.7	11.5	11.4
$CH_3(CH_2)_5C(OH)(H)—(CH_2)_{10}$-	99	88–89	3.0[c]	5.52[c] 5.77[c]	74.2	74.1	12.1	12.1
$CH_3(CH_2)_5C(OH)(H)—CH_2CH(OH)CH(OH)(CH_2)_7$-	Quant.	132–133	2.95[c] 3.02[c]	5.52[c] 5.72[c]	66.8	66.9	10.9	10.9
$CH_3(CH_2)_7CH(OH)CH(OH)(CH_2)_7$-	Quant.	91–92	3.0[c]	5.52[c] 5.72[c]	70.3	70.5	11.5	11.4

[a] Washed and dried products (*cf.* text). [b] Recrystallized prior to analysis (*cf.* text). [c] Smear or Nujol mull. [d] Carbon tetrachloride solution.

TABLE II

ANHYDRIDE DERIVATIVES

Compound	M.p., °C.	Infrared bands[a]: Hydroxyl region, μ	Infrared bands[a]: Carbonyl region, μ	% C: Calcd.	% C: Found	% H: Calcd.	% H: Found	% N: Calcd.	% N: Found
9,10,12-Trihydroxyoctadecanamide	136-137	2.90 3.10	6.05	65.2	65.4	11.2	11.2	4.23	4.16
9,10-Dihydroxyoctadecanamide	113-113.5	2.96 3.10	6.08	68.5	68.4	11.8	11.7	4.44	4.45
12-Hydroxyoctadecanamide	111-112	2.88 3.00 3.08	6.02	72.2	72.1	12.4	12.2	4.68	4.68
12-Hydroxy-*cis*-9-octadecenamide	65.5-66.5[b,c]	2.95 3.10	6.03 6.10	72.7	72.5	11.9	11.7	4.71	4.64
12-Hydroxy-*trans*-9-octadecenamide	86.5-87.5[c,d]	2.90 2.95 3.03	6.02	72.7	72.5	11.9	11.8	4.71	4.52
9,10,12-Trihydroxyoctadecanoic acid	108[e]	3.00	5.90	65.0	65.1	10.9	10.8	...	...
9,10-Dihydroxyoctadecanoic acid	92.5-93.5[f]	2.99 3.05	5.80 5.88	68.3	68.5	11.5	11.4	...	...
12-Hydroxyoctadecanoic acid	80-80.5[g]	3.10	5.90	72.0	71.9	12.1	11.9	...	...
12-Hydroxy-*trans*-9-octadecenoic acid	49.5-50[h]	3.00 3.07	5.90	72.5	72.4	11.4	11.3	...	...
12-Hydroxy-*cis*-9-octadecenoic acid	Oil	2.95	5.85	[i]	...	...	...	...	...

[a] Nujol mulls or smears. [b] M.p. 66°, J. Bouis, *Ann. chim. phys.*, [3] **44**, 77 (1855). [c] No depression on admixture with authentic sample. [d] M.p. 91–93°, T. H. Rowney, *Jahresber. Fortschr. Chem.*, 533 (1855). [e] M.p. 108–109°, J. T. Scanlan and D. Swern, *J. Am. Chem. Soc.*, **62**, 2309 (1940). Starting material used here: 106–108°. [f] M.p. 94–95°, D. Swern, J. T. Scanlan, and G. B. Dickel, *Org. Syn.*, **39**, 15 (1959). Starting material used here: 92–93°. [g] M.p. 80.5–81°, F. Straus, H. Heinze, and L. Salzmann, *Chem. Ber.*, **66**, 631 (1933). Starting material used here: 79.5–80°. [h] M.p. 50.5–51.1°, M. A. McCutchon, R. T. O'Connor, E. F. DuPre, L. A. Goldblatt, and W. G. Bickford, *J. Am. Oil Chemists' Soc.*, **36**, 115 (1959). Starting material used here: 49.8–50.9°. [i] Identical to starting acid with respect to infrared spectrum and R_f on a thin-layer chromatogram.

members of this series show no detectable change after standing at room temperature for several months.

These anhydrides are also relatively inert on treatment with water, dilute acid, or dilute alkali. This is evident in that organic solutions of the anhydrides can be washed with dilute acids, bases, or water without appreciable decrease in yield or purity.

The anhydrides rapidly react to form equimolar quantities of amide and parent acid on treatment with ammonia followed by acidification. These derivatives have the correct infrared spectra, melting points, and elemental analyses (Table II).

$$R—\overset{O}{\overset{\|}{C}}—O—\overset{O}{\overset{\|}{C}}—R \xrightarrow[2.\ H^+]{1.\ NH_3} R—\overset{O}{\overset{\|}{C}}—NH_2 + HO—\overset{O}{\overset{\|}{C}}—R$$

Since limited experimentation with lactic acid in mixed anhydride system led to inconclusive results and

intractable mixtures, no attempt was made to prepare its symmetrical anhydride. We found that mandelic acid undergoes carbethoxylation when treated with equimolar amounts of ethyl chloroformate and triethylamine in the usual mixed anhydride method. Similar results were reported earlier by Fischer and Fischer[9] when they treated mandelic acid with excess methyl chloroformate. This procedure also appears inapplicable to phenols as exemplified by the results with *p*-hydroxycinnamic acid. Attempts to prepare the amide of this acid using the mixed anhydride method led to carbethoxylation of the phenolic hydroxyl rather than to mixed anhydride formation, so again symmetrical anhydride formation was not attempted. Examination of the applications and limitations of this symmetrical anhydride-forming system with other hydroxy acids is now in progress.

Experimental[10]

All melting points were obtained in capillary tubes in an electrically heated block and are uncorrected. Infrared spectra were obtained as Nujol mulls; a Perkin-Elmer Model 137 Infracord with sodium chloride optics was used. Mixed carboxylic–carbonic anhydrides were prepared at 0° in tetrahydrofuran, as previously described,[2b] and used without isolation.

Symmetrical Anhydrides.—Table I. Equimolar quantities (typical 0.01-mole scale) of hydroxy acid and freshly distilled triethylamine were dissolved in about 50 ml. of tetrahydrofuran (THF) for each 0.01 mole of acid. This solution was added from a dropping funnel to a well stirred solution of the corresponding mixed anhydride in tetrahydrofuran kept at or near 0° with an ice–salt bath. One molar equivalent of acid salt was used for each equivalent of mixed anhydride. After this addition, the system was allowed to come to room temperature, with stirring, and to stand overnight. The solution was then filtered from the triethylamine hydrochloride, which had precipitated during preparation of the mixed anhydride, and the precipitate was washed with tetrahydrofuran. The filtrate and washings were combined and the solvent removed *in vacuo* at room temperature on a rotary evaporator. The product was taken up in ether or chloroform, depending on its solubility, and washed with dilute hydrochloric acid and 1 *M* sodium carbonate solution followed with water until the washes tested neutral to pH paper. The organic solutions were dried over magnesium sulfate, filtered, and returned to the rotary evaporator for removal of solvent at room temperature. Yields were determined at this point. After this work-up, all of the compounds were essentially pure (Table I) and free of starting acid (Fig. 1); the only further treatment prior to analysis in the case of the saturated hydroxy anhydrides and 12-hydroxy-*trans*-9-octadecenoic anhydride was drying in a vacuum oven at room temperature and 0.01 mm. The 12-hydroxy-*cis*-9-octadecenoic anhydride was recrystallized from petroleum ether at −10°, then dried at room temperature and 0.01 mm.

Anhydride Derivatives.—Table II. Anhydrous ammonia gas was passed through a solution of hydroxy acid anhydride in tetrahydrofuran at room temperature. The tetrahydrofuran was removed on the rotary evaporator to leave an equimolar mixture of hydroxy acid ammonium salt and the corresponding amide. Weights obtained corresponded to theory. These product mixtures were dissolved in absolute methanol and separated on a column of macroreticular quaternary ammonium ion-exchange resin.[11] After recovery of the amide, a methanol solution of acetic acid was used to remove the hydroxy acid from the column. Each of the derivatives was recrystallized from 95% ethanol, the amides at room temperature and the slightly more soluble acids at 0°, and dried *in vacuo* at 40°.

Acknowledgment.—We thank Miss Geraldine E. Secor for performing the elemental analyses.

(9) E. Fischer and H. O. L. Fischer, *Chem. Ber.*, **47**, 768 (1914).

(10) Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

(11) Amberlyst XN-1001, Rohm and Haas Co., *cf.* R. Kunin, E. Meitzner, and N. Bortnick, *J. Am. Chem. Soc.*, **84**, 305 (1962).

Reaction of Cinnamic Acid Dibromide with Iodide Ion

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The conversion of vicinal dibromides to olefins by reaction with iodide ion has been investigated by several groups.[2-10] The reaction is usually reported to be first order in iodide ion and first order in dibromide. It has been shown that the elimination may follow a direct mechanism involving nucleophilic attack of iodide ion on bromine in a typical E2 process resulting in *trans* elimination[7] or may involve SN2 replacement of bromine by iodine on carbon followed by rapid collapse of the iodobromide.[8] This process gives the appearance of *cis* elimination of the bromine atoms.[9] The E2 mechanism apparently is preferred except for 1,2-dibromo compounds where displacement of the primary bromide is facile.

In connection with other work[11] we had occasion to use the reaction of iodide ion with cinnamic acid dibromides as an analytical method. In view of the fact that third-order kinetics had been reported for this process and because the stereochemistry had not been studied, we investigated the reaction of *erythro*-2,3-dibromo-3-phenylpropionic acid, hereafter referred to as *trans*-cinnamic acid dibromide, in the solvents 80% aqueous acetic acid and 80% aqueous methanol. The reaction was followed by titrating the iodine liberated.

Results

***trans*-Cinnamic Acid Dibromide.**—The conditions and specific rate constants obtained for the second-order reaction of *trans*-cinnamic acid dibromide with iodide ion are listed in Table I. The order of the reaction with respect to iodide ion and with respect to dibromo acid was determined by the method of initial slopes.[12] The values for the order with respect to iodide ion as determined for three different sets of reaction conditions were 0.96, 0.98, and 0.97. Similarly the order with respect to dibromo acid was found to be 1.0. The effect of ionic strength and the specific effect of bromide ion were tested by the addition of sodium perchlorate or of potassium bromide. The specific rate constants were calculated from the rate expression for a second-order reaction in the integrated form. The

(1) Colgate University, Hamilton, N. Y.

(2) A. Slator, *J. Chem. Soc.*, **85**, 1697 (1904).

(3) E. Biilmann, *Rec. trav. chim.*, **36**, 313 (1917).

(4) C. F. van Duin, *ibid.*, **43**, 341 (1924); **45**, 345 (1926); **47**, 715 (1928).

(5) R. T. Dillon, *J. Am. Chem. Soc.*, **54**, 952 (1932).

(6) T. L. Davis and R. Heggie, *J. Org. Chem.*, **2**, 470 (1937).

(7) S. Winstein, D. Pressman, and W. G. Young, *J. Am. Chem. Soc.*, **61**, 1645 (1939).

(8) J. Hine and W. H. Brader, *ibid.*, **77**, 361 (1955).

(9) W. M. Schubert, H. Steadly, and B. S. Rabinovitch, *ibid.*, **77**, 5755 (1955).

(10) W. G. Lee and S. I. Miller, *J. Phys. Chem.*, **66**, 555 (1962).

(11) E. R. Trumbull, R. T. Finn, K. M. Ibne-Rasa, and C. K. Sauers, *J. Org. Chem.* **27**, 2339 (1962).

(12) R. Livingston in Weissberger, "Investigations of Rates and Mechanism of Reactions, Technique of Organic Chemistry," Vol. VIII, Interscience Publishers Inc., New York, N. Y., 1953, p. 182.

TABLE I
RATE CONSTANTS FOR ELIMINATION OF CINNAMIC ACID DIBROMIDE

a	b	Added anion	μ^c	T, °C. ± 0.1	$10^4 k_2$ l. mole^{-1} sec.$^{-1}$	% Reaction
Solvent, 80% acetic acid						
0.030	0.240	0.30 Br^-	0.54	29.9	4.60	68
.030	.240	...	.24	29.9	4.30	76
.030	.180	.18 ClO_4^-	.36	29.9	4.33	61
.030	.090	...	.09	29.9	4.08	44
.015	.240	...	.24	29.9	4.28	71
.030	.180	...	.18	38.4	9.18	64
.030	.180	.18 Br^-	.36	38.4	9.42	65
.030	.180	.18 Br^-	.36	38.4	9.47	64
.030	.180	.27 ClO_4^-	.45	38.4	10.03	62
.015	.120	...	.12	46.0	17.56	
Solvent, 80% methanol						
0.030	0.24	...	0.24	25.0	1.37	56
.0134	.117	0.12 Br^-	.24	45.5	9.63	63
.0134	.117	...	.12	45.5	9.43	63

[a] Initial molarity of *trans*-cinnamic acid dibromide. [b] Initial molarity of iodide ion. [c] μ = ionic strength.

values of k remained constant during each run, the mean deviations being on the order of 3–4%.

The product of reaction was shown to be *trans*-cinnamic acid, isolated in 88% yield from a run in 80% acetic acid. *cis*-Cinnamic acid was shown to be stable under the reaction conditions.

cis-Cinnamic Acid Dibromide.—The reaction of *threo*-2,3-dibromo-3-phenyl propionic acid (*cis*-cinnamic acid dibromide) with iodide ion in 80% acetic acid or in 80% methanol was not simple. Only 40–50% of the theoretical amount of iodine was liberated and an attempt to identify the products of reaction was not successful. It was clear, however, that liberation of iodine from the *cis*-dibromide was considerably slower than is the case for the *trans* isomer. The reaction in 80% acetic acid was followed and specific rate constants calculated from the initial slope of the rate of formation of iodine. Assuming that this is a measure of the elimination reaction and that the elimination is a second-order process, values for the specific rate constant were calculated. At 90.6° runs under identical conditions gave the values 5.5×10^{-4} and 6.0×10^{-4} l. mole^{-1} sec.$^{-1}$. At 72.6° the specific rate constant was 1.9×10^{-4} l. mole^{-1} sec.$^{-1}$.

Discussion

The reaction of *trans*-cinnamic acid dibromide in 80% acetic acid and in 80% methanol is first order in iodide ion and first order in dibromo acid. The reaction shows a slight positive salt effect and no retardation by bromide ion. The difference between 80% acetic acid and 80% methanol as solvent for this reaction is not great, roughly a factor of two at 45°, and is in the direction of greater rate in the solvent of greater Y value.[13] Much larger salt effects are reported for debromination reactions in absolute methanol,[14] a solvent whose Y value is much more negative than is that of 80% methanol. The positive salt effect and tendency for rate to be greater in a solvent of higher ion-solvating power indicate a greater role for solvation in the transition state than in the ground state. This is possible if release of the bromide ion has occurred to a considerable extent in the transition state since the solvation energy of bromide ion is expected to be greater than that of iodide ion.

The production of *trans*-cinnamic acid from the *erythro*-dibromide indicates *trans* elimination and taken together with the kinetic order indicates that the direct mechanism is operative in this case. The entropies of activation, −19.3 e.u. and −18.0 e.u. in aqueous acetic acid and methanol. respectively, are also consistent with this mechanism. Although the molecule contains a bromine atom in the benzylic position, apparently displacement on carbon does not compete successfully with the E2 mechanism. The absolute rate of reaction of cinnamic acid dibromide with iodide ion in 80% methanol is greater than the rate of 2,3-dibromobutane in 99% methanol by a factor of the order of 10^3 at 60°. To some degree this may be a solvent effect but it seems probable that the stabilization of the incipient double bond by conjugation with the phenyl and carboxyl groups is an important factor in this difference in rate.

A ratio for the reactivity of the *erythro* dibromide to the *threo* dibromide was determined by calculating the rate expected of the *erythro* compound at the temperature where the *threo* compound was measured. The ratio for $k_{erythro}/k_{threo}$ was 85. This number is reasonable[15] but of questionable significance because of the uncertainty in the meaning of the rate constant determined for the *threo* dibromide.

Experimental

cis-Cinnamic acid dibromide and *trans*-cinnamic acid dibromide were prepared as described previously.[11] Kinetic runs in 80% acetic acid at temperatures below 50° were carried out by removing samples at intervals, quenching the reaction by running the sample onto crushed ice, and titrating the iodine quickly against thiosulfate. Runs in 80% methanol at 45° and the runs with *cis*-cinnamic acid dibromide at 73° and 91° were conducted in sealed tubes. Blanks were run to correct for the formation of iodine from iodide ion by oxidative processes other than the one under investigation.

Isolation of *trans*-Cinnamic Acid.—A solution of 39.8 g. (0.249 mole) of potassium iodide and 9.24 g. (0.030 mole) of *trans*-cinnamic acid dibromide in 300 ml. of 80% acetic acid was heated at 46° for 6 hr. The solvent was distilled at 40–50° at the aspirator. The residue was treated with 300 ml. of water containing 10 g. of potassium iodide. Insoluble material was collected on a Büchner funnel and washed with water. The solid was taken up in ether and washed with 0.1 N thiosulfate solution. The ether was removed by distillation and the residue dried in a desiccator. The material weighed 3.91 g. (88%) and had m.p. 133–134°, m.m.p. with *trans*-cinnamic acid, 133–134°.

A solution of 4.0 g. (0.013 mole) of *cis*-cinnamic acid, m.p. 57–58°, in 200 ml. of 80% acetic acid containing 20.0 g. of potassium iodide was heated at 46° for 6 hr. The reaction mixture was treated as described earlier to yield 3.52 g. of crude product. This material was recrystallized from low-boiling petroleum ether and 3.37 g. (84%) of *cis*-cinnamic acid, m.p. 57–58°, was recovered.

(13) A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, **78**, 2770 (1956).
(14) W. G. Young, D. Pressman, and C. D. Coryell, *ibid.*, **61**, 1640 (1939).
(15) D. Y. Curtin, Abstracts of the 13th National Organic Symposium, 1953, p. 40.

Alkylation of Benzene with Triphenylmethyl Chloride

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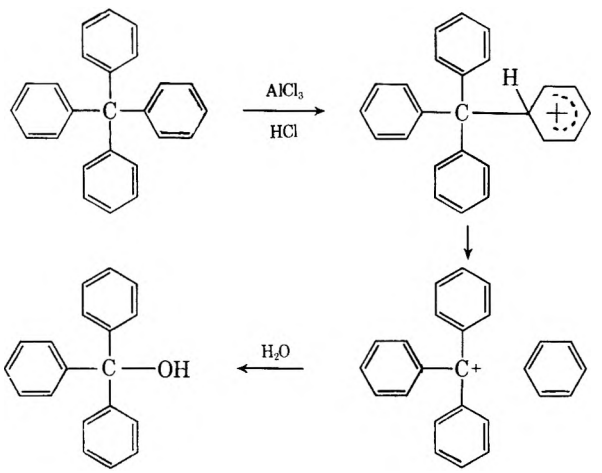
It is common knowledge that benzene and similar aromatic compounds may be readily alkylated with an alkyl halide under Friedel–Crafts conditions. It is, however, a curious fact that tetraphenylmethane cannot be prepared by such direct alkylation procedures.[1] Triphenylmethyl chloride fails to alkylate benzene as do similar systems which presumably involve an intermediate triphenylmethyl cation. Arguments have been presented[2] that this cannot be due to steric hindrance nor to instability of tetraphenylmethane for this substance is "thermally stable."

It appeared reasonable that the thermal stability of tetraphenylmethane should have little or no relationship to the failure of the Friedel–Crafts alkylation reaction but rather the product might well be unstable with respect to reactants under the alkylating conditions. The alkylation process is acknowledged as being in some measure reversible; hence one might anticipate fairly ready dealkylation of the substituted benzene to generate the relatively stable triphenylmethyl cation and benzene. Accordingly we allowed tetraphenylmethane to react with anhydrous aluminum chloride and hydrogen chloride in benzene solution. Hydrolysis of the reaction mixture gave an almost quantitative yield of triphenylcarbinol thus indicating facile dealkylation of the substituted benzene.



In contrast to its ready fragmentation in the presence of aluminum chloride, tetraphenylmethane appears to undergo very little change in concentrated sulfuric acid at room temperature. At higher temperatures the characteristic ultraviolet spectrum of the triphenylmethyl cation could be detected in the solution although the bulk of the tetraphenylmethane could be recovered unchanged from the solution.

The observance of similar behavior in related substances is to be anticipated.

(1) C. A. Thomas, "Anhydrous Aluminum Chloride," Reinhold Publishing Co., New York, N. Y., 1941, p. 116.

(2) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 357.

One might now postulate that the triphenylmethyl cation will alkylate benzene but due to an unfavorable equilibrium one fails to obtain significant quantities of product. As a simple test of this hypothesis we allowed 4-methyltriphenylmethyl chloride[3] to react with benzene in the presence of aluminum chloride. If reversible alkylation and dealkylation occurs one would expect to generate a mixture of benzene, toluene, triphenylmethyl cation, and the cation derived from the original reactant. Such was evidently the case for hydrolysis of the reaction mixture afforded triphenylcarbinol, diphenyl-4-tolylcarbinol, and a liquid fraction containing largely benzene but in which toluene could be identified by vapor phase chromatography.

Experimental

Dealkylation of Tetraphenylmethane.—A solution of 1.60 g. (0.005 mole) of tetraphenylmethane in 20 ml. of anhydrous benzene was saturated with anhydrous hydrogen chloride. Upon addition of 2 g. of anhydrous aluminum chloride the colorless mixture turned deep red in color. The mixture was warmed briefly on a steam cone, poured into water, and extracted with ether. Evaporation of the ether extract left a yellow solid residue which, upon decolorization with charcoal and crystallization, afforded 1.25 g. of triphenylcarbinol, m.p. 162–163°. Admixture with authentic triphenylcarbinol gave no melting point depression. The infrared spectrum was identical with that of authentic material.

Attempted Alkylation of Benzene.—A solution of 5.8 (0.02 mole) of 4-methyltriphenylmethyl chloride and 4 g. of anhydrous aluminum chloride in 20 ml. of dry benzene was stirred for 6 hr. at room temperature and then warmed briefly on a steam cone and poured into ice–water. The organic material was extracted with ether and the extract was carefully fractionated by distillation to give an aromatic fraction which by vapor phase chromatography analysis contained a small but definite quantity of toluene. The distillation residue afforded 0.47 g. of authentic triphenylcarbinol after much tedious handling. Somewhat impure diphenyl-4-tolylcarbinol was also recovered and identified by its infrared spectrum.

(3) A. Bistrzycki and J. Gyr, *Ber.*, **37**, 655 (1904).

t-Butyl S-Methyl and S-Phenyl Thiolcarbonates[1]

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Since the first report[2] in 1956 describing the use of the carbo-*t*-butoxy protective group its numerous advantages over other protective groups have become clear. Sufficient effort has been expended regarding the introduction and removal of this function that it has become one of the most valuable of all amino-protecting groups.[3,4]

(1) Supported by a grant (RG-9706) from the National Institutes of Health.

(2) L. A. Carpino, Abstracts of the 129th National Meeting of the American Chemical Society, Dallas, Tex., April, 1956, p. 59N.

(3) For references to earlier work, see L. A. Carpino, *J. Am. Chem. Soc.*, **82**, 2725 (1960).

(4) For recent examples of the advantageous utilization of the carbo-*t*-butoxy group in the synthesis of complex polypeptides and references to earlier work of the Swiss group, see R. Schwyzer and A. Tun-Kyi, *Helv. Chim. Acta*, **45**, 859 (1962).

It is, therefore, of interest to describe a simple method for the preparation of the heretofore difficultly accessible thiol ester, *t*-butyl S-methyl thiolcarbonate, undoubtedly the best of the currently available intermediates for the preparation of *t*-butyl carbazate,[5] precursor of one of the most important carbo-*t*-butoxylating agents, *t*-butyl azidoformate.[10,11]

An earlier described synthesis[3] of *t*-butyl S-methyl thiolcarbonate suffers from the disadvantage that expensive, relatively inaccessible gaseous carbonyl sulfide is required. It has now been shown that the thiol ester is readily obtained by reaction of commercially available methyl chlorothiolformate[12] with *t*-butyl alcohol in refluxing chloroform in the presence of pyridine.[13] The corresponding S-phenyl ester was also obtained in analogous fashion in 61% yield from phenyl chlorothiolformate. Use of *t*-butyl S-phenyl thiolcarbonate might offer some advantage over the use of the methyl ester in the preparation of *t*-butyl carbazate by virtue of its increased reactivity toward hydrazine. The greater acidity of benzenethiol *vs.* phenol allows clean separation of the resultant *t*-butyl carbazate and the coproduct benzenethiol thus avoiding a difficulty which arises in the use of the corresponding oxygen analog, *t*-butyl phenyl carbonate.[3,6]

Experimental[14]

t-Butyl S-Methyl Thiolcarbonate.—To a solution of 53.6 ml. of pyridine and 62.6 ml. of *t*-butyl alcohol in 200 ml. of chloroform which was stirred mechanically at room temperature there was added dropwise over 15–20 min. 66.4 g. of methyl chlorothiolformate.[12] The mixture was stirred and refluxed for 24 hr. and then washed in a separatory funnel with two 200-ml. portions of water, three 100-ml. portions of 5% hydrochloric acid, and finally 100 ml. of 1 *M* sodium bicarbonate. The solution was dried over magnesium sulfate and most of the solvent removed by distillation at atmospheric pressure followed by the use of a water aspirator.

Distillation of the residue gave 61.5 g. (69%) of the ester, b.p. 62–65° (24 mm.). Redistillation through a 30-cm. helices-packed column gave 50 g. (56%) of the ester, b.p. 60–63° (24 mm.), lit.[3] b.p. 60–62° (20 mm.). Conversion of this ester to *t*-butyl carbazate by heating in an oil bath at 105–110° for 24 hr. has already been described.[3]

t-Butyl S-Phenyl Thiolcarbonate.—A solution of 62.6 ml. of *t*-butyl alcohol and 53.6 ml. of pyridine dissolved in 200 ml. of chloroform was treated at room temperature with stirring over a period of 10 min. with 103.4 g. (81.6 ml.) of phenyl chlorothiolformate.[12] The solution was refluxed with stirring for 55 hr. and worked up essentially as given for the corresponding methyl ester. Distillation from an ordinary Claisen flask gave 70 g. (61%) of the thiol ester, b.p. 88.5° (1.2 mm.) to 102° (1.9 mm.). A center cut for analysis, distilled through a 30-cm. helices-packed column (95% recovery) had b.p. 86° (0.9 mm.).

Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 63.23 H, 7.02.

Conversion of *t*-Butyl S-Phenyl Thiolcarbonate to *t*-Butyl Carbazate.—A mixture of 21 g. of *t*-butyl S-phenyl thiolcarbonate and 10 g. of 64% hydrazine was heated in a water bath to 85–90° with swirling for a few minutes until the two phases coalesced. The resulting solution was warmed in the water bath at 75–80° for 3 hr. and then poured into a solution of 8 g. of sodium hydroxide in 250 ml. of water. The resulting cloudy mixture was treated with decolorizing carbon at room temperature with occasional stirring for 1 hr. and filtered. The clear filtrate was extracted with ether in a continuous extractor for 48 hr.

Evaporation of the dried (magnesium sulfate) ether extract from a water bath with the aid of a water aspirator gave a colorless oil which solidified on cooling or seeding to give 10.5–11 g. (80–83%) of snow white crystals of *t*-butyl carbazate, m.p. 39.5–41° (lit.[6] m.p. 41–42°).

(5) Other methods which have been recommended for the synthesis of *t*-butyl carbazate involve acylation of hydrazine by means of *t*-butyl phenyl carbonate,[6] *t*-butyl *p*-nitrophenyl carbonate,[7,8] and N-*t*-butyloxycarbonylimidazole.[9]

(6) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 98 (1957).

(7) G. W. Anderson and A. C. McGregor, *ibid.*, **79**, 6180 (1957).

(8) F. Eloy and C. Moussebois, *Bull. soc. chim. Belges*, **68**, 409 (1959).

(9) W. Klee and M. Brenner, *Helv. Chim. Acta*, **44**, 2151 (1961).

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(11) R. Schwyzer, P. Sieber, and H. Kappeler, *Helv. Chim. Acta*, **42**, 2622 (1959).

(12) We acknowledge with thanks generous gifts of methyl, ethyl, and phenyl chlorothiolformates from The Stauffer Chemical Co., New York, N. Y.

(13) A number of other bases and solvents proved to be unsatisfactory in the conversion, giving lower yields or other products. These included dimethylaniline, quinoline, triethylamine or pyridine in methylene dichloride, triethylamine in benzene, and trimethylamine or pyridine in dimethylformamide. We are indebted to David Collins for checking some of the preparations.

(14) Analyses are by Galbraith Laboratories, Knoxville, Tenn.

Reductions of 3,6-Diphenyl-*s*-tetrazine[1,2]

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In the course of attempting to prepare 3,6-bis(hydroxymethyl)-*s*-tetrazine *via* the reduction of 3,6-bis(carboxy)-*s*-tetrazine with lithium aluminum hydride, it became apparent that the tetrazine ring was cleaved. In order to facilitate the study of this reduction, 3,6-diphenyl-*s*-tetrazine[2] (I) was utilized instead of the 3,6-bis(carboxy)-*s*-tetrazine since the former is much easier and cheaper to prepare.

When I is slowly added to an ether solution of lithium aluminum hydride, there is an immediate loss of red color. Hydrolysis of the reaction mixture gives a yellow, ether-soluble product. This product has been identified as benzalazine by means of melting point, nitrogen analysis, and mixture melting point with an authentic sample of benzalazine. The infrared spectrum of this material is identical with that of benzalazine.

Hydrazine is identified as one of the products by the addition of benzaldehyde to the aqueous hydrolyzate. A yellow solid is recovered from this reaction and is identified as benzalazine. Ammonia is not observed as a product of the reduction. Sodium borohydride gives essentially the same results in this reaction. The reaction of I with sodium dithionite gives only 1,2-dihydro-3,6-diphenyl-*s*-tetrazine.[2,3] The reduction of this dihydrotetrazine with lithium aluminum hydride gives benzalazine. Benzalazine is not changed when an ether solution of it and lithium aluminum hydride are refluxed overnight. The reduction of 3,6-diphenyl-*s*-tetrazine or 1,2-dihydro-3,6-diphenyl-*s*-tetrazine with zinc dust and acetic acid gives 3,5-diphenyl-1,2,4,4*H*-triazole.[4] This triazole is not changed when it is warmed with lithium aluminum hydride overnight.

(1) Supported by a grant (CY3908) from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Md. Presented at the Southwest Regional Meeting of the American Chemical Society, Dallas, Tex., December, 1962.

(2) A. Pinner, *Ber.*, **26**, 2126 (1893).

(3) P. Chabries and S. H. Renard, *Compt. rend.*, **230**, 1673 (1950).

(4) R. Huisgen, J. Sauer, and M. Seidel, *Ann. Chem.*, **654**, 146 (1962).

Experimental

Reduction of 3,6-diphenyl-s-tetrazine (II). (A) Lithium Aluminum Hydride Reduction.—A 1-l. three-necked flask was fitted with a nitrogen inlet tube, stirrer, and a condenser topped with a calcium chloride drying tube which in turn was connected to a water trap. The flask was charged with 3.0 g. of lithium aluminum hydride and 250 ml. of ether. A steady stream of nitrogen was passed through the flask and a solution of 10 g. (0.043 mole) of 3,6-diphenyl-*s*-tetrazine[5] in 100 ml. of anhydrous ether was added as rapidly as possible through the condenser. There was an immediate loss of purple color. The mixture was refluxed on a steam bath for 1 hr.

The mixture was cooled and 15 ml. of water was added dropwise. This was followed by the addition of 250 ml. of 10% sulfuric acid. The yellow ether layer was separated, dried over sodium sulfate, and the ether evaporated. A yellow solid (6.8 g.) was collected, m.p. 92–93°. This was identified as benzalazine.

Treatment of II with nitric acid did not produce the characteristic purple color of tetrazines. The material did not depress the melting point of an authentic sample of benzalazine[6] and infrared spectrum was identical with that of benzalazine.

Anal. Calcd. for $C_{14}H_{12}N_2$: N, 13.45. Found: N, 13.62.

A 10-ml. sample of the aqueous hydrolyzate from above was heated on a steam bath with 0.1 ml. of benzaldehyde. A yellow solid soon separated and was identified as benzalazine, m.p. 92–93°. The infrared spectrum was also identical with that of benzalazine.

(B) Sodium Borohydride Reduction.—This reduction was carried out in the same manner as A except that methanol was used as a solvent. Five grams of II gave 2.2 g. of benzalazine, m.p. 91–93°.

(C) Sodium Dithionite Reduction.—A solution of 3 g. (0.013 mole) of II, 20 ml. of water, and 15.6 ml. of 4.6 *N* sodium hydroxide was warmed on a steam bath and 6 g. of sodium hydrosulfite added over a period of 15 min. The mixture was stirred and heated until all of the purple color disappeared. The mixture was cooled, filtered, and the precipitate was washed with benzene. The product, m.p. 183–184° (closed tube) and 190–192° (open tube), was identical with 1,2-dihydro-3,6-diphenyl-*s*-tetrazine[3] which had been previously prepared by the reduction of 3,6-diphenyl-*s*-tetrazine with hydrogen sulfide.[7]

(5) J. Allegretti, J. Hancock, and R. S. Knutson, *J. Org. Chem.*, **27**, 1463 (1962).

(6) H. H. Hatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 395.

(7) T. Curtuis, A. Darapsky, and E. Muller, *Ber.*, **40**, 815 (1907).

Some Reactions of Hexaphenyldilead

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At elevated temperatures, hexaphenyldilead is decomposed into tetraphenyllead and elemental lead, two moles of starting material yielding three moles of tetraphenyllead.[2] In the presence of acids, however, decomposition of hexaphenyldilead takes place at room temperatures.[3,4]

Halogen acids cleave, in a stepwise sequence, two of the phenyllead bonds in tetraphenyllead to yield, in the first step, benzene and triphenyllead halide. Triphenyllead halide in turn further reacts to form additional benzene and diphenyllead dihalide (reactions 2 and 3). Hexaphenyldilead, in comparison, when treated with halogen acids yields lead halide as well as triphenyllead halide, diphenyllead dihalide, and benzene.

We were interested in two aspects of these reactions: (a) if hexaphenyldilead decomposes to tetraphenyllead in the molar ratio of 2:3, why the combined yield of the products, triphenyllead halide and diphenyllead dihalide, has never been reported to surpass 50%[3,4] and (b) how it is possible to form lead halide in view of the fact that it is not formed under similar conditions in the reaction of either tetraphenyllead, triphenyllead chloride, or diphenylleaddi halide with halogen acids.

We have found that hexaphenyldilead, in the presence of two molar equivalents of acetic acid, did not react at room temperature when *n*-heptane or benzene were used as solvents. At reflux temperatures, however, the reaction proceeded smoothly. The products obtained were benzene (90% based on acetic acid), lead acetate (41%), tetraphenyllead (25%), triphenyllead acetate (18%), and some unchanged hexaphenyldilead (3%). When hexaphenyldilead was refluxed in acetic acid, however, lead acetate and diphenyllead diacetate were the only products isolated. In a similar manner, excess thiolacetic acid reacted with hexaphenyldilead yielding similar amounts of analogous compounds.

In accounting for the products formed, we have considered the following reaction scheme.

$$Ph_6Pb_2 \rightleftharpoons [2Ph_3Ph] \longrightarrow Ph_4Pb + [Ph_2Pb] \quad (1)$$

$$Ph_4Pb + HOAc \longrightarrow Ph_3PbOAc + PhH \quad (2)$$

$$Ph_3PbOAc + HOAc \longrightarrow Ph_2Pb(OAc)_2 + PhH \quad (3)$$

$$[Ph_2Pb] + 2HOAc \longrightarrow Pb(OAc)_2 + 2PhH \quad (4)$$

The initial assumption is that hexaphenyldilead is thermally decomposed in the presence of acetic acid to tetraphenyllead and the relatively unstable diphenyllead. In the presence of less than an excess of acetic acid, reactions 2 and 4 are competitive, thus accounting for the formation of lead acetate, tetraphenyllead, and triphenyllead acetate. In the presence of excess acetic acid, reactions 2 and 3 go to completion and the final products are diphenyllead diacetate and lead acetate (*via* reaction 4).

Since triphenyllead acetate and diphenyllead diacetate are thermally stable under the conditions used, the accounting for the formation of lead acetate by an alternate reaction to reaction 4, such as a disproportionation of the triphenyllead acetate and diphenyllead diacetate, was ruled out. As no hydrogen evolution was observed during the reaction, it appeared equally unlikely that the formation of lead acetate occurred from reactions of elemental lead and acetic acid or between a triphenyllead hydride intermediate and acetic acid.

Hexaphenyldilead has been reported to react with oxygen to yield triphenyllead oxide.[5,6] In an analogous reaction with sulfur, we obtained triphenyllead sulfide in 59% yield; however, it was interesting to note that detectable amounts of tetraphenyllead and diphenyllead sulfide could be identified as by-products. This lends support to the reaction sequence given, particu-

(1) Research Fellow sponsored by the Lead Industries Association, 292 Madison Ave., New York, N. Y.

(2) For a review, see R. W. Leeper, L. Summers, and H. Gilman, *Chem. Rev.*, **54**, 101 (1954).

(3) P. R. Austin, *J. Am. Chem. Soc.*, **53**, 1548, 3514 (1931); **54**, 3726 (1932).

(4) H. Gilman and J. C. Bailie, *ibid.*, **61**, 731 (1939).

(5) E. Krause and G. G. Reissaus, *Ber.*, **55**, 888 (1922).

(6) G. Bähr, *Z. anorg. allgem. Chem.*, **253**, 334 (1947).

larly as it applies to the decomposition of hexaphenyldilead (reaction 1).

As final evidence for decomposition of hexaphenyldilead into tetraphenyllead and diphenyllead, we studied the reaction of hexaphenyldilead with 1,2-dibromoethane. Recent studies have shown that hexaethyldistannane when treated with 1,2-dibromoethane yields as the main products triethyltin bromide and ethylene.[7] When hexaphenyldilead reacted with 1,2-dibromoethane, the only nonvolatile products were tetraphenyllead (81%) and lead bromide (98%) based upon the assumed disproportionation of diphenyllead to tetraphenyllead and elemental lead followed by the reaction sequence shown.

$$2Ph_6Pb_2 \longrightarrow 2Ph_4Pb + [2Ph_2Pb]$$

$$[2Ph_2Pb] \longrightarrow Ph_4Pb + Pb$$

$$2Ph_6Pb_2 \longrightarrow 3Ph_4Pb + Pb \quad (5)$$

$$Pb + BrCH_2CH_2Br \longrightarrow CH_2{=}CH_2 + PbBr_2[8] \quad (6)$$

It seems consistent with the experimental data now available that hexaphenyldilead undergoes an initial decomposition to tetraphenyllead and elemental lead *via* the unstable intermediate diphenyllead. In the presence of acids this initially formed diphenyllead reacts to form lead acetate and benzene (reaction 4).

This reaction scheme would also explain why, in the presence of acids, the combined yields of triphenyllead halide and diphenyllead dihalides are stoichiometrically limited to 50%.

Experimental

All reactions were followed and products identified by thin layer chromatographic techniques using silica gel G as a solid phase and either carbon tetrachloride or benzene–hexane mixtures as solvents. A dithizone spray (6 mg./100 ml. of chloroform) was used. Triphenyllead compounds gave yellow spots, diphenyllead compounds gave red spots, and tetraphenyllead gave no color reaction with dithizone. Tetraphenyllead gave a yellow spot using a permanganate spray.

Melting points were determined with a Thomas–Hoover melting point apparatus. Where possible, mixture melting points with authentic samples and comparison of infrared spectra with those of authentic samples were used as confirmatory identification of the products.

Hexaphenyldilead was prepared by the established Grignard method. Careful purification by successive recrystallizations resulted in thin layer chromatograms in which the complete absence of tetraphenyllead was demonstrated.

Hexaphenyldilead–Acetic Acid (Ratio 1:2).—Hexaphenyldilead, 4.38 g. (5.0 mmoles), and glacial acetic acid, 0.60 g. (10 mmoles), dissolved in 50 ml. of *n*-heptane was refluxed for 3 hr. No visible evolution of hydrogen was noted during the reaction. During the 3-hr. period, the reaction was followed by thin layer chromatographic techniques as described. Periodic sampling showed the disappearance of hexaphenyldilead and the formation of tetraphenyllead, lead(II) acetate, and triphenyllead acetate. After completion of the reaction, the liquid phase was distilled and investigated using v.p.c. techniques. Vapor phase chromatography indicated the liquid phase to contain only *n*-heptane and benzene and by comparison of peak sizes, the amount of benzene obtained in the reaction was calculated to be 0.7 g. (90%). The solid residue remaining after the removal of the solvent (4.11 g.) was extracted with boiling chloroform. The insoluble residue (1.31 g.) consisted of lead acetate, identified by its solubility in water and black precipitate with hydrogen sulfide. From the chloroform extract, 1.27 g. of tetraphenyllead was precipitated by adding alcohol and identified by mixture melting point. The mother liquor contained 0.87 g. of triphenyllead acetate and 0.13 g. of unchanged hexaphenyldilead, identified by mixture melting point and infrared spectra.

Hexaphenyldilead–Acetic Acid (Excess).—A solution of hexaphenyldilead, 2.20 g. (2.5 mmoles), was refluxed in 20 ml. of glacial acetic acid for 5 min. During the reaction period, a white precipitate formed which, after the reaction was complete, was filtered and extracted with chloroform. The residue (0.81 g.) was shown to be lead(II) acetate (99%), identified as before; the filtrate was evaporated under vacuum; the residue, m.p. 203–206°, recrystallized from benzene–acetic acid to yield 1.41 g. (94%) of diphenyllead diacetate, m.p. 208–209°. Mixture melting point with an authentic sample gave no depression.

Hexaphenyldilead with Excess Thiolacetic Acid.—A solution of 2.20 g. (2.5 mmoles) of hexaphenyldilead was dissolved in 20 ml. of thiolacetic acid and refluxed for 5 min. During the reaction 0.50 g. of a black precipitate of lead sulfide formed, apparently from decomposition of lead (II) thiolacetate. This corresponds to an 89% yield of the latter compound. From the filtrate, after removal of the excess thiolacetic acid, there was obtained 1.58 g. of residue which was recrystallized from ethanol to yield 0.90 g. (70%) of diphenyllead dithiolacetate, m.p. 94–95°. Thin layer chromatography of the mother liquor showed some triphenyllead thiolacetate and possibly diphenyllead sulfide $[(C_6H_5)_2PbS]_n$.

Hexaphenyldilead with Sulfur.—A benzene solution of 64 mg. (2 mmoles) of sulfur was added to a benzene solution containing 1.75 g. (2 mmoles) of hexaphenyldilead and left to stand for 10 days at room temperature. After 1 hr., the clear solution had become turbid. After 10 days, 20 mg. of precipitate was filtered and the solvent evaporated under vacuum to leave a residue of 1.68 g. The residue was dissolved in chloroform, alcohol added, and, after a few minutes, a colorless precipitate, 0.43 g. (24%) of hexaphenyldilead, settled out of solution (identified by infrared spectra). Some tetraphenyllead could be detected in this precipitate using thin layer chromatography techniques. The solvent was partially removed from the mother liquor; the precipitate that formed was filtered and recrystallized from ethanol. The yield was 1.02 g. (59%) of bis(triphenyllead) sulfide, m.p. 139–140°, identified by mixture melting point with an authentic sample. The remaining mother liquor contained some diphenyllead sulfide and bis(triphenyllead) sulfide according to thin layer chromatography experiments.

Hexaphenyldilead with 1,2-Dibromoethane.—Hexaphenyldilead, 4.39 g. (5 mmoles), dissolved in 30 ml. of warm 1,2-dibromoethane was refluxed for 15 min. The solution turned yellow followed by the formation of a white precipitate. The precipitate was filtered (3.83 g.), washed with solvent, and ether extracted with hot chloroform and the insoluble portion filtered. The insoluble residue (0.9 g., 98%) was identified as lead bromide by classical techniques. The chloroform and original 1,2-dibromoethane filtrates were combined, the solvents removed under vacuum, and the residue recrystallized from chloroform to yield 3.14 g. (81% yield) of tetraphenyllead, m.p. 226–228°. The filtrate contained some unchanged hexaphenyldilead as shown by thin layer chromatography experiments.

(7) G. A. Razuvaev, N. S. Vyazankin, and Yu I. Dergunov, *J. Gen. Chem.* (Eng. Transl.), **30**, 1339 (1960).

(8) Razuvaev[7] has carried out the analogous reaction with hexaethyldilead and obtained similar results. Their explanation of the formation of tetraethyllead as a consequence of the disproportionation of triethyllead bromide appeared to be inconsistent with their prior description of the thermal stability of triethyllead bromide.

Friedel–Crafts Isomerization. VI. Aluminum Chloride-Catalyzed Isomerization of Fluorobiphenyls

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Examples of phenyl group migration in substituted aromatics under Friedel-Crafts isomerization conditions are not numerous. Weingarten[1] reported re-

(1) H. Weingarten, *J. Org. Chem.*, **27**, 2024 (1962).

cently on the aluminum chloride-induced isomerization of chlorinated biphenyls. Investigating the isomerization of mono- and dichlorobiphenyls he assumed the transition state of phenyl migration to consist of a bridged phenonium ion as postulated by Cram.[2] In the isomerization of chlorobiphenyls, however, the data do not permit an unambiguous decision whether or not isomerization takes place exclusively by phenyl migration without chlorine migration also being involved.

In the previous paper of this series[3] we reported on the aluminum chloride-induced isomerization of terphenyls. Results were explained by an intramolecular 1,2-phenyl-shift mechanism. The equilibrium composition of terphenyl contained 63% *meta* and 37% *para* isomer. The absence of *ortho*-terphenyl from the equilibrium mixture was explained on the basis of steric hindrance.

Results and Discussions

It seemed to be of interest to extend our investigations to the aluminum chloride-catalyzed isomerization of fluorobiphenyls. It was hoped that the results would give (a) an unambiguous example of phenyl migration in the isomerization of halobiphenyls, as it was established previously that ring bonded fluorine is unable to undergo intra- or intermolecular migration under Friedel–Crafts conditions,[1-4] and (b) to obtain information on the steric *ortho* effect in the formation of *ortho*-halobiphenyls by comparing previous results involving chloro and phenyl substituents to the much smaller fluorine substituent.

Isomerization of *ortho*-, *meta*-, and *para*-fluorobiphenyls with water-promoted aluminum chloride catalysts was carried out under similar conditions to those described previously.[3] The results are summarized in Table I.

The equilibrium mixture obtained starting with any one of the isomers contained about 13% *ortho*-, 58% *meta*-, and 29% *para*-fluorobiphenyl. There is little variation in the composition of final mixture with temperature and time. The isomer distribution does not appear to be influenced by halogen exchange and electrophilic arylation reactions which usually accompany Friedel–Crafts isomerizations,[5] and the experimental isomer distribution is believed to be close to thermodynamic equilibrium. In all runs besides some chlorobiphenyls and biphenyl (3–10%) there were formed varying amounts of insoluble material of higher molecular weight. The inability of ring bonded fluorine to undergo migration, as found in previous work,[3] was confirmed in the present case. From Table I it appears that *ortho*- and *para*-fluorobiphenyl isomerize by an intramolecular 1,2-phenyl shift, the other isomer appearing only after the formation of a substantial amount of *meta*. A 1,2-shift is also assumed in the isomerization of *meta*-fluorobiphenyl.

A comparison of the isomer distribution of fluorobiphenyls with that reported for chlorobiphenyls and terphenyls gives the following information on the amount of *ortho* isomer and, consequently, on the steric requirements of the substituent group (Table II).

(2) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3863 (1949).
(3) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **27**, 3682 (1962).
(4) G. A. Olah, W. S. Tolgyesi, and R. E. Dear, *ibid.*, **27**, 3441, 3449, 3455 (1962).
(5) G. A. Olah and M. W. Meyer, *ibid.*, **27**, 3464 (1962).

TABLE I

ISOMERIZATION OF FLUOROBIPHENYLS WITH WATER-PROMOTED ALUMINUM CHLORIDE

Reaction time	Temp., °C	% Fluorobiphenyl isomer distribution *ortho*	*meta* (normalized)	*para*
		2-Fluorobiphenyl		
5 min.	140	95.7	3.8	0.5
7		59.3	30.8	9.9
10		42.7	43.5	13.8
15		23.8	54.6	21.6
30		20.0	56.6	23.4
60		18.9	57.5	23.6
24 hr.		12	57	31
275		13	58	29
5 min.	200	14.4	59.4	26.2
10		18.0	51.1	23.9
15		16.5	57.5	26.0
20		15.8	57.5	26.7
25		15.8	57.9	26.3
30		14.2	59.4	26.4
60		13	57	30
		3-Fluorobiphenyl		
60 min.	140	14.6	59.1	26.3
180		14	60	26
30	200	12	58	30
60		13	59	28
		4-Fluorobiphenyl		
2 min.	140	0	1.5	98.5
4		0	10.5	89.5
6		0	23.6	76.4
10		5.2	48.3	46.5
15		6.3	51.7	42.0
30		7.5	58.2	34.3
60		9.0	60.3	30.7
120		10.5	59.9	29.6
240		10.2	58.8	31.0
5 min.	200	10.5	58.0	31.5
10		9.9	60.6	29.5
15		11.2	58.4	30.4
20		12.1	57.4	30.5
25		11.9	58.5	29.6
30		12.6	56.4	31.0
60		11.5	58.0	30.5

TABLE II

ISOMER DISTRIBUTION OF SUBSTITUTED BIPHENYLS

R—C_6H_4—C_6H_5

R	% Isomer in equilibrium mixture *ortho*	*meta*	*para*
F	13	58	29
Cl	3	64	33
C_6H_5	0	63	37

The decreasing amount of *ortho* isomer is in accordance with the increasing steric requirement of the following groups.

$$F < Cl < C_6H_5$$

Experimental

Materials.—*ortho*- and *para*-fluorobiphenyl were obtained from Columbia Organic Chemicals Co., Columbia, S. C. *meta*-Fluorobiphenyl was prepared using the procedure as given by Elks, Haworth, and Hey.[6]

Isomerization Procedure.—The amounts of substrate and catalyst in each experiment were 2.0 g. of fluorobiphenyl and 0.3 g. of Al_2Cl_6. To this mixture 0.01 ml. of water was added from a syringe. Isomerizations were carried out in sealed tubes. Prod-

(6) J. Elks, J. W. Haworth, and D. H. Hey, *J. Chem. Soc.*, **1940**, 1284.

ucts were recovered by extraction with boiling carbon disulfide in the presence of water. After drying with calcium chloride the extract was submitted to gas–liquid chromatographic and infrared analysis. The infrared analysis was carried out using the following bands.

ortho-Fluorobiphenyl	1110 cm.$^{-1}$
meta-Fluorobiphenyl	879 cm.$^{-1}$
para-Fluorobiphenyl	837 cm.$^{-1}$
Biphenyl	737 cm.$^{-1}$

The accuracy of the infrared analyses based on mixtures of known composition is within ±3 relative %. The gas–liquid chromatographic analysis has been reported previously.[7]

Separation of the *ortho* isomer from the *meta–para* isomer was good, that of *meta* from *para* reasonable with a higher error of determination when the *meta* isomer was present only in small amounts. Separation of *para* and *meta* isomers on more loosely packed columns than those used in previous work[7] gave shorter retention times and poorer separation. It was possible to obtain partial separation of *meta–para* isomers by lowering the column temperature to 160° with retention times of *meta* isomer of 55.6 and *para* isomer of 56.5 min. (Previous retention times at 190° were 38 and 40 min. on the tightly packed columns used, but only 18 min. under the same conditions, without separation, on presently used looser column.) As these conditions were unsatisfactory, isomer mixtures were analyzed by combining gas chromatography and infrared analyses. The *ortho* isomer was well separable from the combined *para–meta* isomers by gas chromatography and the *para* and *meta* isomers could be determined by infrared analysis. Golay columns (polypropylene glycol) were tried and found unsuitable for the *para–meta* separation.

The normalized per cent isomers in Table I are believed to be correct to within ±1 unit, based on treatment and analysis of mixtures of known composition.

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(7) G. A. Olah and W. S. Tolgyesi, *J. Org. Chem.*, **26**, 2053 (1961).

Molecular Weight Determination by N.m.r. Spectroscopy

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In contrast to other types of spectroscopy used in organic chemistry, nuclear magnetic resonance spectroscopy can be used for quantitative analytical measurements without the knowledge of extinction coefficients, since such a coefficient is constant and independent of the chemical environment of the nuclei under inspection. This makes n.m.r. spectroscopy a very powerful quantitative tool. So far, its application[1] includes the measurement of extent of isotope substitution, the analysis of mixtures, per cents of hydrogen, proton counting, and interpretation of spectra in general, where integration is combined with chemical shift and splittings measurements.

We propose to apply n.m.r. integration for the determination of molecular weights. The method consists of comparing the integrated intensities of an added standard and a recognizable peak or group of peaks of the unknown in a solution containing a known weight of standard and unknown. The molecular weight is then given by the following formula.

$$M = \frac{I_s\, n\, W\, M_s}{I\, n_s\, W_s}$$

M = the molecular weight of the unknown
I_s = the intensity of the standard
I = the intensity of the unknown
n = the number of protons in the recognizable peak or group of peaks of the unknown
n_s = the number of protons of the standard peak
W = the weight of the unknown
W_s = the weight of standard
M_s = the molecular weight of standard

The method can be combined with taking the n.m.r. spectrum of the unknown; the only extra work required is the weighing of sample and standard, and the calculation. The values are not affected by dissociation and solvent interaction phenomena or various other effects that cause great errors in methods dependent on ideality in colligative properties of liquids. The error resulting from impurities is proportional to their weight and not to the molar amount. On the assumption that most impurities are smaller molecules than the unknown, this method gives smaller errors than the cryoscopic, etc., methods. The standard also serves as a marker for chemical shift calibration. Hopefully, in the future n.m.r. tubes and spectrometers can be standardized, stabilized, and precalibrated well enough, so that precise integrations can be performed without the use of a standard, similarly to our present-day ultraviolet intensity measurements.

On the other hand the method requires that at least one peak or group of peaks of the unknown be recognized as to the number of protons it contains; this absorption should not overlap with others, since otherwise the integration is very subjective. Molecules related as monomers and symmetrical dimers cannot easily be distinguished by the n.m.r. method, since they show very similar spectra. In some other cases too, difficulties arise in assigning a chosen absorption the number of hydrogens it represents. In general, however, one knows which hydrogens of a known starting material should end up unchanged in an unknown product under given reaction conditions, and use those for the determination. The choice can best be made once the n.m.r. spectrum is taken and perhaps integrated.

Experimental

The Standard.—Based on our experience the most suitable standard is hexamethyl cyclotrisiloxane, m.p. 64.5°, b.p. 133°, a very soluble inert solid, which can be removed by sublimation. There is no loss by sublimation if it is weighed last and dissolved and stoppered immediately. Its absorption at 9 c.p.s. is conveniently outside other absorptions. Any other (preferably) single peak pure material can be used as standard if its absorption can be separately seen in the spectrum. All these standards mark the chemical shift scale at the same time, and no tetramethylsilane is needed. Other possible standards include: iodoform at 294, benzoquinone at 406, *p*-dinitrobenzene at 507, and 1,3,5-trinitrobenzene at 566 c.p.s. The nitroaromatic standards should be used with caution, since occasional complex formation with aromatic unknowns offsets the results.

Procedure.—The unknown and standard should be weighed into the n.m.r. tube to give about equal intensities, completely homogenized with solvent, the spectrum taken, integrated, the chosen absorption and standard individually integrated accurately, utilizing the full chart range for the bigger of the two,

(1) "Quantitative Measurements by High Resolution NMR," Varian Associates technical information bulletin, Vol. 3, No. 1.

TABLE I

TEST OF MOLECULAR WEIGHT DETERMINATION BY N.M.R.

Unknown	M, calcd.	M, found	Peaks used for integration
Acenaphthene	154.20	155.3[a]	C_2H_4
		148.3	
		152.9	
		152.4	Aromatic hydrogens
		150.6	
		153.6	
4-*t*-Butylcyclohexanol *cis* and *trans* mixture	156.26	150.3	*t*-Butyl group
		150.1	H–C–O–
Dehydroabietonitrile	281.42	271.3	Four methyls
		267.5	Aromatic H_3
2,4-Bispentamethylenespiro-5-carboxymethylene-1,3-dioxacyclopentane in form of methyl ester	266.33	272.4	Methyl ester
2-*p*-Anisoylpropionic acid Me ester	222.23	214.5	Lower aromatic H_2
		223.0	Higher aromatic H_2
		217.7	Aromatic methoxy
		211.0	Methyl ester
		217.3	2-Methylene
		226.0	H_{10} of Me's and C_2H_4
		221.6	Aromatic H_4
Anisaldehyde	136.14	138.7	Methoxy
		141.7	Aromatic H_4
Iodoform	393.78	392.5	Single peak
Benzoquinone	108.09	110.9	
p-Dinitrobenzene	168.11	174.1	
1,3,5-Trinitrobenzene	213.11	221.9	
Diphenylacetic acid	212.24	211.7	Tertiary H
Cholesterol	386.64	374.8[b]	Olefinic H
1,2-Diacetoxy-4-*p*-anisylbutene-3	278.29	280.1	Lower aromatic H_2
		271.0	Higher aromatic H_2, lower olefinic H
		290.8	Acetates
		288.8	
		283.6	
		270.5	Aromatic H_4, lower olefinic H
		268.0	Higher olefinic H–C–O–
		281.9	Aromatic H_4, olefinic C_2H_2, H–C–O–
p-Anisylacetic acid	166.18	163.0	Methylene,
		167.1	methoxy
		162.4	Lower aromatic H_2
p-*t*-Butylacetanilide	191.26	198.8	Acetyl
		196.8[b]	
		187.0	*t*-Butyl

[a] Different values based on the same peaks were determined using different R_f field strength and sweep time. [b] 1,3,5-Trinitrobenzene used as standard. Hexamethylcyclotrisiloxane served as standard in all other determinations.

tracing about five times in both directions. Substitute the average intensities and the weights into the formula. Note that for the purposes of the determination any solvent can be used whose absorption lies outside the standard and region of interest.

Possible Sources of Error.—Inhomogeneity might cause standard and unknown to be exposed to different field strength inside the probe. Hydroxyl groups exchange with moisture in the solvent and should not be used in the determination. Overlap of peaks can seriously reduce the accuracy of the integration. Note that if two peaks of unequal intensity and/or shape overlap, it is erroneous to cut the region by a vertical line at the lowest point of the spectrum between the peaks. Errors from impurities, inaccurate weighing or reading of the integral are self-evident.

TABLE II

EXAMPLES OF CONDITIONS FOR MEASUREMENTS ON THE VARIAN A 60 SPECTROMETER

Filt. bandwidth	1	1	1	1
R_f field	0.02	0.12	0.6	0.14
Sw. time	500	500	50	500
Sw. width	500	1000	500	1000
Sw. offset	0	0	0	0
Spect. amplitude	1.6	10	32	4
Int. amplitude	20	50	20	8
Spin	Yes	Yes	No	Yes
Standard	Sil[d]	Sil[d]	Sil[d]	Sil[d]
Mg.	110.8	11.852	51.6	35.7
Meq.	8.99	0.961	4.18	2.89
Unknown	[a]	CHI_3	[b]	[c]
Mg.	254.8	64.383	101.5	87.4
Obsd. peaks	C_2H_4	CHI_3	Arom.	Ac
Meq. peaks	6.608	0.1636	1.083	1.372
No. traces	5 + 5	1 + 1	5 + 5	1 + 1
Solvent	$CDCl_3$	$CDCl_3$	CCl_4	$CDCl_3$
Ml.	0.5	0.5	0.6	0.9

[a] Acenaphthene. [b] Dehydroabietonitrile. [c] *p*-*t*-Butylacetanilide. [d] Sil, hexamethylcyclotrisiloxane.

Procedures for precise integration are discussed in operating manuals; we mention only a few crucial points here. Saturation must be avoided. Errors from saturation are greatest if sample and unknown peak are of unequal shape or size. Fluctuations due to instability (noise) are corrected by averaging several traces. If overlap is not produced by peak broadening, the sample spinning can be stopped, much higher R_f field used without saturation, and noise greatly reduced.

Tables I and II illustrate the usefulness of the new method and give the relevant information on the conditions of some of the measurements.

Acknowledgment.—The author wishes to express his gratitude to Dr. Gerald Dudek and Professor E. J. Corey for helpful comments and discussions and to the U. S. Public Health Service for a fellowship.

Preparation and Mass Spectrum of Hexachlorocyclopropane

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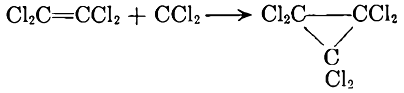
Although hexafluorocyclopropane has been known for some time,[1] hexachlorocyclopropane has not been reported previously.[2] We have prepared this compound

(1) A. F. Benning, F. B. Downing, and J. D. Park, to Kinetic Chemicals, Inc., U. S. Patent 2,394,581 (February 12, 1946).

(2) As this communication was being prepared to go to press, an abstract by S. W. Tobey and R. C. West reported the synthesis of hexachlorocyclopropane from tetrachloroethylene, chloroform, and potassium hydroxide. Their work was presented before the 136th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962. More recently we learned through a referee that W. R. Moore, S. E. Krikorian, and J. E. LaPrade also have prepared this compound and measured its mass spectrum.



by the reaction of dichlorocarbene with tetrachloroethylene.

Experimental

A mixture of 204 ml. (2 moles) of tetrachloroethylene, 25 ml. of dimethoxyethane, and 185 g. (1 mole) of sodium trichloroacetate was stirred and refluxed until no more carbon dioxide was evolved (about 20 hr.). The cooled mixture was filtered, the sodium chloride was washed with three 50-ml. portions of n-hexane, and the combined filtrate and washings were distilled at 150 torr. to a final flask temperature of 115°. The residue solidified on cooling. It was dissolved in 100 ml. of n-pentane; the solution was filtered and chilled to −60°. The crystals (31 g.) were recrystallized from absolute ethanol with a little charcoal to give 26 g. of hexachlorocyclopropane melting at 106°. (Found: C, 14.4; Cl, 85.3. C_3Cl_6 requires: C, 14.5; Cl, 85.5.)

Results

Hexachlorocyclopropane is a white, crystalline solid with a terpene odor. It volatilizes readily at room temperature if left in the open; it is stable at 30° to acid, base, and permanganate. The low yield—10.4%, based on sodium trichloroacetate—might have been anticipated. Dichlorocarbene as a strong electrophile adds readily to olefins with electron-donating substituents, but would not be expected to give good yields with a highly chlorinated olefin. The composition of the other reaction products is being investigated.

The mass spectrum of hexachlorocyclopropane shows a progression of ions of well defined identity. Peaks occur in groups, the profiles of which correspond to statistical distributions of Cl^{35} and Cl^{37} atoms in natural abundance[3] and hence define clearly the number of chlorine atoms contained. Thus, the spectrum shows: $C_3Cl_5^+$, $C_3Cl_4^+$, $C_3Cl_3^+$, $C_3Cl_2^+$, C_3Cl^+, C_3^+; $C_2Cl_4^+$, $C_2Cl_3^+$, $C_2Cl_2^+$, C_2Cl^+; CCl_3^+, CCl_2^+, CCl^+; Cl_2^+, and Cl^+. This spectrum was compared with that of the open-chain isomer, hexachloropropene, and the spectra of the chlorinated isomers, in turn, were compared with those of cyclopropane and propene.

The four spectra are shown in Table I, with intensities expressed as per cents of total ion current. In the interest of simplicity, intensities of the isotopic variants of each ionic species have been summed; thus, the yield of each ion in the spectrum is measured by a single intensity value. Agreement between our spectrum of hexachloropropene and that reported earlier[4] is only fair; however, the earlier report gave no information either on the source and purity of the sample or on experimental conditions used in measuring the spectrum. The samples used in our work included commercial material and that made in our laboratories by dehydrochlorinating both symmetrical and asymmetrical heptachloropropanes with potassium hydroxide in methanol.[5] They all contained appreciable amounts of impurities, of which methyl trichloroacrylate was a major component; these impurities were not reduced below about 5% by gas chromatography.

(3) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry," D. Van Nostrand Company, Princeton, N. J., 1960.

(4) H. R. Harless, presented before A.S.T.M. Committee E-14 on Mass Spectrometry, Chicago, Ill., June, 1961.

(5) F. Bergmann and L. Haskelberg, *J. Am. Chem. Soc.*, **63**, 1437 (1941).

TABLE I

MASS SPECTRA OF C_3Cl_6 AND C_3H_6 ISOMERS

Ion, X = Cl or H	Hexachlorocyclopropane[a]	Hexachloropropene[a,b]	Cyclopropane	Propene
$C_3X_6^+$	...	2.39	24.8	16.2
$C_3X_5^+$	37.6	32.5	23.2	25.9
$C_3X_4^+$	0.35	1.68	7.67	6.97
$C_3X_3^+$	6.68	11.2	18.1	20.1
$C_3X_2^+$	4.74	9.56	3.82	5.52
C_3X^+	5.84	7.32	2.92	4.20
C_3^+	2.41	3.41	0.55	0.84
$C_2X_4^+$	4.72	0.24	0.54	...
$C_2X_3^+$	1.84	0.98	9.45	10.7
$C_2X_2^+$	3.92	2.95	3.54	3.51
C_2X^+	1.13	0.86	0.65	0.85
CX_3^+	9.83	9.43	1.38	1.91
CX_2^+	5.62	1.71	1.80	1.39
CX^+	6.27	4.19	0.74	0.74
C^+	[b]	[b]	0.46	0.55
X_2^+	0.21	0.24	0.12	0.55
X^+	5.75	6.83	[c]	[c]
$C_3X_6^{+2}$	...	2.13	...	...
$C_3X_5^{+2}$	1.16	...	...	...
$C_3X_4^{+2}$	0.39	...	...	...
$C_3X_3^{+2}$	...	0.12	...	...
$C_3X_2^{+2}$	0.97	...	...	...
C_3X^{+2}	...	0.01	...	...
X_2^{+2}	0.52	...	[c]	[c]
Species containing 4, 5, and 6 carbons	...	2.24[d]	...	...

[a] Corrected for HCl, presumably formed by a wall reaction in the ionization chamber. HCl accounted for 0.76% of total ion intensity in the spectrum of hexachlorocyclopropane and 1.20% in that of hexachloropropene. [b] Corrected for 3.6 vol. % methyl trichloroacrylate. [c] Not measured. [d] Due to unknown impurities.

Spectra of the chlorinated compounds were measured on a Consolidated Model 21–103 instrument with the inlet system at a temperature of 140° for the cyclic isomer and 250° for the olefin. Those of the hydrocarbons were measured on another 21–103 instrument with the inlet system at room temperature. All measurements were made with 70-v. electrons.

The spectra of the C_3Cl_6 isomers are generally similar, showing pronounced differences in relative intensity for only three singly charged ions: $C_3Cl_6^+$, $C_2Cl_4^+$, and CCl_2^+. Respective intensities of these ions in the spectrum of hexachlorocyclopropane are zero[6] and greater by factors of 20 and 3 than in that of the olefinic isomer. Spectra of the hydrocarbon analogs resemble each other even more closely. The parent peak of cyclopropane is the more intense by a factor of 1.5 and is, indeed, the most intense peak in the spectrum of this compound. Intensity of $C_2H_4^+$ in the spectrum of cyclopropane is only one-ninth that of $C_2Cl_4^+$ in the spectrum of hexachlorocyclopropane; the spectrum of propene shows no measurable yield of $C_2H_4^+$. Intensities of CH_2^+ in the two spectra differ but little. Distributions of doubly charged ions in the spectra of the chlorinated compounds differ sharply but, at present, inexplicably.

(6) We are indebted to the referee for calling attention to a discrepancy between the spectrum of W. R. Moore, *et al.*, and an earlier spectrum of ours, measured with the inlet system at 250°, which contained small $C_3Cl_6^+$ peaks. Reducing the temperature to 140° removed these peaks, substantiating Dr. Moore's suggestion that the higher temperature causes pyrolysis of hexachlorocyclopropane even at the low sample pressure, 20 to 30 torr., in the inlet system. About 15% conversion to hexachloropropene had occurred; no other products were apparent.

The close similarity of the spectra of C_3X_6 (X = H or Cl) isomer pairs, like that of C_7H_8 isomers,[7,8] suggests that the isomers decompose under electron impact largely through common intermediates. In the case of the hydrocarbons, support for this suggestion can be drawn from evidence, based on appearance-potential measurements, that the $C_3H_5^+$ ion derived from cyclopropane does not have the cyclopropyl structure and is, in fact, the same chemical species as $C_3H_5^+$ ions derived from acyclic compounds.[9,10]

The differences between the spectra of isomers suggest that all or most of the $C_2X_4^+$ and part of the CX_2^+ are formed directly from parent ions with the original cyclopropane structure. The reactions involved presumably resemble the reverse of that by which hexachlorocyclopropane was synthesized. The differences between the spectra of chlorinated and unchlorinated species apparently reflect the greater difficulty of formation of C_3Cl_6 from, and lower stability with respect to, C_2Cl_4 and CCl_2 than of C_3H_6 with respect to C_2H_4 and CH_2. Such a view is in accord with the poor yield obtained by us in the synthesis of hexachlorocyclopropane and with chemical evidence indicating that CCl_2 is more stable than CH_2. For example, dichlorocarbene is easily generated by low-energy processes such as the reaction of base with chloroform[11] or thermal decomposition of sodium trichloroacetate[12]; preparation of methylene, on the other hand, requires photolysis of ketene or diazomethane.[13]

(7) S. Meyerson and P. N. Rylander, *J. Chem. Phys.*, **27**, 901 (1957).
(8) S. Meyerson, J. D. McCollum, and P. N. Rylander, *J. Am. Chem. Soc.*, **83**, 1401 (1961).
(9) F. H. Field, *J. Chem. Phys.*, **20**, 1734 (1952).
(10) R. F. Pottie, A. G. Harrison, and F. P. Lossing, *J. Am. Chem. Soc.*, **83**, 3204 (1961).
(11) W. von E. Doering and A. K. Hoffmann, *ibid.*, **76**, 6162 (1954).
(12) W. M. Wagner, *Proc. Chem. Soc.* (London), 229 (1959).
(13) W. Kirmse, *Angew. Chem.*, **73**, 161 (1961).

Intramolecular Nucleophilic Participation. III. Transition State Geometry in the Hydrolysis of *o*- and *p*-Carbomethoxycumyl Chlorides

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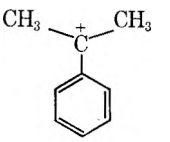
The solvolysis of *o*-carbophenoxybenzhydryl bromide takes place much more rapidly than does that of its *para* isomer.[1] The relatively high reactivity of the *ortho* isomer has been explained on the assumption that its carbophenoxy group can participate electronically in the activation process by releasing electrons to the vacant p-orbital developing at the reaction center. The *o*- and *p*-carbomethoxybenzyl bromides, on the other hand, solvolyze at comparable rates. Failure of the carbomethoxy group to participate effectively in the reaction of the *o*-substituted benzyl bromide has been explained[1,2] on the assumption that it is highly critical energetically for the development of positive charge on carbon at the reaction center that the p-orbital which is being vacated overlap the π electrons of the aromatic nucleus. For maximum overlap of this type the trigonal valences of the carbon atom in question must lie in the ring plane, an arrangement which is not favorable for effective participation by the carbomethoxy group.

The present investigation, in which the hydrolysis rates of cumyl chloride and its *o*- and *p*-carbomethoxy derivatives have been determined, has been conducted to ascertain whether or not it is also important for stabilization of the cumyl cation (I), which is tertiary in character, that the vacant p-orbital on the exocyclic carbon overlap the π molecular orbital of the ring.



I

A summary of the results of the rate runs is given in Table I. As should be characteristic of a solvolysis in which bond breaking, rather than bond making, is the dominant feature of the activation process,[3] the electron-withdrawing carbomethoxy substituent has been found to have a strong deactivating influence in cumyl chlo-

TABLE I
RATE CONSTANTS FOR HYDROLYSIS OF THE SUBSTITUTED CUMYL CHLORIDES

10^2[RCl]$_i$, mole/l.	Solvent, % aqueous acetone[a]	Temp., °C.	$10^5 k_s$, sec.$^{-1}$
Cumyl chloride [$C_6H_5C(CH_3)_2Cl$]			
5.00	80	25.0	103
9.56	85	25.0	68.8
1.76	90	25.0	15.0
11.3	90	25.0	14.4
16.6	90	25.0	14.5
	Av. k_s (90% aq. acetone)		14.6
p-Carbomethoxycumyl chloride[b]			
3.69	70	25.0	4.68
8.06	70	25.0	4.65
10.8	70	25.0	3.68
	Av. k_s (25.0°)		4.34
3.86	70	36.0	19.0
7.66	70	36.0	14.8
8.36	70	36.0	14.9
	Av. k_s (36.0°)		16.2
o-Carbomethoxycumyl chloride[c]			
3.04	70	25.0	11.3
3.94	70	25.0	11.0
6.65	70	25.0	9.2
	Av. k_s (25.0°)		10.5
4.04	70	36.0	36.8
4.45	70	36.0	33.6
	Av. k_s (36.0°)		35.2

[a] Prepared by mixing 100 − x volumes of acetone with x volumes of water to give (100 − x)% of aqueous acetone. [b] Values of E_a = 22 kcal./mole and ΔS^* = −7 e.u. have been calculated for *p*-carbomethoxycumyl chloride using the average k_s values at 25.0° and 36.0°. [c] Values of E_a = 19 kcal./mole and ΔS^* = −16 e.u. have been calculated for *o*-carbomethoxycumyl chloride using the average k_s values at 25.0° and 36.0°.

(1) A. Singh, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **84**, 1179 (1962).
(2) R. E. Lovins, L. J. Andrews, and R. M. Keefer, *ibid.*, **84**, 3959 (1962).
(3) C. G. Swain and W. P. Langsdorf, Jr., *ibid.*, **73**, 2813 (1951).

ride hydrolysis (*cf.* k_s values for the substituted and unsubstituted halides). Evidence that *ortho* participation makes a dramatically significant contribution to the activation process for hydrolysis of *o*-carbomethoxycumyl chloride has not been found. Under comparable conditions the hydrolysis rate constant for the *o*-substituted halide is only twice that for the *para* isomer. Since in those cases in which the substituents are functionally incapable of participation the *o*-substituted benzyl,[1] cumyl,[4,5] and benzhydryl[1] halides are (probably because of unfavorable steric situations) generally somewhat less reactive than their *para* isomers,[1] it cannot be concluded that the *o*-COOR group makes no contribution as a neighboring group in the hydrolysis of *o*-carbomethoxycumyl chloride. It does, however, appear that the *o*-COOR group participates considerably more effectively in benzhydryl halide solvolysis than in cumyl halide solvolysis. Two possible explanations for this difference may be proposed on the grounds that a perpendicular orientation of the plane of the trigonal bonds to the exocyclic carbon atom with respect to the ring plane is not the most favored conformation for the cumyl cation (it is assumed in this discussion that the organic moiety of the transition state for hydrolysis of a cumyl halide is carbonium ion-like in character). Such a conformation provides for maximum *ortho* substituent participation.

It is proposed first that for maximum stabilization the vacant p-orbital of *o*-carbomethoxycumyl cation must indeed overlap the π orbital of the aromatic nucleus to a significant degree. In order that the plane of the trigonal valences of the exocyclic carbon of the latter ion fully coincide with the ring plane, the carboalkoxy group must, for steric reasons, be twisted somewhat out of the ring plane. The fact that *o*-carbomethoxycumyl chloride is somewhat more reactive than its *para* isomer may result, at least in part, because the carbomethoxy group of the *ortho* substituted halide is sterically prevented from entering the ring plane and thus cannot exert fully its electron-withdrawing effects on the polarization of the C–Cl bond.

Alternately it is proposed that the conformational situation in the *o*-carbomethoxycumyl cation is actually such as to provide for maximum electron release by the carbomethoxy group to the reaction center. If this is the case, the stabilizing effect thus produced by the carbomethoxy group must be canceled to a considerable degree by the loss of stability which results because under these circumstances the vacant p-orbital at the reaction center cannot overlap the π orbital of the aromatic nucleus.

Experimental

Methyl *o*- and *p*-Isopropylbenzoates.—A sample of Eastman Organic Chemicals *p*-isopropylbenzoic acid was converted to the acid chloride by refluxing for 4 hr. with thionyl chloride. The excess thionyl chloride was removed by distillation, and the residue was added dropwise to methanol. The resulting solution was refluxed for 30 min. and then distilled to obtain methyl *p*-isopropylbenzoate, b.p. 124° (16 mm.), n^{25}D 1.5080.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.49; H, 7.70.

To prepare methyl *o*-isopropylbenzoate, cumene was first nitrated by the procedure of Brown and Bonner,[6] and the *o*- and *p*-nitrocumenes were separated by fractionation at reduced pressure. The *p*-nitrocumene, b.p. 127° (12.5 mm.), thus obtained was converted to 2-bromo-4-nitrocumene, b.p. 166–172° (26 mm.), by treatment with bromine in the presence of silver sulfate.[7] The 2-bromo-4-nitrocumene was reduced to the corresponding amine, b.p. 175–178° (48 mm.), and the latter was deaminated by treatment of its diazonium salt with hypophosphorus acid,[7] to provide *o*-bromocumene, b.p. 104–110° (22.5 mm.), n^{26}D 1.5398. This was converted to *o*-isopropylphenylmagnesium bromide by reaction with magnesium, activated with iodine, in tetrohydrofuran, and the Grignard reagent was carbonated[4] to provide *o*-isopropylbenzoic acid, m.p. 61–64° (lit.[4] m.p. 63–64°). The acid was converted to methyl *o*-isopropylbenzoate, b.p. 114–115° (16 mm.), n^{25}D 1.5065, by the same procedure used in esterifying its *para* isomer.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.60; H, 7.88.

Preparation of the Cumyl Chlorides by Photochlorination.—Cumene and methyl *o*- and *p*-isopropylbenzoates undergo photochlorination rapidly in carbon tetrachloride. All attempts which have been made to isolate pure samples of the carbomethoxycumyl chlorides from the crude photochlorination products of the esters have been unsuccessful. Like other substituted cumyl chlorides[4] these are highly unstable (with respect to the loss of hydrogen chloride) in the pure state. A procedure has, therefore, been developed for preparing crude samples of cumyl chloride and its carbomethoxy derivatives by photochlorination of cumene, or its substitution products, with considerably less than a molar equivalent of chlorine (to avoid formation of polychlorination products). Generally a substantial amount of chlorine was lost by volatilization during the photochlorination process. As documented later in more detail, a sample of cumyl chloride prepared in this way was essentially identical, insofar as solvolysis rate was concerned, with another sample prepared from phenyldimethylcarbinol and hydrogen chloride.

A typical preparation of a sample for rate work, using methyl *o*-isopropylbenzoate as starting material, is described. A 9.0-g. (0.051 mole) sample of the ester was cooled to 0°, and 25 ml. of a solution of 1.76 *M* chlorine in carbon tetrachloride (established by iodometric analysis) was added dropwise to the ester with stirring. The mixture was irradiated simultaneously in a manner similar to that used for photobromination of substituted toluenes.[8] When addition of the chlorine solution was complete, the solvent was removed over a 1-hr. period at room temperature using a rotary film evaporator. The residue contained traces of carbon tetrachloride, removable only by prolonged evaporation, a procedure which was avoided because of possible decomposition of the substituted cumyl chloride.

To initiate a rate run a 5.04-g. sample of the colorless residue was diluted to 50.0 ml. with 70% aqueous acetone. A 5.00-ml. sample of this solution was dissolved in 75 ml. of aqueous ethanol, and the resultant solution was immediately analyzed for chloride by the addition of 5.00 ml. of 0.1 *N* standard silver nitrate solution followed by back titration with standard 0.1 *N* potassium thiocyanate according to the usual Volhard procedure. Assuming that tertiary chlorides, but not primary or secondary chlorides, are rapidly solvolyzed, in 80% aqueous ethanol[9] under these conditions, the initial concentration of *o*-carbomethoxycumyl chloride in the aqueous acetone solution was calculated as 6.65×10^{-2} *M*.

The Rate Runs with the Cumyl Chlorides.—Aqueous acetone solutions were prepared from the crude photochlorination product as described in the preceding paragraph. Samples (5 ml.) of these rate mixtures were removed from time to time and shaken with mixtures of water and ether. The chloride contents of the aqueous phases were determined by the addition of 5 ml. of 0.1 *N* silver nitrate followed by back titration with 0.1 *N* potassium thiocyanate solution using the standard Volhard procedures. Other details of the kinetic experiments, including the purification of solvents, were much the same as those of earlier experiments on the solvolysis of benzyl and benzhydryl bromides.[1]

The solvolysis rate constants, k_s, as defined in equation 1

$$-d[\mathrm{RX}]/dt = k_s[\mathrm{RX}] \qquad (1)$$

(4) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *J. Am. Chem. Soc.*, **79**, 1897 (1957).
(5) H. C. Brown, Y. Okamoto, and G. Ham, *ibid.*, **79**, 1906 (1957).
(6) H. C. Brown and W. H. Bonner, *ibid.*, **76**, 605 (1954).
(7) M. Crawford and F. H. C. Stewart, *J. Chem. Soc.*, 4443 (1952).
(8) E. L. Eliel and D. E. Rivard, *J. Org. Chem.*, **17**, 1252 (1952).
(9) G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 4025 (1955).

were calculated from the slopes of plots $\log([v_i - v_\infty]/[v_t - v_\infty])$ *vs.* time, where v is the volume of standard potassium thiocyanate solution used in the Volhard analysis of rate samples and the subscripts, i, t, and ∞, apply, respectively, to samples taken at the outset of reaction, at time t and at infinite reaction time. These plots generally were linear to at least 80% of completion of the reactions, and the analysis for chloride ion at infinite reaction time checked well with the analysis for tertiary chloride at the outset of reaction (see preceding).

Two sets of check experiments were conducted to establish the validity of rate constants obtained in runs with unpurified samples of the carbomethoxycumyl chlorides (obtained by the photochlorination procedure) as comparative measures of the relative reactivities of the tertiary halides. In the first case a pure sample of cumyl chloride was prepared from phenyldimethylcarbinol and hydrogen chloride[4] and its solvolysis rate in 90% aqueous acetone at 25° was compared with that of a crude sample prepared by photochlorination of cumene in an over-all procedure similar to that described for the runs on the carbomethoxycumyl chlorides. The k_s values for these two samples were respectively 14.5×10^{-5} sec.$^{-1}$ and 15.1×10^{-5} sec.$^{-1}$.

The second check experiment was designed to determine the possible influence of unphotochlorinated cumenes and of traces of carbon tetrachloride solvent on solvolysis rate constants evaluated in rate runs using crude samples of the cumyl chlorides (prepared by the photochlorination procedure described earlier). A sample of cumyl chloride, prepared from phenyldimethylcarbinol and hydrogen chloride, was used in making a rate run (25°) in which the initial concentrations of materials in 90% aqueous acetone solution were 0.113 *M* cumyl chloride, 0.590 *M* carbon tetrachloride, and 0.31 *M* cumene. The k_s value for this run was 14.4×10^{-5} sec.$^{-1}$

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

Nucleophilic Substitution at the Pyridazine Ring Carbons. II. Synthesis of Pyridazinonyl- and Bispyridazinonylpyridazines[1,2]

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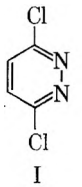
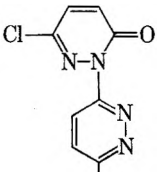
While preparing 3,6-dichloropyridazine (I), Druey and co-workers[3] isolated a small amount of another compound which on the basis of analytical, molecular weight, and infrared data was assigned the structure 3-(3′-chloro-6′(1′*H*)-pyridazinonyl)-6-chloropyridazine (II).



I

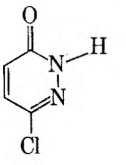


II

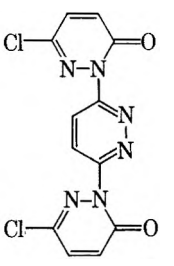
Feuer and Rubenstein[4] published experimental details for obtaining this product in small yield (less than 11%) by means of a long and tedious process.

Since compound II would be a starting material with interesting possibilities for synthetic work, possessing two halogens with strikingly different activities toward substitution, a search was undertaken in this laboratory for a synthetic route for preparation of this compound from readily obtainable materials.

The approach to this goal was to accomplish a nucleophilic displacement of one of the halogens of compound I using 6-chloro-3-(2*H*)-pyridazinone (III) as the nucleophile. It is of interest to note the difference of activity toward nucleophilic substitution of the chloro atom in compound III and the chloro atoms in compound I. Actually, compound III is prepared by boiling compound I in 3 *N* sodium hydroxide[5] or in 10% hydrochloric acid.[6] Once the pyridazinone is formed, the remaining chloro atom is stable toward nucleophilic attack by these reagents. Since attempts to synthesize II in an aqueous media failed,[3,4] different solvents were tested, such as xylene, tetrahydronaphthalene, and dichloropyridazine, the latter being the most successful. With a molar ratio of dichloropyridazine to 6-chloro-3(2*H*)-pyridazinone of 2:1, yields averaging 66% of compound II were obtained. In addition, a small amount (about 11%) of a higher melting compound was obtained which differed markedly in physical properties and solubility from compound II. Elemental and spectral analysis suggest the formation of a bispyridazinonylpyridazine, compound IV.



III



IV

By changing the molar ratio of 3,6-dichloropyridazine to 6-chloro-3(2*H*)-pyridazinone from 2:1 to the reverse ratio, 1:2, a 75% yield of compound IV was obtained. Compound IV was also prepared by heating compound II with excess compound III. It is of interest to note that compound III is stable at temperatures well over 200° and does not react with itself. Thus, the nucleophilic attack on compound II clearly occurs at the pyridazine ring carbon to give compound IV.

This method was used successfully to prepare 3-(6′(1′*H*)-pyridazinonyl)-6-chloropyridazine (V) and 3,6-bis(6′(1′*H*)-pyridazinonyl)pyridazine (VI). 3,6-Dichloropyridazine (I) was condensed with 3(2*H*)pyridazinone (VII) in the preceding manner. Compound VII forms an extremely stable hydrate.[7] Anhydrous VII was prepared previously by decarboxylation[8,9] of carboxy-3(2*H*)-pyridazinone or by hydrogenation of 4,5-dichloro-3(2*H*)-pyridazinone[12] with isolation according to special techniques described by Eichenberger

(1) Presented before the Pacific Southwest Regional Meeting of the American Chemical Society, December 1, 1962.

(2) For paper I, see P. Coad, R. A. Coad, S. Clough, J. Hyepock, R. Salisbury, and C. Wilkins, *J. Org. Chem.*, **28**, 218 (1963).

(3) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

(4) H. Feuer and H. Rubenstein, *J. Org. Chem.*, **24**, 811 (1959).

(5) S. Du Breuil, *ibid.*, **26**, 3382 (1961).

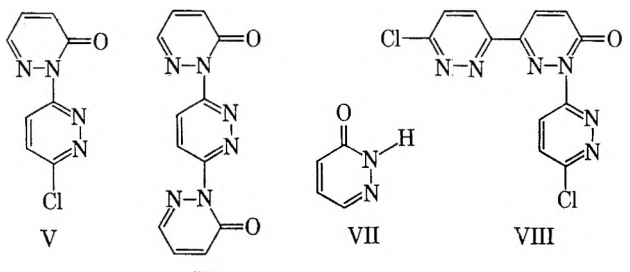
(6) H. Feuer and H. Rubenstein, *J. Am. Chem. Soc.*, **80**, 5873 (1958).

(7) C. Grundmann, *Ber.*, **81**, 6 (1948).

(8) F. McMillan and J. A. King, *J. Am. Chem. Soc.*, **77**, 3376 (1955).

(9) S. Gabriel, *Ber.*, **42**, 657 (1909).

and co-workers[10] and by Igeta.[11] The method of Mowry[12] was employed. However, significant improvements in the synthesis of 4,5-dichloro-3(2*H*)-pyridazinone and in the isolation of anhydrous VII have been made.



V VI VII VIII

From the reaction of I with anhydrous VII, 3-(6′-(1′*H*)-pyridazinonyl)-6-chloropyridazine (V) was obtained in yields of approximately 33%. Only traces of compound VI (5% or less) could ever be obtained in this reaction regardless of variation of ratio of reactants, solvents, temperature, reaction time, or pH. Traces (approximately 5%) of a new compound were isolated, and on the basis of elemental and spectral analysis and chemical solubility it has been assigned the tentative structure, VIII. The major product in each run was black polymeric material. A small part of this polymeric material was soluble in acid; a second small part was soluble in base; and the major portion was not soluble in acid, base, or common organic solvents.

The polymeric material was formed due to the activity of the hydrogens α to the ring nitrogen in compounds V, VI, and VII. It should be noted that α hydrogens are lacking in compounds II, III, and IV, and polymerization does not occur in these cases. Thus, the bifunctional nature of compound VII as an attacking nucleophile with centers at ring atoms 2 and 6 becomes monofunctional in compound III with the lone center at ring atom 2 due to the replacement of the hydrogen at ring atom 6 with the more electronegative chlorine atom.

Experimental

3,6-Dichloropyridazine (I) was prepared by the method of Coad, Coad, *et al.*,[2] from maleic hydrazide and phosphorus oxychloride with one modification. After the maleic hydrazide had dissolved in the phosphorus oxychloride, an equivalent amount of granular sodium chloride was added with a resulting evolution of hydrogen chloride. The mixture was heated an additional hour and was cooled, triturated, and extracted as previously described. Dichloropyridazine was obtained in a yield of 54%, m.p. 67–68° (lit.[2] 39%, m.p. 67–68°).

3-(3′-Chloro-6′(1′*H*)-pyridazinonyl)-6-chloropyridazine (II).—A finely ground mixture of 5.96 g. (0.04 mole) of 3,6-dichloropyridazine and 5.35 g. (0.041 mole) of 6-chloro-3(2*H*)-pyridazinone[5] was placed in a three-necked flask equipped with a thermometer, a nitrogen inlet, and an exit tube. The exit tube was connected to a trap cooled with an ice–salt bath. The exit gases were titrated with standardized sodium hydroxide to follow the course of the reaction. The flask was heated in an oil bath maintained at 134°. The internal temperature of the contents of the flask was 120°. Gas was evolved continuously from the surface of the solution. At the end of 20 min. a second phase appeared. The reaction was stopped at the end of 30 min. by sudden cooling of the flask in an ice bath. Sweeping with nitrogen was continued until all of the hydrogen chloride gas was removed. There was titrated 0.037 equivalent of acid. The solid was removed from the flask, powdered, and thoroughly ground in 50 ml. of cold 1 *N* sodium hydroxide, and separated by filtration. The solid was added to 50 ml. of cold water. The supernatant liquid was neutralized with cold hydrochloric acid. The mixture was filtered. The residue was extracted with three 100-ml. portions of boiling water. The extracts were combined and cooled. Slightly beige crystals of II were formed giving 3.0 g., m.p. 149–151°. An additional amount, 3.5 g., m.p. 149–151°, of II was obtained by concentrating the filtrate to 50 ml. and cooling, yielding a total of 6.5 g. (67%) of II. Recrystallization from cyclohexane gave white needles, m.p. 151–152°. This material has an infrared spectrum identical with authentic II as prepared by the method of Feuer and Rubenstein.[4] From the residue which was not dissolved during the hot water extractions, 1.5 g., m.p. 263–264°, of pure compound IV was isolated.

3,6-Bis(3′-chloro-6′(1′*H*)-pyridazinonyl)pyridazine (IV).—An intimately ground mixture of 5.96 g. (0.04 mole) of I and 10.44 g. (0.08 mole) of III was placed in a flask equipped as before. The bath was warmed to 160°, and hydrogen chloride was rapidly evolved. After 45 min. 0.064 mole of hydrogen chloride (80% of the stoichiometric amount) was evolved and the reaction rate markedly decreased. The mixture was poured into a mortar and ground with 100 ml. of cold 1 *N* sodium hydroxide solution and separated by filtration. The solid was treated with 150 ml. of water and the supernatant liquid was neutralized with hydrochloric acid. The mixture was boiled for 15 min. and filtered hot. This was repeated with an additional 500 ml. of boiling water. There remained a light gray powder, 10.1 g. (75% yield), m.p. 263–264°, infrared carbonyl band at 5.93 μ. White crystals could be obtained from dioxane by continuous extraction of the light gray solid for 48 hr. However, only the color was altered. Melting point, analysis, and spectrum did not change.

Anal. Calcd. for $C_{12}H_6Cl_2N_6O_2$: C, 42.73; H, 1.77; N, 24.92; Cl, 21.02. Found: C, 42.68; H, 1.86; N, 24.14; Cl, 20.1.

4,5-Dichloro-3(2*H*)-pyridazinone.—The method of Mowry[12] was modified. To a solution of 34 g. of hydrazine (95%) and 500 ml. of water was added 110 ml. of concentrated hydrochloric acid. The solution was placed in a flask equipped for stirring and was heated to boiling. A boiling solution of 169 g. (1 mole) of mucochloric acid and 200 ml. of water was added slowly with stirring. The reaction was exothermic and heat was discontinued during the course of the addition. The mixture was stirred for 15 min. and filtered warm. The precipitate was a beige solid, 157 g. (95.2%), m.p. 200–202° (lit. m.p. 201–202°).[10]

3(2*H*)-Pyridazinone (VII). **A. From 6-Chloro-3(2*H*)-pyridazinone** (III). **B. From 4,5-Dichloro-3(2*H*)-pyridazinone.**—The Parr hydrogenation apparatus was used in the hydrogenolysis of 0.4 mole of the respective halopyridazine using Shellacol,[13] a slight excess of concd. ammonium hydroxide, and 5.0 g. of activated 10% palladium on carbon. The solution was cooled and filtered. The residue was washed with 50 ml. of Shellacol. The solution and wash were combined and flash distilled using a bath temperature of at least 120° to prevent foaming and bumping. When the total volume was reduced to about 70 ml., 150 ml. of dry xylene was added and distillation was continued with a bath temperature of about 160°. When the distillation temperature reached 139°, an additional 150 ml. of hot dry xylene was added. The mixture was filtered hot, stoppered, and allowed to cool. Long pale yellow needles formed at room temperature to give 32 g. (85%), m.p. 102–103° (lit.[9] m.p. 103–104°).

3-(6′(1′*H*)-Pyridazinonyl)-6-chloropyridazine (V). **A. Tetralin as Solvent. Type I.**—In a flask equipped with a thermometer, a nitrogen inlet, a dropping funnel, and a reflux condenser with exit tube, was placed 29.8 g. (0.2 mole) of I and 50 ml. of tetralin. The flask was heated with an oil bath at 205°; the internal temperature varied from 180–195° during the course of the reaction. Over a period of 1 hr. a hot solution of 9.6 g. (0.1 mole) of VII in 50 ml. of tetralin was added through the dropping funnel. The reaction was continued for 2 hr. with smooth evolution of hydrogen chloride, at which time 0.09 equivalent of hydrogen chloride had been evolved. The mixture was filtered hot to remove a black solid. The bulk of this solid was insoluble in acid, base, and the usual organic solvents. The hot tetralin filtrate was cooled overnight. Beige crystals, 8.2 g., were formed which were fractionally recrystallized from Shellacol and

(10) K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta*, **39**, 1755 (1956).

(11) H. Igeta, *Chem. Pharm. Bull.*, **8**, 559 (1960).

(12) T. Mowry, *J. Am. Chem. Soc.*, **75**, 1909 (1953).

(13) Commercial Solvents Corp. anhydrous denatured ethanol.

decolorized. The less soluble material, VIII, was isolated as white crystals, 1.5 g., m. p. 239–240°. The more soluble material was V. It was isolated as white crystals and recrystallized from butanol to give 6.6 g. (33%), m.p. 173–174°, carbonyl band at 5.92 μ.

Anal. Calcd. for $C_8H_5ClN_4O$: N, 26.87; Cl, 16.94. Found: N, 26.17; Cl, 16.6.

Type II.—Using a molar ratio of 1:1 of compounds I and VII with the conditions described earlier, the yield of V dropped to 5.0 g. (25%). No compound VIII was found.

B. Compound I as Solvent.—Into an erlenmeyer flask equipped with a magnetic stirrer and thermometer was placed 30.0 g. of I. The flask was warmed to 130°. Over a period of 45 min. 9.6 g. of VII was added. The yellow solution turned black and copious amounts of hydrogen chloride were evolved. The black melt was poured directly into a mortar, allowed to solidify, and ground to a fine powder. The powder (39.0 g.) was extracted for 4 hr. in a Soxhlet extractor. There remained after extraction 17.5 g. of the powder. This black powder was boiled in 500 ml. of Shellacol and filtered hot. The precipitate, 5.0 g., was a black solid, the bulk of which was not soluble in base, acid, nor the usual organic solvents. The hot Shellacol solution was treated with Norit and cooled. A black solid, 6.7 g., was separated. When recrystallized from butanol, using Norit as a decolorizing agent, there were produced white needles, 5.0 g. (25%), m.p. 173–174°.

C. Compound VII as Solvent.—In a three-necked flask equipped as described previously, was placed a finely ground mixture of 19.6 g. (0.2 mole) of VII and 14.9 g. (0.1 mole) of I. Once the internal temperature reached 118° the reaction became violent and exothermic. It was completed in 10 min. The black solid was removed from the flask, ground to a powder, and triturated consecutively with 3 *N* ammonium hydroxide, 300 ml. of Shellacol, and 300 ml. of ether. The black solid, 12.0 g., was extracted using a Soxhlet extractor for 48 hr. with dioxane. From the dioxane was isolated 1.3 g. of VI, m.p. 244–245°. None of compound V was isolated from the Shellacol fraction.

Acknowledgment.—The authors express their gratitude to Miss June Hyepock for preparation of several of the starting materials. The authors are indebted to the Analytical Staff of Riker Laboratories, Inc., Northridge, California, for providing analytical data.

The Pyrolysis of Pyrazineethanol and 2-Pyridineethanol

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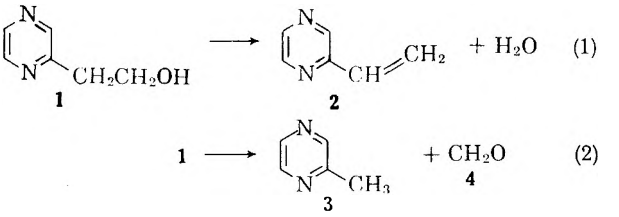
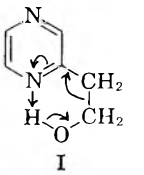
Received February 4, 1963

Gas chromatographic examination of a sample of pyrazineethanol (**1**) revealed the presence of small amounts of three lower boiling substances with retention-times corresponding to vinylpyrazine (**2**), methylpyrazine (**3**), and formaldehyde (**4**). On the assumption that these minor peaks did not represent impurities in **1** but were artefacts formed in the preheater ($T\sim$ 240°) of the chromatography column according to equations 1 and 2, samples of **1** were chromatographed at progressively higher preheater temperatures giving correspondingly larger amounts of the more volatile substances. At a preheater temperature of 370° only about 20% of the injected sample emerged unchanged.

If the dehydration (equation 1) were the result of a base-catalyzed bimolecular elimination and the fragmentation (equation 2) that of a unimolecular reaction, a change in the preheater assembly should affect the ratios of the products formed. The glass wool in the preheater, serving as a site for bimolecular elimination, was removed leaving the preheater as a hot tube with greatly diminished surface area. Samples of **1** were then chromatographed giving only traces of decomposition at 225° and about 85% decomposition at 380°. From ratios of peak areas it was estimated that the decomposition proceeded almost exclusively (~99%) *via* equation 2, whereas with a packed preheater about 10% of the decomposition proceeded *via* equation 1. That the decomposition products were in fact **2**, **3**, and **4** was established by comparison of derivatives, retention times, and physical measurements of collected samples.

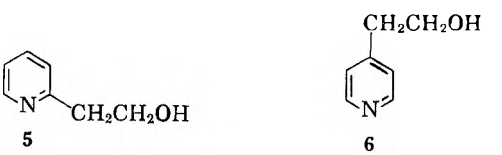


Based on the foregoing observations the following mechanism involving a cyclic transition state was considered for the formation of **3** and **4** from **1**.

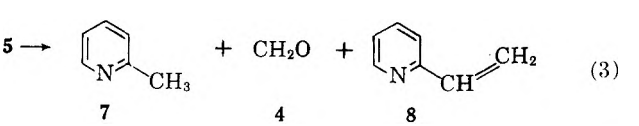


I

As a test of this hypothesis samples of 2-pyridineethanol (**5**) and 4-pyridineethanol (**6**) were chromatographed over a range of preheater temperatures. Compounds **1** and **5** are structurally analogous and should undergo an analogous pyrolytic breakdown, while **6**, though electrically similar,[2] does not embody the structural features required for facile fragmentation.



Samples of **5** were chromatographed at preheater temperatures of 195° to 390° giving the anticipated products (equation 3). As in the pyrolysis of **1**, only traces of decomposition occurred at 195° with progressively more up to about 90% at 390°. In analogy to



(3)

the pyrolysis of **1** about a per cent of **8** was formed. An additional small broad peak which emerged from the column prior to unchanged **5** was observed in the lower temperature runs and was shown to be **8**, probably

(1) (a) Research Associate, 1958–1960; (b) Medical Research Laboratories, Chas. Pfizer and Co. Inc., Groton, Conn.

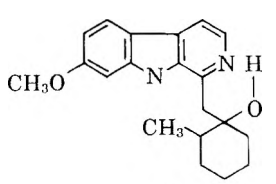
(2) For discussions of similarity between the pyridine 2- and 4-positions see (a) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947) and (b) H. S. Mosher, "The Chemistry of the Pyridines" in Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 337.

formed by dehydration of **5** during passage through the column.

The decomposition pattern seen in the chromatograms of **1** and **5** was not shown by 4-pyridineethanol (**6**). Samples of **6** were chromatographed at temperatures of 190° to 355° giving over the entire range about 5% decomposition to 4-vinylpyridine, as seen in the appearance of a broad peak emerging prior to unchanged **6**. The increased amount of column dehydration of **6** over **5** is consistent with the possibility that the amines themselves catalyzed the dehydrations. At 355° there was only a suggestion of decomposition of **6** in the preheater. The pattern of small peaks indicated that the fragmentations at this temperature might be going *via* a different mechanism.[3]

Although these experimental findings do not rigorously establish the mechanism or pyrolytic breakdown of **1** and **5**, they are consistent with the postulated cyclic transition state. The assumption of a unimolecular mechanism is supported by (1) the observation that higher preheater temperatures (which would lead to increased vaporization of the injected samples) led to increased decomposition of **1** and **5** without affecting **6**, (2) the fact that both **5** and **6** are easily dehydrated when heated in the liquid state,[4] and (3) reports that **1, 5,** and **6** are smoothly converted to the corresponding olefins when heated in the presence of potassium hydroxide.[5,6]

The enamines of **3** and **7** which would be formed directly in the pyrolyses of **1** and **5** are thought to tautomerize rapidly upon contact with the column packing. The proposed cyclic transition state is directly analogous to many of those from the ever-increasing catalog of reactions which are postulated to occur *via* 6-ring transition states. In another closely analogous reaction it has been shown that the carbinol **9** is converted to harmine and 2-methylcyclohexanone upon being



9

heated in a test tube at 240°.[7] This interesting degradation was explained in terms of the same 6-ring transition state as was postulated before, although the possibility of a bimolecular reaction in the melt is not excluded.

Experimental[8]

Gas Chromatography. Pyrolysis.—The pyrolyses were carried out in the preheater section of a conventional gas chromatography apparatus. The short (12 × 90 mm.) glass preheater was heated by an external spiral of resistance wire. Preheater (pyrolysis) temperatures are probably correct to about ±10° (external thermocouple). Helium was used at a flow rate of about 60 cc./min. A U-shaped Pyrex column (8 mm. o.d. × 7 ft.) was packed to a point 5 cm. from the preheater section. The column packing consisted of 30% of Dow-Corning "550" silicone fluid on Johns-Manville 60/80-mesh Chromosorb which had been pretreated with 3% methanolic potassium hydroxide. The exit to the detector block was constructed so as to facilitate sample collection in Dry Ice-cooled capillaries.

Materials.—Methylpyrazine (Wyandotte), and 2- and 4-methylpyridine (Eastman) were used without further purification. 2-Pyridineethanol (Aldrich) was purified by distillation, $n^{25}D$ 1.5359 (lit.[5a] $n^{20}D$ 1.5374). The picrates of these substances were prepared in the usual way. Methylpyrazine picrate (ethyl acetate) had m.p. (capillary) 129–131° (lit.[9] m.p. 133°). 2-Mehtylpyridine picrate (methanol) had m.p. (capillary) 166–167.5° (lit.[10] m.p. 165°). 2-Pyridineethanol picrate (ethyl acetate) had m.p. (hot stage) 120.5–121° (lit.[11] m.p. 120–121°).

Pyrazineethanol was prepared according to Kitchen and Hanson.[5a] The pure material (b.p. 84° at 0.5 mm.) had $n^{25}D$ 1.5362 lit.[5a] $n^{25})D$ 1.5378); picrate (ethyl acetate), m.p. (hot stage) 73–74°.

Anal.[12] Calcd. for $C_{12}H_{11}O_8N_5$: C, 40.80; H, 3.14; N, 19.83. Found: C, 40.84; H, 3.18; N, 20.13.

Vinylpyrazine was available in 80% yield from pyrazineethanol.[5a] The pure olefin had $n^{25}D$ 1.5542 (lit.[5a] $n^{20}D$ 1.5565); picrate (ethanol), m.p. (capillary) 100–101.5° dec. (lit.[5a] m.p. 101°). Ultraviolet spectrum (ethanol): 229.5 mμ, ε 12,900; 286.5 mμ, ε 6900. The olefin instantly decolorized 2% permanganate whereas pyrazineethanol did not.

4-Pyridineethanol was prepared from 4-methylpyridine and formalin,[13] $n^{24}D$ 1.5410 (lit.[14] $n^{25}D$ 1.5388), m.p. 8–9.5° (lit.[14] m.p. 13.1–13.3°); mol. wt., 123 (mass spectrum)[15]; m.p. (hot stage) 133–134.5° (lit.[5b] m.p. 134–135°).

4-Vinylpyridine[14] was synthesized from 4-pyridineethanol by distillation from potassium hydroxide at 130°. The pure olefin had λ_{max}^{EtOH} 243 mμ; picrate (benzene), m.p. (capillary) (135–160° changed form) 200–204° dec. (lit.[5b] m.p. 198–199° dec., sintering at 158–165°).

Pyrolysis of Pyrazineethanol (Preliminary Runs).—Preheater (pyrolysis section) was packed with glass wool; column *T*, 205°; sample size, 2 μl. Pyrazineethanol was chromatographed at preheater temperatures of 245, 285, 315, 350, and 370° giving trace, trace, 10, 50, and 80% decomposition, respectively.[16] New peaks appeared at retention times corresponding to those of air (a triplet with one major peak), methylpyrazine, and vinylpyrazine. Ratios of peak areas of vinylpyrazine to methylpyrazine were 3, 1, and 1/9 at pyrolysis temperatures of 245, 285, and 370°, respectively.

Pyrolysis of Pyrazineethanol (Final Runs).—Preheater was empty; column *T*, 190°; sample size 6 μl. Pyrazineethanol was chromatographed unchanged at preheater *T*, 190° (infrared spectrum of eluate, retention time 13.6 min.). Pyrazineethanol was then chromatographed at preheater temperatures of 225, 265, 305, 340, 360, and 380° giving <1, <1, 10, 30, 60, and 85% decomposition, respectively, to increasing amounts of two substances with retention times of 0.8 and 2.7 min. The first peak (0.8 min.) was identified as formaldehyde by passage of the effluent helium through 3 ml. of an aqueous dimedon solution and

(3) Phenethyl alcohol exhibited a similar decomposition pattern at preheater temperatures of 345–390°. For pyrolysis of phenethyl alcohol, see L. R. Herndon and E. E. Reid, *J. Am. Chem. Soc.*, **50**, 3066 (1928).

(4) E. Profft, *Chem. Tech.* (Berlin), **8**, 378 (1956).

(5) (a) L. J. Kitchen and E. S. Hanson, *J. Am. Chem. Soc.*, **73**, 1838 (1951); (b) J. Meisenheimer, J. Neresheimer, and W. Schneider, *Ann.*, **420**, 190 (1920).

(6) *Cf.* J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5666 (1959), who have demonstrated a base-catalyzed reversal in the substituted pyrazineethanol series (1,1-diphenylpyrazineethanol) where the steric requirements favored the reversal (to methylpyrazine and benzophenone) rather than dehydration.

(7) C. F. Huebner, H. B. MacPhillamy, A. F. St. André, and E. Schlittler, *J. Am. Chem. Soc.*, **77**, 472 (1955).

(8) Melting points were taken on a Kofler hot-stage microscope or in open capillaries (as noted) and are not corrected.

(9) C. Stoehr, *J. prakt. Chem.*, **51**, 464 (1895).

(10) A. Ladenburg, *Ann.*, **247**, 7 (1888).

(11) W. Koenigs and G. Happe, *Ber.*, **35**, 1343 (1902).

(12) Microanalysis by S. M. Nagy, Massachusetts Institute of Technology.

(13) E. E. Mikhlina and M. V. Rubtsov, *Zh. Obshch. Khim.*, **28**, 103 (1958); *Chem. Abstr.*, **52**, 12864 (1958).

(14) H. C. Brown and N. R. Eldred, *J. Am. Chem. Soc.*, **71**, 445 (1949).

(15) The author is grateful to Prof. Biemann for this spectrum and interpretation.

(16) As approximated by decrease in area of the peak corresponding to pyrazineethanol, 2- or 4-pyridineethanol.

isolation (after 16 hr.) of formaldimedon (ethanol–water), m.p. 192–192.5°, pure or mixed with an authentic sample. The second peak (2.7 min.) was condensed in a small capillary and identified as methylpyrazine; infrared spectrum (carbon tetrachloride) identical with that of authentic material; picrate (ethyl acetate), m.p. 127°, softening at 128.5–130.5°, pure or mixed with an authentic sample of methylpyrazine picrate (m.p. 129–131°).

A third peak corresponding in retention time (4.1 min.) to vinylpyrazine built up gradually to about 1% yield at 380°. Collection of this substance did not afford enough material for derivative formation, but instantaneous decoloration of permanganate provided additional support for the assignment of vinylpyrazine to this peak.

Pyrolysis of 2-Pyridineethanol.[17]—Preheater was empty; column *T*, 190°; sample size, 6 μl. 2-Pyridineethanol was chromatographed essentially unchanged[18] at preheater *T*, 190° (infrared spectrum of eluate, retention time 11.2 min.). 2-Pyridineethanol was then chromatographed at preheater temperatures of 195, 230, 265, 285, 310, 340, 370, and 390° giving <1, ~1, 5, 10, 35, 55, 70, and 90% decomposition, respectively, to increasing amounts of two substances with retention times of 0.8 and 2.6 min. The first peak (0.8 min.) was identified as formaldehyde by conversion to formaldimedon (see preceding). Second peak (2.6 min.) was identified as 2-methylpyridine; infrared spectrum (chloroform); picrate (methanol), m.p. 165°, softening at 166–167°, pure or mixed with an authentics ample of 2-methylpyridine picrate. A third peak of retention time 4.0 min. built up gradually to about 1% yield at 370–390°. Two collections of this substance did not afford material for derivative formation. This material decolorized permanganate instantly and showed λ_{max}^{EtOH} 235 mμ,[19] thereby supporting the assignment of 2-vinylpyridine to this peak. A fourth broad peak, retention time 5.4–8.4 min., was present in the low-temperature runs but diminished in intensity at higher temperatures. Small samples were collected from 215° runs. This material decolorized permanganate instantly and showed $\lambda\lambda_{max}^{EtOH}$ 235 and 277.5 mμ.[19] An infrared spectrum (very weak, cavity cell, chloroform) showed all of the major bands for 2-vinylpyridine.[20]

Pyrolysis of 4-Pyridineethanol.—Preheater was empty; column *T*, 190°; sample size, 6 μl. 4-Pyridineethanol was chromatographed at temperatures of 190, 240, 280, 320, and 355° giving over the entire range about 5% decomposition to a low, broad peak of retention time 6.8–13.6 min. At 355° there was only a small amount (~1%) of decomposition in the preheater to form peaks with retention times of 0.8, 1.0, 2.8, 3.2, 3.7, and 5.1 min. —a pattern which was qualitatively similar to that from a sample of phenethyl alcohol.[4] The main peak, retention time 18.4 min., was collected and identified as unchanged 4-pyridineethanol (infrared spectrum, chloroform). Material collected from the broad peak decolorized permanganate instantly and showed λ_{max}^{EtOH} 243 mμ. An infrared spectrum (weak, cavity cell, chloroform) showed all of the major bands for 4-vinylpyridine.

Pyrazineethanol and 2-pyridineethanol[21] can form strong intramolecular H-bonds. It is interesting to compare the retention times of pyrazineethanol (13.6 min.) and 2-pyridineethanol (11.2 min.) with that of 4-pyridineethanol (18.4 min.) which cannot form an intramolecular H-bond.[22]

Acknowledgment.—The author is indebted to Dr. Max Stoll of Firmenich et Cie., Geneva, for generous financial support, to Dr. F. D. Greene for helpful discussions, and to Professor G. Büchi for many useful suggestions and continuing encouragement.

(17) In a preliminary run with a preheater packed with glass wool 2-pyridineethanol was chromatographed over a range of preheater temperatures. The decomposition was analogous to that from the corresponding series with pyrazineethanol: new peaks emerged at retention times corresponding to air, methylpyridine, and 2-vinylpyridine (estimated; no comparison with authentic material).

(18) Small peaks (~1%) at 4.0 and 5.8–8.4 min.

(19) Sample rinsed from collection capillary directly into cuvette. R. P. Mariella, L. F. A. Peterson, and R. C. Ferris, *J. Am. Chem. Soc.*, **70**, 1494 (1948), report for 2-vinylpyridine λ_{max} 235 mμ, log ε 4.1, and λ_{max} 278, mμ, log ε 3.7.

(20) Satdler curve #6654.

(21) P. R. Schleyer, C. Wintner, D. S. Trifan, and R. Bacskai, *Tetrahedron Letters*, **14**, 1 (1959), report for 2-pyridineethanol $\Delta\nu$ = 205.

(22) C. H. DePuy and P. R. Story, *Tetrahedron Letters*, **6**, 20 (1959), report that internal H-bonding decreases retention time.

A Convenient Separation of *cis*- and *trans*-Methoxycyclohexanols

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A recent communication[2] regarding the separation of *cis*- and *trans*-cycloalkanediols by means of *n*-butylboronic acid prompts us to report some observations made about two years ago regarding the separation of the corresponding monoalkyl ethers by means of a lithium aluminum hydride–aluminum chloride reagent.[3] In attempts to equilibrate the epimeric 4-methoxycyclohexanols by this reagent (presumably[4,5] $AlHCl_2$) as previously described for the corresponding 4-methylcyclohexanols[6] we observed the immediate formation of a granular precipitate when ethereal solutions of the two alcohols were mixed with similar solutions of the hydride reagent. When the precipitate was collected, washed with ether, and then slurried with fresh ether and treated with 10% aqueous sulfuric acid, the 4-methoxycyclohexanol recovered from the ether layer was almost exclusively (>95%) the *cis* isomer as indicated by gas chromatographic analysis and preparation of the known[7] crystalline *p*-toluenesulfonate. In contrast, decomposition of the ethereal filtrate with 10% sulfuric acid led to *trans*-4-methoxycyclohexanol, identified by its crystalline hydrogen phthalate,[7] and shown, gas chromatographically, to be 87% isomerically pure.

Similar results were obtained with the 3-methoxycyclohexanols. Here, again, the precipitated material returned mainly *cis*-3-methoxycyclohexanol (90% pure by gas chromatography), identified by its hydrogen phthalate,[8] whereas the filtrate yielded the hitherto unknown *trans*-3-methoxycyclohexanol, characterized as its 3,5-dinitrobenzoate, in over 99% purity.

It was further observed that: (a) no separation occurred with the 2-methoxycyclohexanols (a precipitate formed but, upon decomposition, it yielded a mixture of isomers identical with the starting mixture); (b) the 4-methoxycyclohexanols yielded no precipitate with aluminum chloride alone and with lithium aluminum hydride alone they gave rise to a different precipitate which lead to little separation of isomers; (c) for obvious reasons, no precipitate formed from very *trans*-rich mixtures of 4-methoxycyclohexanol.

The previous observations may be explained readily if it is granted that the granular precipitates are intramolecular chelates as depicted in Fig. 1. Clearly such chelates can form only from the *cis*-4 and *cis*-3 isomers (not the corresponding *trans* forms), but presumably

(1) The Radiation Laboratory is operated under contract with the U. S. Atomic Energy Commission. This note is taken in part from the Ph.D. dissertation of T. J. B.

(2) H. C. Brown and G. Zweifel, *J. Org. Chem.*, **27**, 4708 (1962).

(3) *Cf.* E. L. Eliel, *Rec. Chem. Progr.*, **22**, 129 (1961).

(4) E. Wiberg and M. Schmidt, *Z. Naturforsch.*, **6b**, 460 (1951).

(5) G. G. Evans, J. K. Kennedy, and F. P. Del Greco, *J. Inorg. Nucl. Chem.*, **4**, 40 (1957).

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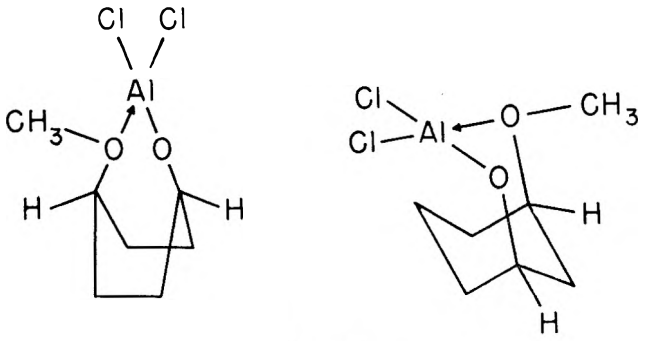

Figure 1

they might be formed from *both* isomers of 2-methoxycyclohexanol. Analysis of the chelates proved difficult (and is responsible for the delay in the publication of these results), for once formed the solids (which are quite hygroscopic) cannot be redissolved without decomposition. However, material was eventually obtained which was free of lithium (flame test) and which gave satisfactory analyses for C, H, and Al in the case of the 3-isomer and for Al and Cl in the case of the 4-isomer.[9]

Isolation of the species shown in Fig. 1 supports the hypothesis[3] that the active reagent formed from lithium aluminum hydride (1 mole) and aluminum chloride (>3 moles) is, in fact, $AlHCl_2$ and that the complexes formed from this reagent and substituted cyclohexanols which are subject to equilibration by ketones[6] are, in fact, of the composition $ROAlCl_2$.

The method here described probably lends itself to the separation of other epimeric pairs of alkoxycycloalkanols.

Experimental

4-Methoxycyclohexanol.—*cis*-Rich material was obtained by hydrogenating 124 g. (1.0 mole) of *p*-methoxyphenol in 300 ml. 95% ethanol at 130° and 2000 p.s.i. in the presence of 10 g. of Raney nickel. The theoretical amount of hydrogen was absorbed in 12 hr. The solution was filtered, concentrated, and partitioned between ether and water. The ether layer was washed, with 10% sodium hydroxide, followed by saturated aqueous sodium chloride, dried over magnesium sulfate, concentrated, and the residue distilled at 108–113° (24 mm.) to give 100.1 g. (77%) 4-methoxycyclohexanol. Gas chromatographic analysis on Tide (180°, He flow 24 ml./min.) indicated 61.6% *cis* isomer (retention time 13.7 min.) and 38.4% *trans* isomer (retention time 17.2 min.).

Chelate.—The mixed hydride reagent was prepared from 13.35 g. (0.10 mole) of aluminum chloride in 75 ml. of anhydrous ether and 0.025 mole of ethereal lithium aluminum hydride (*ca.* 1 *M*). To this solution was added with stirring 13.0 g. (0.10 mole) of the previous mixture of 4-methoxycyclohexanols in 50 ml. of anhydrous ether. The solution was stirred for 15 min., filtered in a dry atmosphere, and the precipitate was washed with four portions of anhydrous ether. It was dried in a desiccator at room temperature overnight for analysis.

Anal. Calcd. for $C_7H_{13}AlCl_2O_2$: Cl, 31.23; Al, 11.88. Found: Cl, 31.12; Al, 11.91.

In another run, the solid was stirred with ether and 10% aqueous sulfuric acid until two clear layers resulted. The ether layer was separated, washed successively with water, saturated sodium carbonate, and brine, dried over magnesium sulfate, and concentrated to give 4.09 g. (31.5% over-all or 51.1% of total *cis* isomer) of *cis*-4-methoxycyclohexanol of over 95% purity. The *p*-toluenesulfonate, formed in 75% yield, melted at 88–89.5° (lit.[7] m.p. 87.8–88.2°). Infrared spectrum of the alcohol was identical with one of pure *cis*-4-methoxycyclohexanol kindly provided by D. S. Noyce.

The ethereal filtrate by similar treatment yielded 3.90 g. (30% overall, or 78% of total *trans* isomer) of *trans*-4-methoxycyclohexanol of 87% purity, characterized by conversion to the hydrogen phthalate, m.p. 151–152° (lit.[7] m.p. 148.6–149.0) in 66% yield.

3-Methoxycyclohexanol.—Catalytic hydrogenation of 50.0 g. (0.40 mole) of *m*-methoxyphenol in 125 ml. 95% ethanol in the presence of 10 g. of 5% rhodium on alumina at 52 p.s.i. and room temperature was complete in 2.5 hr. The material was worked up as described for the 4-isomer to give 47.9 g. (92%) of 3-methoxycyclohexanol, b.p. 112–116° (28 mm.). Gas chromatographic analysis on a 5-ft. silicone QF-1 column at 155° and 40 ml./min. of helium indicated the product to contain 45.5% *trans* isomer (retention time 8.3 min.) and 54.5% *cis* isomer (retention time 11.0 min.). In a second hydrogenation, the product was 60% *trans* isomer.

Chelate.—To the mixed hydride solution prepared from 20.0 g. (0.15 mole) of aluminum chloride in 100 ml. of anhydrous ether and 0.0375 mole of ethereal lithium aluminum hydride was added 15.6 g. (0.12 mole) of 3-methoxycyclohexanol (60% *trans*) in 75 ml. of ether. The complex was collected after 30 hr. and weighed 10.3 g.; it was dried *in vacuo* at 56° for 16 hr.

Anal. Calcd. for $C_7H_{13}AlCl_2O_2$: C, 37.02; H, 5.77; Al, 11.88. Found: C, 36.76; H, 6.08; Al, 11.90.

In another run, starting with 28.6 g. (0.22 mole) of material containing 45.5% *trans* isomer, 0.20 mole of aluminum chloride in 100 ml. of ether and 0.05 mole of ethereal lithium aluminum hydride there was obtained 26.8 g. of solid complex which was decomposed as described for the 4-isomer and yielded 11.4 g. (39.5% over-all or 72.5% of total *cis* isomer) of *cis*-3-methoxycyclohexanol of 90% purity. This was characterized as the hydrogen phthalate, m.p. 103–104° (lit.[8] m.p. 104–105°), obtained in 51% yield.

Decomposition of the filtrate as described for the 4-isomer gave 9.85 g. (34.5% over-all or 76% of total *trans* isomer) of *trans*-3-methoxycyclohexanol of over 99% purity (gas chromatography), b.p. 105–106° (24 mm.), $n^{20}D$ 1.4670. It was characterized as the 3,5-dinitrobenzoate, m.p. 104–105°.

Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97. Found: C, 52.16; H, 5.28.

2-Methoxycyclohexanol.—Catalytic hydrogenation of guaiacol over rhodium on alumina (as described for 3-methoxycyclohexanol) yielded 2-methoxycyclohexanol, b.p. 66–67° (16 mm.), which was quite impure and required purification by preparative gas chromatography. The material collected was 90.3% *cis* and 9.7% *trans*. The pure *trans* isomer, b.p. 91.5–93.0° (24 mm.), $n^{20}D$ 1.4595 (lit.[10] b.p. 72.5–73.2° (10 mm.), $n^{25}D$ 1.4586), was obtained from cyclohexene oxide and methanol as previously described.[10] A mixture of the two preparations (5.20 g.) containing 52.3% *trans* alcohol was converted to the solid chelate in the manner described earlier. The alcohol recovered from the chelate (4.15 g.) contained 53.1% *trans* isomer whereas that recovered from the filtrate (0.58 g.) contained 73.1% *trans* isomer.

(9) Inner complexes of aluminum similar to those shown in Fig. 1 have been described previously by G. Bähr and G. E. Müller, *Chem. Ber.*, **88**, 251 (1955).

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Dibutyl 2-Bromoethaneboronate[1]

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Radical-catalyzed additions to dibutyl ethyleneboronate have made a variety of new types of carbon-functional organoboron compounds available.[2] Extension

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(2) D. S. Matteson, *J. Am. Chem. Soc.*, **82**, 4228 (1960).

$$CH_2{=}CHB(OC_4H_9)_2 + HBr \xrightarrow{\text{ultraviolet}} BrCH_2CH_2B(OC_4H_9)_2$$

to hydrogen bromide has resulted in the efficient preparation of dibutyl 2-bromoethaneboronate.

We expected that the 2-bromoethaneboronate would be deborobrominated in the presence of bases.[3] The general reaction with a base, Z^-, presumably proceeds *via* addition of the base to the boron atom.[2]

$$BrCH_2CH_2B(OC_4H_9)_2 + Z^- \longrightarrow BrCH_2CH_2B(OC_4H_9)_2^- \longrightarrow$$
$$\begin{array}{c} | \\ Z \end{array}$$
$$Br^- + C_2H_4 + ZB(OC_4H_9)_2 \longrightarrow$$
$$BZ_3 + B(OC_4H_9)_3 \text{ (or solvolysis products)}$$

Accomplishment of this elimination under mild conditions would, in addition to the method of synthesis, serve as a structure proof.[2] Treatment with water at 25° has turned out to be sufficient.

$$BrCH_2CH_2B(OC_4H_9)_2 + 3H_2O \longrightarrow$$
$$C_2H_4 + B(OH)_3 + HBr + 2C_4H_9OH$$

The hope that weakly basic but highly nucleophilic reagents might displace bromide ion from dibutyl 2-bromoethaneboronate was realized only with iodide ion, which yielded the iodo compound, $ICH_2CH_2B(OC_4H_9)_2$. Competition experiments indicated that allyl bromide reacts 4 to 5 times as fast as dibutyl 2-bromoethaneboronate with sodium iodide in acetone. Since allyl bromide reacts 65–70 times as fast as butyl bromide,[4] the bromoethaneboronic ester must react a number of times as fast as ordinary alkyl bromides. A competition experiment with ethyl bromide confirmed this order of reactivity, although the onset of side reactions after a time made it impossible to run the reaction long enough to get accurate data. This activating effect of the dibutoxyboryl group is consistent with the expectation that the boron atom should be electron-donating toward carbon in the absence of π-bonding[2] and contrasts with the very slight deactivating effect (relative to hydrogen) of a carbethoxy group at the same position. However, there is some uncertainty in this interpretation because of some anomalously high reactivities in the carbonyl series.[5]

With reagents more basic than iodide ion, dibutyl 2-bromoethaneboronate yielded only ethylene, bromide ion, and boric acid derivatives. The most carefully studied reaction was that with sodium thiocyanate in acetone. Sodium bromide crystallized from the reaction mixture, ethylene was evolved in 90% yield, and the remaining solution contained tributyl borate and an unstable oily liquid partially immiscible with tributyl borate, presumably tri(iso)thiocyanoboron. Similar gas evolution and butyl borate formation occurred with potassium cyanate in acetone, aniline in tetrahydrofuran, pyridine, sodium nitrite in dimethylformamide, and others. Even lithium bromide in acetone catalyzes the elimination after an induction period of a few minutes, and decomposition sets in within a few hours in the reaction mixtures with sodium iodide. Boron bromide (or iodide), a product which would result from the elimination reaction in a nonbasic medium, is presumably the active catalyst in these autocatalytic decompositions; boron trifluoride etherate catalyzes similar decomposition.

In the hope that steric hindrance about the boron atom might retard elimination enough to permit displacements of bromide, the butyl ester was transesterified with diisobutylcarbinol, chosen because tris(diisobutylcarbinyl) borate hydrolyzes far more slowly than most borate esters.[6] Somewhat surprisingly, the transesterification proceeded without difficulty, suggesting that anions of the type $BrCH_2CH_2B(OR)_3^-$ are not intermediates; the necessary proton shifts could be concerted or acid catalyzed. Treatment of bis(diisobutylcarbinyl) bromoethaneboronate with sodium thiocyanate resulted in the usual elimination.

Experimental[7]

Dibutyl 2-Bromoethaneboronate.—Dibutyl ethyleneboronate (16.7 g.) in a Pyrex flask was kept at approximately 70°, stirred, and irradiated with a Hanovia 500-watt mercury vapor ultraviolet lamp for 4 hr. while hydrogen bromide was bubbled through the liquid. Distillation through a short column packed with Podbielniak nichrome helices yielded 18.2 g. (76%) of dibutyl 2-bromoethaneboronate, b.p. 48–50° (0.1 mm.).

Anal. Calcd. for $C_{10}H_{22}BO_2Br$: C, 45.32; H, 8.37; B, 4.08; Br, 30.16. Found: C, 45.54; H, 8.60; B, 4.34; Br, 29.94.

Dibutyl 2-Iodoethaneboronate.—A solution of 5.0 g. of sodium iodide and 6.21 g. of dibutyl 2-bromoethaneboronate in 30 ml. of acetone was allowed to stand under nitrogen in the dark 30 min. After filtration of the sodium bromide the solution was distilled through a spinning band column to yield 1.5 g. (20%) of dibutyl 2-iodoethaneboronate, b.p. 66° (0.2 mm.), with up to 1 g. loss in the forerun. The following infrared bands are useful for distinguishing the iodo from the bromo compound: 3.23 (m), 8.67 (m), 9.15 (w), 11.46 (w), 12.25 (w), 13.78 (w) microns for the iodo compound; 8.51 (m), 8.67 (w), 9.03 (w), 12.03 (w), 13.46 (w) for the bromo; the other bands differ only slightly.

Anal. Calcd. for $C_{10}H_{22}BO_2I$: C, 38.49; H, 7.11; B, 3.47; I, 40.67. Found: C, 38.73; H, 7.18; B, 3.68; I, 40.50.

Relative Rates.—A solution 0.5 *M* each in allyl bromide, dibutyl 2-bromoethaneboronate, and sodium iodide in acetone was allowed to stand 45 min. at 23–25°. The yield of precipitated sodium bromide was 94%. Vacuum distillation yielded a mixture of the 2-haloethaneboronic esters shown by infrared comparison with authentic mixtures to contain 26 (±3) mole per cent dibutyl 2-iodoethaneboronate. Assuming 100% completion of the reaction, the rate constant for allyl bromide is 4.5 times that for dibutyl 2-bromoethaneboronate. The uncertainties in the ratio of products and extent completion of the reaction lead to an uncertainty in the ratio of rate constants which we judge to be about ±25%. In a similar competition with ethyl bromide run 90 min. the resulting mole ratio of dibutyl 2-bromo- to 2-iodoethaneboronate was 47:53 (±5%), but the reaction was estimated to be only 80–90% complete under these conditions and some tributyl borate formed as a by-product. Further confirmation of the order of rate constants, allyl > dibutoxyboronoethyl > ethyl bromide, was obtained by examining the order of appearance of sodium bromide precipitates in a set of reaction mixtures at the same molar concentrations. The gradual appearance of the precipitates seemed to indicate that supersaturation sufficient to reverse any apparent order of reactivities was not occurring. These qualitative tests support the assumption that the competition experiments measure rate constants, not equilibrium constants.

Bis(diisobutylcarbinyl) 2-Bromoethaneboronate.—Simple distillation of butanol at 20 mm. from a mixture of 23.9 g. of dibutyl 2-bromoethaneboronate and 50 ml. of diisobutylcarbinol (redistilled) in a bath at 65° 2.5 hr., then up to 90°, then distillation of diisobutylcarbinol at 0.2 mm. followed by fractionation of the residue yielded 33.4 g. (91%) of the diisobutylcarbinyl ester, b.p. 92–93° (0.1 mm.).

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(6) H. Steinberg and D. L. Hunter, *Ind. Eng. Chem.*, **49**, 174 (1954).

(7) Microanalyses by Galbraith Laboratories, Knoxville, Tenn.

Anal. Calcd. for $C_{20}H_{42}BO_2Br$: C, 59.31; H, 10.38; B, 2.67; Br, 19.73. Found: C, 59.64; H, 10.43; B, 2.95; Br, 19.47.

Eliminations.—Treatment of 0.28 g. of dibutyl-2-bromoethaneboronate with 10 ml. of water yielded 96% of ethylene, confirmed by infrared comparison with an authentic sample. Treatment of 0.5 g. of dibutyl 2-bromoethaneboronate with 0.6 g. of sodium thiocyanate in 3 ml. of acetone yielded 90% of ethylene in 2 hr. Tributyl borate (identified by infrared) and an unstable oil were isolated from the solution. The oil was only slightly soluble in butyl borate, but appeared to separate slowly over a period of several days. The infrared spectrum was consistent with the presence of thiocyano or isothiocyano groups. Extensive decomposition occurred on attempted distillation. Bis(diisobutylcarbinyl) 2-bromoethaneboronate underwent similar elimination in the presence of sodium thiocyanate to yield tris(diisobutylcarbinyl) borate,[6] m.p. 102°, further confirmed by microanalysis. In the other eliminations mentioned in the discussion section, evolution of gas on mixing and isolation of butyl borate from the reaction mixture were considered sufficient evidence that elimination was occurring.

Acetylation of Serine during Bradykinin Synthesis

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In a previous report[1], we described two carbobenzoxypentapeptide intermediates obtained during the synthesis of bradykinin which did not appear to be identical, but which gave the same carbobenzoxyhexapeptide on further reaction. The pentapeptides were obtained by different procedures. In the first case carbobenzoxy-L-phenylalanine *p*-nitrophenyl ester reacted with L-seryl-L-prolyl-L-phenylalanylnitro-L-arginine methyl ester and secondly, carbobenzoxy-L-phenylalanyl-L-seryl azide reacted with L-prolyl-L-phenylalanylnitro-L-arginine methyl ester. Both of the pentapeptides were crystalline but differed in melting point by 65° and in rotation by 15°. The infrared curves of the two compounds were not significantly different enough to confirm any structural anomalies. X-Ray diffraction patterns of the two peptides revealed dissimilarities which could possibly be due to different crystalline forms, but seeding a solution of one of the pentapeptides with the other failed to induce crystallization.

The solution to the problem of the two pentapeptides came with the attempted preparation of the O-acetyl analog of bradykinin. The intermediate carbobenzoxy 6-O-acetylserine pentapeptide was found to possess the physical properties of the pentapeptide obtained by the one plus four coupling. O-Acetyl analysis confirmed the presence of this functional group in both compounds while the pentapeptide prepared by the two plus three reaction did not contain an O-acetyl. Reexamination of the other bradykinin intermediates from the hexapeptide to the tricarbobenzoxynonapeptide also revealed the presence of O-acetyl groups. The results are given in Table I. The acetate group is undoubtedly lost during hydrolysis of the protecting methyl ester since it does not appear in any of the products after this step.

The O-acetyl group on serine probably is introduced during the hydrobromine acid–acetic acid cleavage of the carbobenzoxy group since this side reaction has been reported previously.[2] The consequences of this reaction are usually not troublesome and in practice we have found that the products containing this group are higher melting and more easily crystallized than peptides without it. Care should be exercised, however, in preparing peptides containing serine in which a step involving hydrolysis with alkali is not involved.

Experimental[3]

Carbobenzoxy-O-acetyl-L-seryl-L-propyl-L-phenylalanylnitro-L-arginine Methyl Ester.—To a cold (5°) solution of 4.3 g. (0.0078 mole) of L-propyl-L-phenylalanylnitro-L-arginine methyl ester hydrobromide[1] in 50 ml. of dimethylformamide was added 1.5 g. of triethylamine. After 5 min., the precipitate was removed by filtration; to the filtrate was added 3.2 g. (0.078 mole) of N-carbobenzoxy-O-acetyl-L-serine *p*-nitrophenyl ester.[4,5] The yellow solution was kept 18 hr. at 25°, diluted with 250 ml. of ethyl acetate, and washed with water, aqueous 5% sodium carbonate, water, dilute hydrochloric acid, dried, and evaporated. Ether was added giving a white solid which was recrystallized from methanol–ether, 4 g. (70%), m.p. 166–168°, $[\alpha]^{23}D$ −55.7° (*c* 1.06, dimethylformamide); reported[5] m.p. 170–172°, $[\alpha]^{20}D$ −56.6° (*c* 1.06, dimethylformamide).

Anal. Calcd. for $C_{34}H_{44}N_8O_{11}$: C, 55.12; H, 5.98; N, 15.12. Found: C, 54.96; H, 6.17; N, 15.12.

Carbobenzoxy-L-phenylalanyl-O-acetyl-L-seryl-L-prolyl-L-phenylalanylnitro-L-arginine Methyl Ester.—To a cold (10°) solution of the carbobenzoxytetrapeptide, 7 g. (0.0095 mole), in 100 ml. of glacial acetic acid was added 6 g. of anhydrous hydro-

TABLE I

BRADYKININ INTERMEDIATES

			Calcd. %				Found, %			
		Formula	C	H	N	O-Ac	C	H	N	O-Ac
1.	CBZ-L-Phe-O-Ac-L-Ser-L-Pro-L-Phe-NO_2-L-Arg-OCH_3	$C_{43}H_{53}N_9O_{12}$	58.17	6.02	14.20	4.85	58.05	6.06	14.83	5.9
2.	CBZ-Gly-L-Phe-O-Ac-L-Ser-L-Pro-L-Phe-NO_2-L-Arg-OCH_3	$C_{45}H_{56}N_{10}O_{13}$	57.20	5.97	14.83	4.56	57.43	6.11	15.00	4.15
3.	CBZ-L-Pro-Gly-L-Phe-O-Ac-L-Ser-L-Phe-NO_2-L-Arg-OCH_3	$C_{50}H_{63}N_{11}O_{14}$	57.62	6.09	14.78	4.12	57.34	6.10	15.24	3.50
4.	CBZ-L-Pro-L-Pro-Gly-L-Phe-O-Ac-L-Ser-L-Pro-L-Phe-NO_2-L-Arg-OCH_3	$C_{55}H_{70}N_{12}O_{15}$	57.99	6.19	14.76	3.92	57.66	6.13	14.98	4.23
5.	TRICBZ-L-Arg-L-Pro-L-Pro-Gly-L-Phe-O-Ac-L-Ser-L-Pro-L-Phe-NO_2-L-Arg-OCH_3	$C_{77}H_{94}N_{16}O_{20}$	59.14	6.06	14.34	2.75	58.92	6.14	14.66	3.24

(1) E. D. Nicolaides and H. A. DeWald, *J. Org. Chem.*, **26**, 3872 (1961).

(2) St. Guttmann and R. A. Boissonnas, *Helv. Chim. Acta*, **41**, 1852 (1958).

(3) Melting points were taken using a Thomas-Hoover capillary melting point apparatus and are corrected.

(4) H. A. DeWald and E. D. Nicolaides, to be published.

(5) M. A. Ondetti, *J. Med. Chem.*, **6**, 10 (1963).

gen bromide. The solution was kept 2 hr. at 25°, poured into 1 l. of dry ether, and the precipitate removed, washed with ether, and dried *in vacuo*. The resulting crude hydrobromide salt of the tetrapeptide, 9 g., was dissolved in 50 ml. of dimethylformamide, cooled to 0°, and 4 g. of triethylamine added. After 5 min., the solid was removed and 4.5 g. (0.0107 mole) of carbobenzoxy-L-phenylalanine *p*-nitrophenyl ester was added to the filtrate. The yellow solution was stirred 18 hr. at 25°, diluted with 250 ml. of ethyl acetate; the solution was washed with water, aqueous 5% sodium carbonate, water, and dilute hydrochloric acid. The solution was dried over magnesium sulfate, evaporated to a small volume, and ether added. The solid was removed and recrystallized from dimethylformamide–ether; yield 5 g. (50%), m.p. 215–216°, $[\alpha]^{23}D$ −60° (*c* 1.1, dimethylformamide); reported[5] m.p. 214–216°, $[\alpha]^{20}D$ −57° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{43}H_{53}N_9O_{12}$: C, 58.17; H, 6.02; N, 14.20; O-Ac, 4.85. Found: C, 58.10; H, 6.17; N, 14.29; O-Ac, 4.55.

Carbobenzoxyglycyl-L-phenylalanyl-O-acetyl-L-seryl-L-prolyl-L-phenylalanylnitro-L-arginine Methyl Ester.—The carbobenzoxy group was removed from 3.5 g. (0.004 mole) of the pentapeptide with hydrobromic acid–acetic acid. The crude product was dissolved in 50 ml. of dimethylformamide, cooled to 5°, and 1 g. of triethylamine added. The precipitate was removed and 1.5 g. (0.0045 mole) of carbobenzoxyglycine *p*-nitrophenyl ester was added to the filtrate. After 3 days at room temperature, the solution was diluted with four volumes of ethyl acetate giving a white solid which was recrystallized from methanol–ether; 3 g. (79%), m.p. 222–224°, $[\alpha]^{23}D$ −55.8° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{45}H_{56}N_{10}O_{13}$: C, 57.20; H, 5.97; N, 14.83; O-Ac, 4.56. Found: C, 57.19; H, 5.96; N, 14.92; O-Ac, 4.20.

Penicillin Sulfones

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We wish to report an improved procedure for preparing penicillin sulfones. Recent syntheses[1,2] have required that the carboxyl group be esterified during oxidation, and the protecting group be subsequently removed by hydrogenolysis. Using potassium permanganate in neutral aqueous solution, we prepared the sulfones of benzylpenicillin, 2,6-dimethoxyphenylpenicillin (methicillin[3]), 5-methyl-3-phenyl-4-isoxazolylpenicillin (oxacillin[3]), D-(−)-α-aminobenzylpenicillin (ampicillin[3]), and *dl*-α-phenoxyethylpenicillin (phenethicillin[3]) by direct oxidation of their salts or free acids. Ampicillin was oxidized as its N-carbobenzyloxy derivative which yielded ampicillin sulfone on hydrogenolysis.

The products were easily isolated and purified in satisfactory yields. Infrared spectra of the sulfones showed the characteristic shift of the β-lactam band from 5.6 to 5.50–5.53 μ, and the appearance of bands at 7.6 and 8.9 μ due to the sulfone group.

Experimental[4]

The sulfones prepared in this work, their physical constants, elemental analyses, and other data are listed in Table I.

General Procedure for the Preparation of Penicillin Sulfones.—The appropriate penicillin salt or free acid (0.035 mole) was added to 180 ml. of water, the pH was adjusted to 7.0–7.5, and the resulting solution was cooled to 0–5°. A solution of 5.5 g. (0.035 mole) of potassium permanganate, 1.80 ml. of 85% phosphoric acid (specific gravity 1.70), and 140 ml. of water was added to the penicillin solution at such a rate as to keep the temperature below 10°. The pH was maintained between 6.0 and 7.5 using 5–10% aqueous sodium hydroxide or 10% phosphoric acid. About 10 min. after the addition, excess potassium permanganate was destroyed with sodium bisulfite, if necessary. The manganese dioxide was removed by passing the mixture through a Dicalite-precoated filter, and the pH of the cooled filtrate was then slowly adjusted to 2.0–2.3 with 10% phosphoric acid. The penicillin sulfone-free acid which precipitated was collected and washed with cold water. It was usually dried by storing overnight in a vacuum desiccator over Drierite.

Two compounds needing special comment are described.

D(−)-α-Aminobenzylpenicillin Sulfone.—D(−)-α-N-Carbobenzyloxyaminobenzylpenicillin sulfone, 7.5 g. (0.0146 mole) was added to 70 ml. of water and dissolved by adjusting the pH to 6.5 with 10% sodium hydroxide. The previous solution was added to 7.5 g. of prehydrogenated 30% palladium-on-diatomaceous earth catalyst in 25 ml. of water and shaken under 48 p.s.i.g. of hydrogen for 2.25 hr. Methyl isobutyl ketone (50 ml.) was added, the

(1) A. W. Chow, N. M. Hall, and J. R. E. Hoover, *J. Org. Chem.*, **27**, 1381 (1962).

(2) E. Guddal, P. Morch, and L. Tybring, *Tetrahedron Letters*, **9**, 381 (1962).

(3) The trade-marks of Bristol Laboratories, a division of Bristol-Myers Co., for methicillin, oxacillin, ampicillin, and phenethicillin are, respectively, Staphcillin, Prostaphlin, Polycillin, and Syncillin.

(4) All melting points are corrected. Microanalyses were performed by Richard M. Downing, and the infrared measurements were performed by David F. Whitehead.

TABLE I

PENICILLIN SULFONE FREE ACIDS

Penicillin sulfone	Molecular formula	Yield, %	M.p., °C. dec.	Recrystallization solvent	Analyses—Calcd. % C	Analyses—Calcd. % H	Analyses—Found % C	Analyses—Found % H
Benzyl	$C_{16}H_{18}N_2O_6S$	84–87	123.0–124.0	Ethyl acetate and petroleum ether	52.46	4.95	52.70	5.14
2,6-Dimethoxyphenyl	$C_{17}H_{20}N_2O_8S$	55–70	174.5–174.8	Ethyl acetate and petroleum ether	49.51	4.89	49.45	5.30
5-Methyl-3-phenyl-4-isoxazolyl	$C_{19}H_{19}N_3O_7S$	35–61	132.0–134.0	Water	52.65	4.42	52.74	4.49
D-(−)-α-N-Carbobenzyloxyaminobenzyl-hemihydrate[a]	$(C_{24}H_{25}N_3O_8S)_2H_2O$	30–42	115.0–116.5	Ethyl acetate and petroleum ether	55.00	4.99	55.20	4.67
D-(−)-α-Aminobenzyl	$C_{16}H_{19}N_3O_6S$	30	228.6–229.4	Aerosol OT-methyl isobutyl ketone	50.39	5.02	50.80	5.05
dl-α-Phenoxyethyl(*sym*-dibenzylethylenediamine salt)	$C_{60}H_{60}N_6O_{14}S_2$	60	118.0–118.3	Methyl isobutyl ketone	58.05	5.81	57.70	5.86

[a] Calcd. for water: 1.7%. Found: 1.6%

pH was adjusted to 2.0, and the mixture was passed through a Dicalite-precoated filter. The aqueous layer was then extracted with 6.5 g. (0.0146 mole) of Aerosol OT in 80 ml. of methyl isobutyl ketone while the temperature was held at 0–5° and the pH held at 2.0. The organic layer was passed through a Dicalite-precoated filter and adjusted to a pH of 5.8 with triethylamine. Crystals of D-(−)-α-aminobenzylpenicillin sulfone separated. After stirring cold for 10 min. they were collected by filtration, washed with petroleum ether (b.p. 60–70°), and dried.

N,N′-Dibenzylethylenediamine Di-*dl*-α-phenoxyethylpenicillinate Sulfone.—This sulfone was prepared by the general procedure described before with these exceptions. The aqueous solution, after the manganese dioxide was removed, was mixed with 300 ml. of methyl isobutyl ketone, and the pH was adjusted to 2.0 with 10% phosphoric acid. The organic layer was dried over anhydrous sodium sulfate and, after the drying agent was removed, was treated with 4.2 g. (0.018 mole) of *sym*-dibenzylethylenediamine. The crystalline dibenzylethylenediamine salt of *dl*-α-phenoxyethylpenicillin sulfone precipitated almost immediately. After stirring cold for 1 hr., the mixture was filtered, washed with methyl isobutyl ketone and petroleum ether (b.p. 60–70°), and dried.

Synthesis of Trimethylhydroquinone

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It is known that tocopherols (vitamin E) are synthesized by condensation of trimethylhydroquinone with phytol[1] or its derivatives.[2–5]

Trimethylhydroquinone is an important starting material in synthesizing tocopherol. A number of investigations on the synthesis of trimethylhydroquinone have been carried out with 2,3,5-trimethylbenzene,[6] 2,3,5-trimethylphenol,[7] and 3,5-dimethylphenol[8] as the starting material.

Recently Burke[9] succeeded in a synthesis of trimethylhydroquinone from 4-benzyloxyphenol.

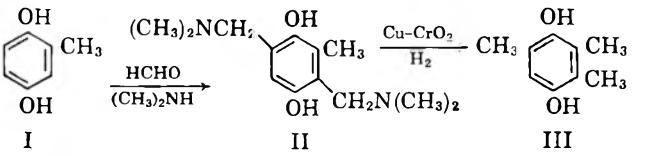
Caldwell and Thompson[8] prepared 3,5-dimethyl-2-dimethylaminomethylphenol by the condensation of 3,5-dimethylphenol with dimethylamine and formaldehyde, which was then converted into 2,3,5-trimethylphenol.

They also prepared 2,5-dimethylhydroquinone from 2,5-bis(dimethylaminomethyl)hydroquinone, obtained in the condensation of hydroquinone with dimethylamine and formaldehyde. However, efforts to obtain the required tris(dimethylaminomethyl)hydroquinone were not successful.

A new way of synthesizing trimethylhydroquinone presented in this paper comprises only two steps from 2-methylhydroquinone, which is the smallest in number ever attained in any procedures so far reported.

This investigation was carried out independently of the synthesis of trimethylhydroquinone from 4-benzyloxyphenol by Burke and co-workers.[9]

The conversion of 2-methylhydroquinone into trimethylhydroquinone involves the following steps.

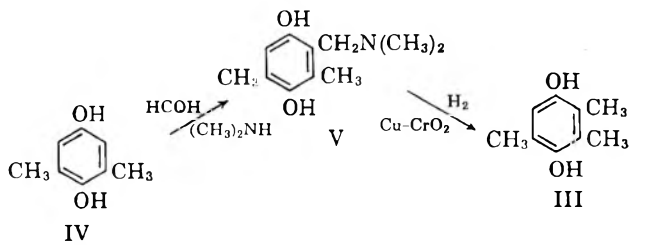


2-Methylhydroquinone (I) reacts smoothly with dimethylamine and formaldehyde to give 2-methyl-3,6-bis(dimethylaminomethyl)hydroquinone (II) in 72% yield.

The di-Mannich base (II), recrystallized from ether as colorless needles, is very unstable and upon heating or even exposure to air for a long time, polymerized to a dark brown sticky mass.

The base (II) was hydrogenolyzed in the presence of copper chromium oxide in dioxane at 180° under a pressure of about 140 atm. of hydrogen to trimethylhydroquinone (III) in 58% yield. From the fact that the base (II) shows a sharp melting point (97–99°) and no characteristic absorption band for the free phenolic group in the infrared spectrum, the position of the dimethylaminomethyl groups must be 3,6- or 5,6- and not a mixture, and from the point of the spacial effect it may be the 3,6-disubstituted compound as shown in II.

Similarly, 3,5-dimethylhydroquinone is converted into trimethylhydroquinone.



The condensation of 3,5-dimethylhydroquinone (IV) with dimethylamine and formaldehyde in dioxane under mild conditions gives 3,5-dimethyl-2-dimethylaminomethylhydroquinone (V) in 75% yield.

The hydrogenolysis of the mono-Mannich base (V) in dioxane gives trimethylhydroquinone (III) in 60% yield.

This represents a new and more practical synthesis of trimethylhydroquinone.

Experimental[10]

2-Methyl-3,6-bis(dimethylaminomethyl)hydroquinone (II).—To a solution of recrystallized 2-methylhydroquinone (I, 5.0 g.,

(1) P. Karrer, H. Salmon, and H. Fritzshe, *Helv. Chim. Acta*, **21**, 309 (1938); Hoffmann-La Roche and Co., Swiss Patent 212,353 (1941); P. Karrer and O. Isler, U. S. Patent 2,411,968 (1946); O. Ehrman, German Patent 1,015,446 (1958).

(2) Hoffman-La Roche and Co., Swiss Patent 208,446 (1940); P. Karrer and O. Isler, U. S. Patent 2,411,969 (1946).

(3) P. Karrer, R. Esher, H. Fritzsche, K. Keller, B. Ringier, and H. Salmon, *Helv. Chim. Acta*, **21**, 939 (1938); P. Karrer and H. Keller, *ibid.*, **21**, 1161 (1938); J. D. Surmatis and J. Weber, U. S. Patent 2,723,278 (1955); J. D. Surmatis and J. Weber, Canadian Patent 530,254 (1956).

(4) L. I. Smith and H. E. Ungnade, U. S. Patent 2,421,811 (1947).

(5) J. Weicht, *Chem. Listy*, **52**, 722 (1958); L. Blaha, J. Hodosova, and J. Weicht, *Collection Czech. Chem. Commun.*, **24**, 2023 (1959); L. Blaha and J. Weicht, Czech. Patent 88,904 (1959).

(6) L. I. Smith, J. W. Opie, S. Wawzoneck, and W. Prichard, *J. Org. Chem.*, **4**, 318 (1939); A. Pongratz and K. L. Zirm, *Monatsh.*, **83**, 13 (1952); C. K. Hui, *J. Vitaminol.* (Japan), I, 8 (1957); F. L. Grinberg and A. A. Svishchuk, *Ukr. Khim. Zh.*, **23**, 79 (1957).

(7) H. J. Teuber and W. Reu, *Chem. Ber.*, **86**, 1036 (1953); R. J. Boscott, *Chem. Ind.* (London), 201 (1955).

(8) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).

(9) W. J. Burke, J. A. Warburton, J. L. Bishop, and J. L. Bilis, *J. Org. Chem.*, **26**, 4669 (1961).

(10) Melting points are uncorrected. Infrared spectra were recorded with a Shimadzu Model AR 275 spectrophotometer.

0.04 mole, m.p. 124–125°[11]) in dioxane (5.0 ml.) cooled in an ice bath was added 40% aqueous dimethylamine (9.1 g., 0.08 mole).

Then 38% aqueous formaldehyde (6.4 g., 0.08 mole) was added drop by drop to the previous mixture with stirring while keeping the temperature between 0–5°. The reaction mixture was allowed to stand in an ice–salt bath for 2 or 3 days, and the crude 2-methyl-3,6-bis(dimethylaminomethyl)hydroquinone was obtained in a yield of 6.0–6.9 g. (62–72%) as a light brown solid. It was readily soluble in cold water and organic solvents. By concentrating the ethereal solution of the crude product at room temperature, under reduced pressure, the di-Mannich base crystallized as colorless needles, m.p. 97–99°.

Infrared, 3300–2000 (cm.$^{-1}$) ν str. OH; 1042 (cm.$^{-1}$) ν asym. $N^{CH_3}_{CH_3}$; 990.1 (cm.$^{-1}$) ν sym. $N^{CH_3}_{CH_3}$; 902.5 (cm.$^{-1}$), 816.3 (cm.$^{-1}$), 752.4 (cm.$^{-1}$) ν C–N, ν C–C; 873.4 (cm.$^{-1}$), 863.6 (cm.$^{-1}$) ν arom. C–H; 1192 (cm.$^{-1}$), 1181 (cm.$^{-1}$), 1160 (cm.$^{-1}$), 1103 (cm.$^{-1}$), 1024 (cm.$^{-1}$) ν arom. C–H; 1195 (cm.$^{-1}$), 1182 (cm.$^{-1}$), 1161 (cm.$^{-1}$) ν C–O.

Anal. Calcd. for $C_{13}H_{22}O_2N_2$: C, 65.54: H, 9.24: N, 11.76. Found C, 65.36: H, 9.14: N, 11.60.

Trimethylhydroquinone (III).—2-Methyl-3,6-bis(dimethylaminomethyl)hydroquinone (II, 2.3 g., 0.01 mole) in dioxane (25 ml.) was hydrogenolized in the presence of copper chromium oxide[12] (3.0 g.) under an initial hydrogen pressure (146 atm.) at 160° for 4 hr. After opening the bomb, the catalyst was removed by filtration, and the solvent distilled. A solution of concentrated hydrochloric acid (3 ml.) in water (14 ml.) was added to the residue. The mixture was saturated with sodium sulfate and extracted with ether three times and the extract was dried with calcium chloride. After removing the ether, the solid residue (0.8 g., 58% yield) was recrystallized from water, m.p. 167–168° (lit.[13] m.p. 170°).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.05: H, 7.89. Found C, 70.85: H, 7.85.

3,5-Dimethyl-2-dimethylaminomethylhydroquinone (V).—Dimethylamine (40% aqueous, 3.5 g., 0.03 mole) was added to a solution of recrystallized 3,5-dimethylhydroquinone (IV, 4.2 g., 0.03 mole, m.p. 150–151°[7]) in ethanol (6.0 ml.) at room temperature (15–20°). Then 38% aqueous formaldehyde (2.5 g., 0.03 mole) was added drop by drop to preceding mixture with stirring while keeping the temperature between 15–20°. The oily layer, upon cooling in the ice–salt bath for a day, solidified to light brown crystals (4.0–4.5 g., 70–75% yield). They were insoluble in water or organic solvents and could not be purified by recrystallization. By washing with the ether several times, the mono-Mannich base was obtained as white needles, m.p. 102–103°.

Anal. Calcd. for $C_{11}H_{16}O_2N$: C, 67.66: H, 8.78: N, 7.19. Found C, 67.60: H, 8.57: N, 7.49.

Trimethylhydroquinone (III).—3,5-Dimethyl-2-dimethylaminomethylhydroquinone (V, 2.0 g., 0.01 mole) in dioxane (20 ml.) was hydrogenolized in the presence of copper chromium oxide[12] (3 g.) under an initial hydrogen pressure of 146 atm. at 160° for 4 hr. After opening the bomb, the catalyst was removed by filtration, and the solvent distilled. A solution of concentrated hydrochloric acid (3 ml.) in water (20 ml.) was added to the residue. The mixture was saturated with sodium sulfate and extracted with ether three times, and the extract was dried with calcium chloride. After removing the ether, the solid residue (0.9 g., 60% yield) was recrystallized from water, m.p. 168–169° (lit.[13] m.p. 170°).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.05: H, 7.89. Found C, 70.88: H, 7.91.

Acknowledgment.—The authors wish to express gratitude to Dr. Kuroiwa and the staff of the Tekkosha Company for measurements of infrared spectra. The authors are also grateful to Mr. G. Shioya and Mr. K. Kurihara of our laboratory for their great help in carrying out the study presented in this report.

(11) K. Schniter, *Ber.*, **20**, 2283 (1887).

(12) Prepared by slight modification of Adkins' method, Lazier and Arnold, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 144, note 11.

(13) R. Nietzki and Schneider, *Ber.*, **27**, 1430 (1894).

D-*gluco*-L-*glycero*-3-Octulose, a Crystalline Ketose from D-Erythrose

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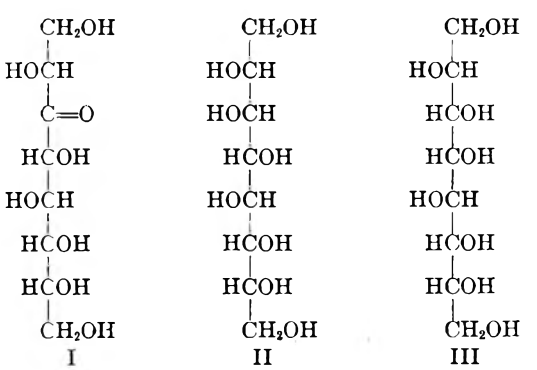
Our continuing studies of syntheses of higher, branched-chain aldoses[1] and higher ketoses[2] by aldol reactions have now led to discovery of the title compound (I), which is readily obtained from D-erythrose. Chromatography was used at first to obtain the crystalline product, but, in subsequent preparations, I was isolated directly from the reaction mixture in a yield of 16%. Compound I reduces Benedict solution, and, on chromatography, the new sugar travels slightly more slowly than D-glucose. It is readily visible with silver nitrate and sodium hydroxide sprays.

That compound I might be a branched-chain octose, *e.g.*, a 3-*C*-formylheptitol related to the aldols obtained with aldose reactants,[1] was ruled out by the stability it shows to hypoiodite oxidation. That it is, instead, a ketose follows from the isolation of two crystalline octitols after reduction. One of these octitols (II) is a new compound, but the other proved to be D-*erythro*-L-*galacto*-octitol (III), a known substance.[3] Acetylation of compound III gives an acetate identical with D-*erythro*-L-*galacto*-octitol octaacetate.[3c,d]



The normal-chain structure of III shows that a ketose having a carbonyl group at C-3 must have been produced by an aldol reaction in which carbon atom 1 of an enolized tetrose molecule had attacked the carbonyl carbon atom of a second molecule of tetrose; thus, carbon atoms 1 to 4 of a molecule of "D-erythrose-1,2-enediol" become carbon atoms 4 to 1 at the reducing end of the 8-carbon ketose, and carbon atoms 1 to 4 of a molecule of D-erythrose become the remainder, namely, carbons 5 to 8, respectively. The configurations of the asymmetric carbon atoms of such a ketose should be the same as they were in the reactants at C-2, C-6, and C-7, and, according to earlier studies of aldol syntheses of ketoses,[2] should be *threo* at C-4 and C-5.

(1) (a) R. Schaffer and H. S. Isbell, *J. Am. Chem. Soc.*, **80**, 756 (1958); (b) **81**, 2178 (1959); (c) R. Schaffer, *ibid.*, **81**, 2838 (1959); (d) **81**, 5452 (1959).

(2) R. Schaffer and H. S. Isbell, *J. Org. Chem.*, **27**, 3268 (1962).

(3) (a) E. Fischer, *Ann.*, **270**, 95, 101 (1892); (b) L. H. Philippe, *Ann. chim. phys.*, **26**, 356 (1912); (c) R. M. Hann, Alice T. Merrill, and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 1912 (1944); (d) the authors are indebted to N. K. Richtmyer for a sample of this compound.

In compound III, the configurations of its carbon atoms confirm those expectations, and, from this, the structure of the aldol product could be predicted to be that of I. However, in the alkaline medium in which it is formed, such a compound theoretically might isomerize to other octuloses[4] that would be reduced to compound III. All of these possibilities were eliminated by degrading compound I with an equimolecular proportion of periodic acid,[5] and finding D-arabinose and D-glucono-1,5-lactone among the products. No octulose structure other than that proposed for compound I can give both products; and, of the remaining 5 ketoses, the 2-octulose could give only D-arabinose. Furthermore, compound I cannot be this 2-octulose, D-*glycero*-D-*gulo*-octulose, for it is a known substance[6] whose properties are different from those of I. Thus, the new sugar has structure I; and compound II, the new octitol, is D-*erythro*-L-*gulo*-octitol.

The readiness with which D-erythrose undergoes aldol reaction to afford compound I makes it seem odd that the new sugar (or its phosphate) has not yet been observed in biological systems. Perhaps, this nondetection is due to its low sensitivity to the orcinol–trichloroacetic acid spray, which produces a faint gray spot on paper chromatograms; however, under ultraviolet light a resulting yellow-orange fluorescence can be detected more readily. D-*manno*-3-Heptulose, which has been synthesized[1c] and crystallized,[7] reacts analogously. This behavior may be characteristic of 3-ketoses.

Further work on this and related aldol syntheses is in progress. Additional details will be published later.

Experimental

D-*gluco*-L-*glycero*-3-Octulose (I).—A solution of 2.4 g. of D-erythrose (prepared from 2,4-*O*-ethylidene-D-erythrose[1c]) in 200 ml. of a filtered, saturated solution of calcium hydroxide (prepared at 5°) was kept at room temperature until a maximum dextrorotation was reached (about 2 hr.), and then treated with excess carbon dioxide, filtered, and concentrated under reduced pressure. After removal of an additional precipitate, the concentrate was taken up in methanol, from which compound I crystallized; yield 16%, m.p. 164–165°, $[\alpha]^{26}D$ +59.3° (*c* 10, water), no mutarotation observed.

Anal. Calcd. for $C_8H_{16}O_8$: C, 40.0; H, 6.7. Found: C, 39.8; H, 6.7.

On being paper chromatographed, I traveled only a little more slowly than D-glucose in 1-butanol–ethanol–water (40:11:19) and in 1-butanol–pyridine–water (6:4:3). It reacts readily with silver nitrate and sodium hydroxide sprays, but poorly with orcinol and trichloroacetic acid (faint gray that is yellow-orange under ultraviolet light), and gives no reaction with aniline hydrogen phthalate.

Degradation with Periodic Acid.—At 0°, a solution of 5 mg. of compound I in 1 ml. of water was treated with 5 mg. of periodic acid. The mixture was allowed to warm to room temperature after 1 hr., and, an hour later, a sample was paper chromatographed using 1-butanol–ethanol–water (40:11:19) containing 1% of ammonium hydroxide. Aniline hydrogen phthalate spray gave a reddish pink color at a position corresponding to that for D-arabinose. The remainder of the oxidation mixture was neutralized with barium carbonate, treated with Amberlite IR-120 H^+, and concentrated under reduced pressure. The concentrate was dissolved in 2-methoxyethanol and reconcentrated, and this process was repeated several times. A sample of the concentrate was chromatographed in a solution of 1-butanol saturated with water and containing 2% of formic acid. Silver nitrate and sodium hydroxide sprays showed a spot corresponding to D-glucono-1,5-lactone. The 3-octulose and D-arabinose spots were near the spot for D-glucono-1,4-lactone, and this circumstance made difficult the positive identification of this D-gluconic acid derivative, too.

Reduction with Sodium Borohydride.—At 0°, a stirred solution of 1 g. of I in 50 ml. of water was treated with 1 g. of sodium borohydride, and allowed to warm to room temperature overnight. Excess borohydride was decomposed with Amberlite IR-120 H^+. Boric acid was removed by repeated evaporation with methanol; during this process, a new, crystalline material appeared. From the first crops, there was obtained D-*erythro*-L-*gulo*-octitol (II), m.p. 164.5–165°, $[\alpha]^{23}D$ 171° (in 5% ammonium molybdate[8]).

Anal. Calcd. for $C_8H_{18}O_8$: C, 39.7; H, 7.5. Found: C, 40.0; H, 7.7.

Acetylation with acetic anhydride in pyridine gave the octaacetate, m.p. 110–111°, $[\alpha]^{20}D$ 47° (*c* 0.4, chloroform).

Anal. Calcd. for $C_{24}H_{34}O_{16}$: C, 49.8; H, 5.9. Found C, 49.8; H, 5.8.

The mother liquor contained some of II, together with D-*erythro*-L-*galacto*-octitol (III). The latter was obtained crystalline from methanol–water. Its m.p. of 153–154°, undepressed mixture melting point, and the correspondence of its infrared spectrum with that of the authentic material[3c,d] established its identity. Its octaacetate, obtained from its interaction with acetic anhydride in pyridine, had m.p. 88–89°, an undepressed mixture melting point, and an identity of infrared spectrum with that of authentic D-*erythro*-L-*galacto*-octitol octaacetate.[3c,d]

Acknowledgment.—The authors express their appreciation to R. A. Paulson of this bureau for microanalyses.

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3,4,6-Tri-*O*-acetyl-2-*O*-nitro-α-D-glucopyranosyl Chloride and the Anomeric Tetraacetates of 2-*O*-Nitro-D-glucopyranose

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The synthesis of α-D-glucosides in a Koenigs–Knorr reaction[3] has been of great difficulty either because of the unavailability of stable poly-*O*-acyl-β-D-glucosyl halides or because of the tendency of these materials to react with hydroxylic compounds by a mechanism involving participation of the *trans* 2-*O*-acyl group in the displacement at C-1 leading to products of the β-D-configuration. Schlubach[4] prepared an unstable tetra-*O*-acetyl-β-D-glucopyranosyl chloride from the treatment of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with "active" silver chloride. Lemieux and Brice[5] reported an improved synthesis of this material by the action of titanium tetrachloride on β-D-glucopyranose pentaacetate. The β-D-glucosyl chloride readily isomerized to the α-D-anomer and was thus unsuited for the synthesis of α-D-glucosides. Brigl[6] has shown that

(1) Deceased.

(2) Research Associate (A. T.) and Fellow of the Corn Industries Research Foundation.

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fusion of β-D-glucose pentaacetate and phosphorus pentachloride yields 3,4,6-tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucopyranosyl chloride, from which 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl chloride can be obtained. Wolfrom, Pittet, and Gillam[7] reported the synthesis of β-isomaltose octaacetate using stable 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride as the glycosyl halide component of a modified Koenigs–Knorr reaction. This β-D-glucosyl chloride could not be anomerized[7] without concomitant cleavage of the 2-*O*-nitro group, thus illustrating the deactivating power of the 2-*O*-nitro moiety.

It was of interest to attempt the synthesis of a β-D-glucosyl bromide with a nonparticipating group substituted on C-2. Low temperature nitration of 3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride[8] yielded a sirupy product which resisted all efforts at crystallization. Elemental analysis and specific rotation indicated that this sirup was 3,4,6-tri-*O*-acetyl-2-*O*-nitro-α-D-glucopyranosyl chloride. Attempted conversion of this substance to the corresponding β-D-glucopyranosyl bromide using the conditions cited by Schlubach[4] yielded only recovered starting material. The nitrate group evidently deactivates the chloride to such an extent that halogen exchange would not occur, under the conditions used, with an "active" silver bromide prepared according to Schlubach.

Acetylation of 3,4,6-tri-*O*-acetyl-2-*O*-nitro-α-D-glucopyranosyl chloride with mercuric acetate and acetic acid[9] yielded crystalline 1,3,4,6-tetra-*O*-acetyl-2-*O*-nitro-β-D-glucopyranose and acetylation of 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride[7] in the same manner yielded crystalline 1,3,4,6-tetra-*O*-acetyl-2-*O*-nitro-α-D-glucopyranose.

Experimental

3,4,6-Tri-*O*-acetyl-2-*O*-nitro-α-D-glucopyranosyl Chloride.—A mixture of 45 ml. of glacial acetic acid and 75 ml. of acetic anhydride was cooled to −20° (solid carbon dioxide–acetone), and 60 ml. of absolute nitric acid was added portionwise while maintaining the temperature below 0°. The solution was then cooled to −40° and 9.6 g. of 3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride[8] was added portionwise, with vigorous stirring, while maintaining the temperature between −36 and −42°. The mixture was allowed to warm to 0°, with stirring, and the clear solution was poured into 2 kg. of ice with stirring. The ice was allowed to melt over a 2- to 3-hr. period, and the solid material was separated by filtration. The amorphous product was dissolved in 250 ml. of ethylene dichloride, washed with aqueous sodium hydrogen carbonate, dried over calcium chloride, filtered, and the solvent removed under reduced pressure; yield, 7.47 g. of clear yellow sirup, $[\alpha]^{20}D$ +125° (c 1.18, chloroform).

Anal. Calcd. for $C_{12}H_{16}ClNO_{10}$: N, 3.79. Found: N, 4.15.

Attempted Synthesis of 3,4,6-Tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl Bromide.—A solution of 3,4,6-tri-*O*-acetyl-2-*O*-nitro-α-D-glucopyranosyl chloride (5 g.) in 50 ml. of ether (dried according to Schlubach[4]) was refluxed, with stirring, for 5 hr. with 11 g. of "active" silver bromide (the silver bromide from 10 g. of silver nitrate according to Schlubach). The mixture was filtered and the residue washed with the same ether. The solvent was concentrated to a small volume under reduced pressure at low bath temperature. No crystalline material was obtained from this solution. Only sirupy starting material was recovered, 3.88 g., $[\alpha]^{18}D$ +130° (c 2.0, chloroform).

1,3,4,6-Tetra-*O*-acetyl-2-*O*-nitro-β-D-glucopyranose.—The previously described, sirupy 3,4,6-tri-*O*-acetyl-2-*O*-nitro-α-D-glucopyranosyl chloride (2.5 g.) was dissolved in 20 ml. of glacial acetic acid containing 3.0 g. of mercuric acetate and maintained at room temperature for 1 hr. with occasional shaking. The mixture was diluted with 75 ml. of chloroform, washed thrice with water, the chloroform layer dried over anhydrous calcium chloride, filtered, and the solvent removed under reduced pressure. The resulting sirup was crystallized from ether–petroleum ether and recrystallized from hot ethanol; yield, 178 mg. (after three recrystallizations), m.p. 120–121°, $[\alpha]^{20}D$ +21° (*c* 2, chloroform); X-ray powder diffraction pattern[10]: 9.94 s (2), 7.56 s (1), 5.59 s (3), 5.40 vw, 4.87 m, 4.29 vw, 4.06 m, 3.88 w, 3.55 w, 3.25 w, 3.04 vw, 2.72 vw.

Anal. Calcd. for $C_{14}H_{19}NO_{12}$: C, 42.75; H, 4.83; N, 3.56. Found: C, 42.79; H, 4.95; N, 3.65.

1,3,4,6-Tetra-*O*-acetyl-2-*O*-nitro-α-D-glucopyranose.—3,4,6-Tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride[7] (2.5 g.) was treated with mercuric acetate as described before; yield, 1.43 g. (after three recrystallizations from ethanol), m.p. 92–93°, $[\alpha]^{22}D$ +107° (*c* 2, chloroform); X-ray powder diffraction pattern[10]: 8.31 s (2), 7.23 m, 6.68 w, 5.63 m, 5.05 vw, 4.68 vs (1), 4.24 m, 4.04 m, 3.91 w, 3.74 s (3), 3.54 w, 3.43 w, 3.24 w, 3.03 vw, 2.89 w, 2.72 vw, 2.51 vw, 2.27 vw, 2.18 w, 2.03 vw, 1.89 vw, 1.85 vw.

Anal. Calcd. for $C_{14}H_{19}NO_{12}$: C, 42.75; H, 4.83; N, 3.56. Found: C, 42.97; H, 5.13; N, 3.80.

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(10) Interplanar spacing, Å., CuKα radiation. Relative intensities, estimated visually: s, strong; m, medium; w, weak; v, very. Strongest lines numbered, 1 strongest.

Oxidative Dimerization of Benzimidazole

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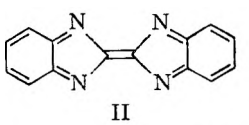
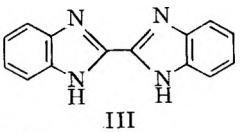
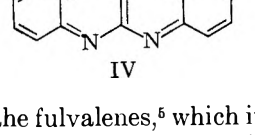
Benzimidazole (I) has been converted into $\Delta^{2,2'}$-biisobenzimidazolylidene (II), a nitrogen analog of the unknown 2,2′-biisoindene,[1,2] a dibenzofulvalene. Oxidation of I by potassium permanganate[3] or potassium dichromate[4] is known to produce imidazole-4,5-dicarboxylic acid. Prolonged oxidation of I by lead dioxide in refluxing benzene produces II, if azeotropic drying is carried out simultaneously. This reaction is slow and inefficient and the same product can be prepared more efficiently by oxidation of 2,2′-bibenzimidazole (III) under the same conditions. In this case the reaction is complete in twenty-four hours.



II



III



IV

In contrast to the fulvalenes,[5] which it resembles in its planarity and molecular structure, II is stable to heat.

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It sublimes with decomposition above 200°. It is unaffected by cold dilute alkali, but it is destroyed by hot alkali or cold dilute mineral acid. From the products of reaction with mineral acid, III can be isolated in small yield. II does not form a maleic anhydride adduct.

Structure II is indicated by the satisfactory elemental analyses and molecular weight and by absorption and p.m.r. spectroscopy. Because of the symmetry of the molecule the infrared spectrum of II is simple. In chloroform it consists of five sharp peaks assignable as follows[6]: 3050 cm.$^{-1}$ (C—H, aromatic or *cis*-vinyl), 1516 cm.$^{-1}$, 1455 cm.$^{-1}$, 1395 cm.$^{-1}$ (C—C or C—N), 1100 cm.$^{-1}$ (C—H in-plane deformation). In a potassium bromide mull three additional peaks at 768 cm.$^{-1}$, 760 cm.$^{-1}$ (very intense), and 728 cm.$^{-1}$ are observed which can be assigned to C—H out-of-plane deformation. The N—H region shows no absorption.

The p.m.r. spectrum[7] of II in deuteriochloroform (80 mg./ml.) shows only a symmetrical multiplet centered at 1.72 τ. This multiplet is of the A_2B_2 type[8] and is consistent with a structure having two pairs of equivalent protons on either end of the molecule. A very similar spectrum has been observed for naphthalene[9] which has a similar arrangement of protons.

The possibility exists that the product from oxidation of I or III is quinoxalino[2,3-*b*]quinoxaline (IV), which would be expected to have a similar infrared and p.m.r. spectrum to that described for II. However comparison of the absorption spectrum of IV in the visible and ultraviolet[10] with that of II shows that II and IV are not the same. Although both compounds are red, II in carbon tetrachloride shows an intense maximum at 409 mμ with subsidiary maxima at 386 mμ, 397 mμ, and 462 mμ, while IV shows strong maxima at 395 mμ, 410 mμ, 420 mμ and, in contrast to II, strong absorption even at 600 mμ. Furthermore reduction of II to III was carried out in good yield with hydrazine and Raney nickel.

Gieseman[11] has presented evidence that isomerization of 1-tritylimidazoles to 2-tritylimidazoles proceeds by rearrangement of a 1-radical to a 2-radical after dissociation of the trityl group from the molecule. By analogy to this it is tentatively proposed that II is produced by initial formation of a 1-benzimidazolyl radical that isomerizes to a 2-benzimidazolyl radical by a 1,2-shift. Dimerization to III followed by oxidation produces a diradical that isomerizes to II. Formation of 1,1′-bibenzimidazole is a possibility, though attempts to prepare it by treatment of silver benzimidazole with iodine in dry benzene at room temperature gave only III in poor yield. This indicates that dimerization is slow compared to the 1,2-shift.

Experimental[12]

2,2′-Bibenzimidazole (III).—This was prepared as described[13] except that diglyme was substituted for ethylene glycol. Recrystallization from aqueous diethylene glycol gave a yellow powder, m.p. >350°.

III was also prepared as follows: a solution of 5.4 g. (0.05 mole) of *o*-phenylenediamine and 3.0 g. (0.025 mole) of dithiooxamide in 150 ml. of ethanol was refluxed until the red color disappeared. The mixture was diluted to 300 ml. with water and the precipitate was crystallized from aqueous diethylene glycol to give 5.0 g. (91%) of III, m.p. >350°. λ_{max}^{EtOH} (log ϵ): 240 mμ (4.28), 251 mμ (4.18), 316 mμ (4.42), 325 mμ (4.51), 342 mμ (4.43), 380 mμ (3.28), 400 mμ (3.41), 421 mμ (3.45), 448 mμ (3.15). The product was identical to that from the previous preparation as shown by comparison of the infrared spectra (potassium bromide).

Anal. Calcd. for $C_{14}H_{10}N_4$: N, 23.92. Found: N, 23.80.

$\Delta^{2,2'}$-Biisobenzimidazolylidene (II). A.—A mixture of 3.2 g. (0.025 mole) of I and 10 g. of lead dioxide[14] in 100 ml. of benzene was refluxed for 240 hr.; water produced was removed continuously by azeotropic drying. The mixture was filtered while hot and cooled. Unchanged I that crystallized was removed by filtration. The filtrate was concentrated to 25 ml., cooled, and filtered again. This filtrate was shaken with a 2% aqueous solution of silver nitrate adjusted to pH 9 with ammonia. The mixture was filtered and benzene layer of filtrate dried (magnesium sulfate) and evaporated to dryness *in vacuo*. The red residue was crystallized twice from carbon tetrachloride to give 0.26 g. (8.5%) of crimson needles, which decompose above 200° with sublimation to a green solid. The infrared spectrum (chloroform) of the crimson needles was superimposable on that of the product obtained subsequently.

B.—A suspension of 15 g. of lead dioxide[14] and 2.0 g. (0.0085 mole) of III in 100 ml. of benzene was refluxed for 24 hr.; the water produced was removed continuously by azeotropic distillation. The mixture was filtered hot and the filtrate and benzene washings of the residue were combined and concentrated to 10 ml. Cooling overnight resulted in the separation of 1.3 g. (65%) of crimson needles which decomposed above 200° with sublimation to a green solid. $\nu_{max}^{CHCl_3}$: 3050 cm.$^{-1}$, 1516 cm.$^{-1}$, 1455 cm.$^{-1}$, 1395 cm.$^{-1}$, 1100 cm.$^{-1}$ (all sharp). λ_{max}^{EtOH} (log ϵ): 262 mμ (4.93). $\lambda_{max}^{CCl_4}$ (log ϵ): 386 mμ (4.33), 399 mμ (4.30) shoulder, 409 mμ (4.66), 435 mμ (3.83), 462 mμ (3.53).

Anal. Calcd. for $C_{14}H_8N_4$: C, 72.40; H, 3.45; N, 24.15; mol. wt., 232. Found: C, 72.51; H, 3.73; N, 23.92; mol. wt., 227, 239 (cryoscopic in benzene).

Reduction of II to III.—A solution of 0.36 g. (0.00155 mole) of II in 50 ml. of ethanol was treated with a few drops of hydrazine hydrate and 0.19 g. of Raney nickel. The mixture was stored at 40° overnight, heated to reflux, and filtered hot. The filtrate was diluted with 50 ml. of water and III separated as a yellow powde, 0.28 g. (78%). The infrared spectrum (potassium bromide) of this material was superimposable on that of the authentic material.

Reaction of Silver Benzimidazole with Iodine.—A stirred suspension of 5.0 g. (0.022 mole) of silver benzimidazole[15] in 150 ml. of dry benzene at room temperature was treated with a solution of 2.53 g. (0.02 mole) of iodine in 50 ml. of dry benzene, which was added dropwise with stirring. Care was taken to exclude atmospheric moisture. Decolorization was slow. When the addition was complete the mixture was stirred for 2 hr. longer and filtered. On evaporation the filtrate gave 0.16 g. of I, m.p. 168–170°. The residue was washed with ethanol and then extracted in a Soxhlet with ethylene glycol for 4 hr. Dilution of the extract with water gave III, 0.65 g. (27%), as a yellow powder. Its infrared spectrum (potassium bromide) was superimposable on that of the authentic material.

Acknowledgment.—Thanks are due to Dr. J. L. Kice of Oregon State University for the p.m.r. spectrum and to the Research Committee of Hobart and William Smith Colleges for a grant-in-aid.

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A Study of Solvent Effects in the Reactions of Methylene[1,2]

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Only slight differences have been reported in relative rates of carbon–hydrogen bond insertion by methylene generated photochemically from diazomethane in the vapor and liquid phase,[4a] although methylene generated by ketene photolysis in the vapor phase is considerably more selective.[4b] In order to ascertain the influence of solvents on the reactions of methylene, diazomethane has been photolyzed in a variety of solvent mixtures. The effect of benzene on the relative rates of the carbon–hydrogen bond insertion in 2,3-dimethylbutane (Table I) and the effect of various solvents on the reaction of methylene with benzene have been determined (Table II).

TABLE I

METHYLATION OF 2,3-DIMETHYLBUTANE IN THE PRESENCE OF BENZENE AT 25°

Benzene concn., *M*	2,3-DMP/-2,2,3-TMB[a]	k_p/k_t[b]
0.00	4.8 ± 0.4	0.81 ± 0.07
1.97	5.1 ± 0.1	0.85 ± 0.02
3.93	5.1 ± 0.1	0.85 ± 0.02
	Av. 5.0	0.835[c]

[a] Ratio of 2,3-dimethylpentane and 2,2,3-trimethylbutane in the reaction product. [b] Relative reactivity of the primary and tertiary hydrogen atoms. [c] Doering, *et al.*, ref. 4a, reported a value of 0.815.

TABLE II

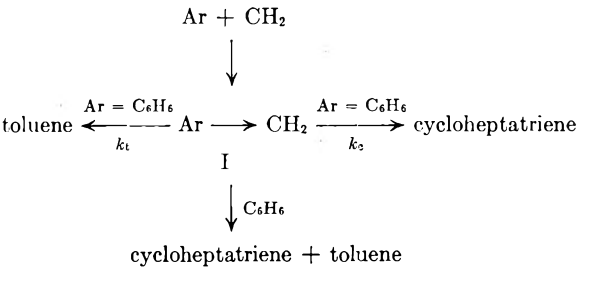
REACTION OF BENZENE WITH METHYLENE

Solvent, concn.	Benzene concn., *M*	Temp.	CHT/-toluene[a]
t-Butylnaphthalene, 4.3 *M*	2.0	25	7.0 ± 0.2
Benzene	11.4	25	4.8 ± 0.4
t-Butylbenzene, 4 *M*[b]	2.0	25	4.4 ± 0.3
Chlorobenzene, 4 *M*[c]	2.0	25	3.6 ± 0.4
2,3-Dimethylbutane, 3.6 *M*	5.9	25	4.2 ± 0.02[e]
2,3-Dimethylbutane, 4.9	4.0	25	4.0 ± 0.02[e]
2,3-Dimethylbutane, 6.1 *M*	2.2	25	3.8 ± 0.2
Cyclohexane, 7.5 *M*	2.0	25	3.7 ± 0.2
Vapor phase	[d]	155	3.3 ± 0.2
Vapor phase	[d]	180	3.1 ± 0.2
Vapor phase	[d]	200	3.3 ± 0.2
Vapor phase	Av.		3.2 ± 0.1[e]

[a] Ratio of cycloheptatriene and toluene in reaction product. [b] 2,3-Dimethylbutane (3.6 *M*) used as a cosolvent. [c] 2,3-Dimethylbutane (3.2 *M*) used as a cosolvent. [d] Approximately 500 mm. of benzene and 250 mm. of nitrogen. [e] Standard deviation.

Benzene as well as a variety of other aromatic substances tested, did not appear to have any effect on the relative rates (1° *vs.* 3°) of the insertion reaction with 2,3-dimethylbutane. The low selectivity (tertiary/primary = 1/0.835) is consistent with an indiscriminate methylene[4a,5] not deactivated by the presence of benzene. In addition, the relative reactivity of benzene and 2,3-dimethylbutane is independent of the benzene concentration. The experiments listed in lines 5 and 7 of Table II indicated that, in 5.9 *M* benzene, 2,3-dimethylbutane was (0.58 ± 0.06)*z* as reactive as benzene, whereas in the presence of 2.2 *M* benzene the relative reactivities were (0.56 ± 0.03)*z* where *z* is a correction factor for conversion of the area ratio of cycloheptatriene and 2,2,3-trimethylbutane in a gas chromatograph into the mole ratios.

Various solvents had an effect on the relative amounts of cycloheptatriene and toluene formed in the reaction with benzene.[6] The ability of solvents to increase the yield of cycloheptatriene relative to toluene (Table II) roughly parallels the ability of these solvents to affect the selectivity of the chlorine atoms.[7] The change in selectivity of the chlorine atom has been shown to be due to the formation of π-complexes with the aromatic solvent and to be proportional to the basicity and concentration of the aromatic molecule. A similar interaction of methylene with aromatic compounds to form a π-complex seems likely since carbenes are electron deficient. Thus, a possible explanation of the observed solvent effect is that an initially formed methylene–aromatic complex (I), where Ar is benzene or some other aromatic, can react with another molecule of benzene to yield cycloheptatriene or at least yield a higher ratio of cycloheptatriene to toluene than the unimolecular decomposition of I when Ar is benzene. An alternate explanation might be that aromatic solvents somehow influence the ratio of k_c/k_t for the decomposition of I with Ar = benzene.



Methylene produced photolytically from diazomethane is known to possess excess electronic[8] as well

(1) Part VII. Solvent Effects in the Reactions of Free Radicals and Atoms. For Part VI see *Tetrahedron*, **8**, 101 (1960).

(2) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of the Petroleum Research Fund.

(3) Alfred P. Sloan Foundation Fellow.

(4) (a) W. E. Doering, R. G. Buttery, R. G. Laughlin, and N. Chandburi, *J. Am. Chem. Soc.*, **78**, 3224 (1956); H. M. Frey, *ibid.*, **80**, 5005 (1958). (b) J. H. Knox and A. F. Trotman-Dickenson, *Chem. Ind.* (London), 731 (1957); H. M. Frey and G. B. Kistiakowsky, *J. Am. Chem. Soc.*, **79**, 6373 (1957).

(5) D. B. Richardson, M. C. Simmons, and I. Dvoretzky, *ibid.*, **82**, 5001 (1960); **83**, 1934 (1961).

(6) Doering and Knox [W. E. Doering and L. H. Knox, *ibid.*, **75**, 297 (1953)] report a ratio of cycloheptatriene to toluene (by distillation) of 32/9 from liquid phase ultraviolet photolysis while Lemmon and Strohmeier [(R. M. Lemmon and W. Strohmeier, *ibid.*, **81**, 106 (1959)] report a ratio of 3.5 (distillation) at 20° from liquid phase photolysis with sunlight or ultraviolet radiation.

(7) G. A. Russell, *ibid.*, **80**, 4987 (1958).

(8) H. M. Frey, *ibid.*, **82**, 5947 (1960); F. A. L. Anet, R. F. W. Bader, and A.-M. Auwera, *ibid.*, **82**, 3217 (1960); G. Hertzberg and J. Shoosmith, *Nature*, **183**, 1801 (1959).

as excess kinetic and vibrational energy.[9] The effect of aromatic solvents on the ratio of cycloheptatriene and toluene formed from benzene cannot be readily explained by the loss of this excess energy to the solvent since (1) this ratio is temperature independent in the vapor phase, and (2) solvents that affect this ratio do not affect the selectivity of the insertion reaction in 2,3-dimethylbutane or the relative reactivity of benzene and 2,3-dimethylbutane toward methylene. The latter observations also rules out a reversible formation of I, since such a process would be expected to affect the energy and hence the selectivity of methylene.

The fact that solvents affect the cycloheptatriene/-toluene ratio but not the relative reactivity of 2,3-dimethylbutane and benzene clearly indicates that there is some irreversibly formed intermediate in the reaction between benzene and methylene and would appear to exclude the formation of cycloheptatriene and toluene from two different electronic states of methylene. The present results add little to the question of the possible intermediacy of norcaradiene in the reactions of benzene and methylene.[10] Of course, complex I could be interpreted as being a norcaradiene. Careful investigation by gas–liquid chromatography of the reaction products did not give evidence for any initially formed C_7 hydrocarbons other than toluene and cycloheptatriene. Moreover, the ratio of areas of peaks attributed to cycloheptatriene and toluene did not change during reaction, after reaction, or upon heating. This result indicates that one of the peaks was not partially norcaradiene. If all toluene and cycloheptatriene are formed *via* an isomerization of a norcaradiene intermediate, the liquid phase results might be explained by postulating a different ratio of products from an energy rich norcaradiene (I) and a low energy norcaradiene formed from the transfer of methylene from I to another molecule of benzene.

The ratio of cycloheptatriene to toluene formed in the vapor phase from the pyrolysis of diazomethane in the presence of benzene agrees closely with the ratio observed for photolysis experiments in cyclohexane solution. These results are in agreement with the conclusion that methylene generated either photochemically or pyrolytically from diazomethane is initially in the singlet state,[11] as evidenced by similar selectivities in a number of insertion reactions.[12]

Experimental

Diazomethane was generated in a 125-ml. distillation flask fitted with a small addition funnel and modified with a nitrogen inlet tube which extended to the bottom of flask. Immediate formation of diazomethane occurred upon the dropwise addition of *ca.* 1 *M* N-methyl-N-nitroso-*p*-toluenesulfonamide in carbitol solution to 50 ml. of 50% aqueous potassium hydroxide which has been preheated to about 55°. As the diazomethane was formed it was carried by nitrogen to the reaction vessel through the side arm of the distillation flask and through a second inlet tube that extended to the bottom of the reaction vessel. The reaction vessel was constructed from a quartz tube 1.2 × 8 cm. and had a test tube bottom and a ground glass joint at the top for connection of the vessel to a condenser. The second inlet tube and the condenser were of one construction so the inlet tube entered the reaction vessel through the center of the glass joint. The system was swept with nitrogen prior to each experiment to remove oxygen. Generally a ratio of nitroso compound to substrate of 1 to 5 was employed. After the diazomethane was generated and almost completely transferred to the reaction vessel, irradiation with a General Electric UA-2 lamp was begun with both the reaction vessel and the lamp immersed in a water bath. The irradiation was continued until the color of the diazomethane had disappeared. Generally about an hour was required except when large amounts of aromatic compounds were employed as solvents. Control experiments indicated that the cycloheptatriene/toluene ratio did not change with irradiation over the period of time required for photolysis of diazomethane. However, other control experiments indicated that these ratios were not reproducible when oxygen was present, the presence of oxygen always resulting in the destruction of some cycloheptatriene.

Prolonged irradiation destroys cycloheptatriene as does exposure to air in the absence of light. Table III gives the cycloheptatriene to toluene ratios observed as a function of irradiation time in experiments in which the diazomethane generated from 10 mmoles of the nitroso compound was added to 90 mmoles of benzene.

TABLE III

EFFECT OF IRRADIATION TIME ON CYCLOHEPTATRIENE/TOLUENE RATIO

Time, (hours)	CHT/-toluene
1.0[a]	4.68 ± 0.06
2.0	4.67 ± 0.03
6.0[b]	4.34 ± 0.12[c]
6[d]	4.56
12[d]	4.57

[a] The diazomethane was consumed during the first hour of reaction. [b] Unknown substance having a retention time 0.74 that of toluene detected. [c] Area ratio (CHT + unknown)/toluene = 4.58. [d] Irradiation stopped after 1 hr.

The product of photochemical decomposition of cycloheptatriene was not investigated but was probably the $\Delta^{2,6}$-bicyclo[3.2.0]heptadiene.[13] Experiments using sunlight or illumination from a tungsten filament to decompose the diazomethane in benzene solution gave the same cycloheptatriene/toluene ratios (5.0 ± 0.2 *vs.* 4.8 ± 0.4). Under the conditions employed the yield of cycloheptatriene and toluene was in the range of 10% based on the nitroso compound or 2% based on benzene. The yield varied with the nature of the cosolvent.

The vapor phase reactions were carried out in a Pyrex tube 1.7 × 35 cm. The heated portion of the tube was 25 cm. in length. The diazomethane was generated in the same apparatus as used previously. Benzene was allowed to enter the reaction tube as the vapor from boiling benzene and the reaction products collected in a 0° trap. A control experiment showed that the cycloheptatriene/toluene ratio did not change under the conditions of the reaction.

In all cases gas–liquid chromatography was used for the analysis of the reaction products. Correction factors were determined to convert product area ratios obtained in the analysis to molar ratios. Since control experiments showed that passing a benzene solution of diazomethane through the gas–liquid chromatography unit gave cycloheptatriene and toluene, presumably by a metal-catalyzed reaction, all unchanged diazomethane was removed by degassing or destroyed by phenol before analysis. Gas–liquid chromatography was performed at 85° with a flow rate of 75 ml. of helium per minute. A 0.25 in. × 6 ft. squalene column in series with a 0.25 in. × 6 ft. methylsilicone grease column gave relative retention times of benzene, 0.40; toluene, 0.85; and cycloheptatriene, 1.0 (6.3 min.).

Phillips 99 mole % 2,3-dimethylbutane was redistilled before use. 2,3-Dimethylpentane and 2,2,3-trimethylpentane were obtained from the National Bureau of Standards. Cycloheptatriene was prepared from norbornadiene by pyrolysis.[14]

(9) H. M. Frey, *Proc. Roy. Soc.* (London), **250A**, 409 (1959); **251A**, 575 (1960).

(10) See, for example, H. Meerwein, H. Disselnkötter, F. Rappen, H. Rintelen, and H. Vloed, *Ann.*, **604**, 151 (1957).

(11) P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **78**, 4496 (1956); R. C. Woodworth and P. S. Skell, *ibid.*, **81**, 3383 (1959).

(12) B. S. Rabinovitch and D. W. Setser, *ibid.*, **83**, 750 (1961); K. R. Kopecky, G. S. Hammond, and P. A. Leermakers, *ibid.*, **84**, 1015 (1962).

(13) W. G. Dauben and R. L. Cargill, *Tetrahedron*, **12**, 186 (1961).

(14) W. G. Woods, *J. Org. Chem.*, **23**, 110 (1958).

The Reaction of ϵ-Caprolactone with Inorganic Cyanide

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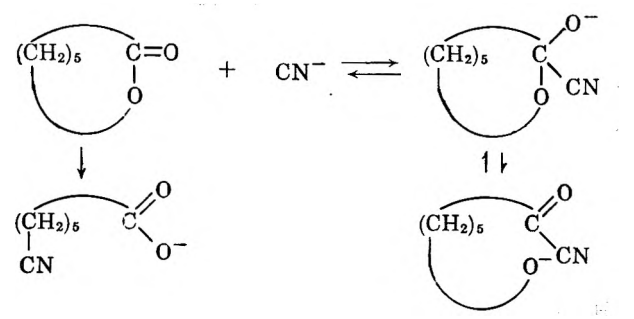
The reaction of γ-lactones with inorganic cyanides to give cyano acids apparently was first studied by Wislicenus[2,3] and Blaise,[4] and Blanc[5] applied the reaction in structure determinations. More recently a patent[6a] and publication[6b] described improvements in the reaction as applied to γ-butyrolactone and Price[7] has used it in a synthetic sequence. Reppe[8] found that the reaction could be extended to δ-valerolactone to give 5-cyanovaleric acid. It was of interest to see if the reaction might be extended to the next higher homolog, the seven-membered ring lactone, ϵ-caprolactone.

When the reaction of dry powdered potassium cyanide with ϵ-caprolactone was carried out at a temperature of 240–280°, a 95% yield of poly-ϵ-caprolactone was obtained and 95% of the potassium cyanide was recovered. However at 300° a rapid exothermic reaction, accompanied by decomposition, gave potassium 6-cyanohexanoate, isolated as its ethyl ester. The proof of structure was based on the hydrolysis of the cyano acid ester to pimelic acid, which was identical with an authentic sample. The yield in the ϵ-caprolactone–potassium cyanide reaction varied from 49–71% depending on the maximum temperature reached and the time the mixture was heated after the reaction began.[9]

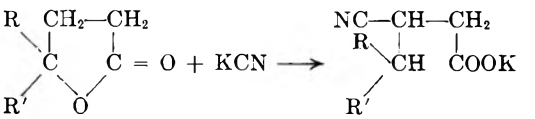
Since the possibility existed that the reaction was taking place between the inorganic cyanide and the linear (or macrocyclic) polyester, the reaction was investigated with an aliphatic ester. Indeed when the reaction of potassium cyanide and *n*-butyl stearate (used because of its high boiling point) was carried out at 350°, valeronitrile was obtained, identical with an authentic sample. It seems unusual that no reaction was observed with potassium cyanide and benzyl benzoate under the same conditions in view of the results of Wislicenus[3] with phthalide. However, Koelsch[10] previously had observed that γ-phenyl-γ-butyrolactone did not react at 250°.

The reaction is possibly best explained in terms of a competition between a reversible reaction of the cyanide ion at the carbonyl group and an irreversible,



probably much slower, nucleophilic attack of cyanide on the alkyl carbon of the ester.[11]

It is worth remarking that γ,γ-dimethyl-γ-butyrolactone (I)[4] and γ-*p*-anisyl-γ-butyrolactone (II)[7] give rearranged β-cyano acids.



I, R = R′ = CH_3
II, R = *p*-$CH_3OC_6H_4$; R′ = H

Presumably β,γ-unsaturated acids are formed by pyrolysis of these tertiary and benzylic esters and undergo rearrangement to α,β-unsaturated acids to which the cyanide then adds. There was, however, no evidence of the formation of other isomeric cyanohexanoic acids of unsaturated acids from ϵ-caprolactone.

Experimental[12]

Ethyl 6-Cyanohexanoate.—A mixture of 5.7 g. (0.05 mole) of ϵ-caprolactone and 3.26 g. (0.05 mole) of dry, powdered potassium cyanide was heated in a test tube in a nitrogen atmosphere initially at 210°. During a period of 22 min. the temperature was raised to 287°. The lactone refluxed for a short period at 258° and then the mixture became quite viscous. A plot of pot temperature *vs.* bath temperature showed little deviation from a constant difference. After cooling the reaction mixture was treated with 50 ml. of acetone and the insoluble salt removed by filtration. The salt was shown to be potassium cyanide by formation of a white precipitate with silver nitrate and by giving a potassium color in the flame test. The isolation of 3.01 g. represented a recovery of 95.3%. The acetone filtrate was evaporated and heated at 80° at 3-mm. pressure for 3 hr. to give 5.17 g. of a brittle yellow-tan solid, m.p. *ca.* 60°. This poly-ϵ-caprolactone sample gave an infrared spectrum identical with an authentic sample of the polyester prepared by the thermal polymerization of ϵ-caprolactone.

When the reaction of ϵ-caprolactone (0.30 mole) and potassium cyanide (0.3 mole) was repeated at an even higher temperature, an exothermic reaction set in at 296° which continued for 4 min. The total heating time was 41 min. and the final temperature of reaction mixture 314°. The cooled residue was treated with 20 ml. of concentrated sulfuric acid in 200 ml. of absolute ethanol and the precipitated potassium sulfate removed by filtration. An additional 200 ml. of absolute ethanol and 200 ml. of benzene were added to the filtrate and the resulting solution was refluxed for 10 hr. The reaction mixture was treated with potassium bicarbonate to neutralize the sulfuric acid and filtered to remove the solid potassium sulfate. The filtrate was stripped of solvent

(1) To whom inquiries should be addressed.
(2) W. Wislicenus, *Ber.*, **18**, 172 (1885).
(3) W. Wislicenus, *Ann.*, **233**, 101 (1886).
(4) E. Blaise, *Compt. rend.*, **124**, 89 (1897); *Bull. soc. chim. France*, (3) **29**, 335 (1903).
(5) G. Blanc, *ibid.*, (3) **33**, 886, 904 (1905).
(6a) German Patent 707,853 (1941); (b) J. W. Reppe, *Ann.*, **596**, 158 (1955).
(7) C. C. Price and W. Kaplan, *J. Am. Chem. Soc.*, **66**, 477 (1944).
(8) J. W. Reppe, *Ann.*, **596**, 80 (1955).
(9) These conditions are probably not yet optimal because the high temperature accentuates their importance. The use of a suitable solvent offers an attractive possibility of improving the yield. Reaction conditions are somewhat milder for γ-butyrolactone and δ-valerolactone, which react at about 200°[6b] and 230°[8], respectively.
(10) C. F. Koelsch, *J. Am. Chem. Soc.*, **65**, 2093 (1943).
(11) A similar mechanistic path is probably involved in the reaction of methoxide ion with methyl benzoate [J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Am. Chem. Soc.*, **72**, 2378 (1950)] to give dimethyl ether in 74% yield. Here the fast reversible reaction regenerates the starting materials, hence the only product possible is that derived from the slower irreversible reaction. This paper discusses additional reactions of this type. In the case of caprolactone it is possible that the reaction could proceed through the monomeric lactone, despite the fact that polymerization precedes the reaction which would form the cyano acid. A small amount of the monomeric lactone in reversible equilibrium with the polymer could give rise to the observed result.
(12) All melting points and boiling points are uncorrected.

and flash distilled to give 37.17 g. of crude product, b.p. 82–103° at 0.8–1.7 mm. Distillation through a Podbielniak column with 13 in. of "Heli-pak" packing gave 3.73 g. of pure ethyl 6-cyanohexanoate, b.p. 99–100° at 1.3 mm., $n^{35}D$ 1.4292. The column holdup, 4.57 g., was 98% pure cyano ester and these two fractions represent a 16% yield. Other fractions contained considerable amounts of the cyano ester.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 64.13; H, 8.54; N, 8.26.

A more effective method of separating the hydroxy ester from the cyano ester was found to be chromatography on alumina. Thirty grams of a mixture of the hydroxy ester and cyano ester (64% cyano ester by infrared analysis[13]) in 100 ml. of benzene was passed over a 1 × 12 in. column of wet packed chromatographic alumina (Fisher 80–200 mesh) and eluted with benzene. Five 200-ml. fractions were collected. The first fraction gave 16.9 g. of ethyl 6-cyanohexanoate after evaporation of the benzene. Infrared analysis of the material showed it to be 90% pure cyano ester with trace impurities of benzene and the hydroxy ester. The other four fractions from the elution with benzene gave a total of 7.55 g. of residues which were mixtures of the hydroxy ester and the cyano ester. Elution of the column with 200 ml. of formula 30 ethanol gave an additional 6 g. of material, which by infrared analysis was shown to contain a maximum of 9% of the cyano ester and was predominately the hydroxy ester (some ethanol was present in the sample).

One gram (5.96 mmoles) of ethyl 6-cyanohexanoate was refluxed with 3 g. (54 mmoles) of potassium hydroxide in 15 ml. of water for 4.25 hr. The cooled hydrolysate was neutralized to pH 2 with concentrated hydrochloric acid and saturated with salt. The white solid which separated was filtered and the aqueous solution was extracted with three 30-ml. portions of ether. The residue from the evaporation of the ether was combined with the solid and recrystallized from benzene to give 0.3 g. of pimelic acid, m.p. 104.5–106.5°. A mixture melting point with authentic sample of pimelic acid, m.p. 105–106°, gave no depression.

Valeronitrile.—A mixture of 6.51 g. (0.1 mole) of dry, powdered potassium cyanide and 34.1 g. (0.1 mole) of *n*-butyl stearate in a 250-ml. reaction flask equipped with a stirrer, thermometer, nitrogen inlet, and side arm for distillation was heated by means of a Woods metal bath (at 260° initially) to 350° during 40 min. During the next 8 min. a liquid distilled from the reaction flask. Thirty-four minutes additional heating up to 397° yielded little more distillate. Infrared analysis showed the nitrile to be contaminated with alcohol. Redistillation of the distillate, 6.2 g., yielded 1.63 g. (19.7%) of valeronitrile, b.p. 139.8–140°, $n^{35}D$ 1.3908. The infrared spectrum of the product was identical with an authentic sample of valeronitrile (Eastman Kodak White Label).

(13) Infrared analyses were performed by H. J. Sloane and R. A. Nyquist.

Steroids. LXX.[1,2] The Preparation of Some Pentacyclic Steroid Derivatives

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Received January 4, 1963

A recent report[1b] from this laboratory describes the base-catalyzed condensation of acetone with steroidal Δ^{16}-20-ketones to produce pentacyclic products containing a 16,17-butanoandrostane ring system. We describe here an alternate approach to this class of compounds employing a Diels–Alder reaction[3] for the ring forming step.

3β,20-Diacetoxy-pregna-5,16,20-triene (I),[4] prepared by enol acetylation of 16-dehydropregnenolone acetate, reacted readily with dimethyl acetylene dicarboxylate to yield a mixture of epimeric (at C-16) adducts from which the major component, m.p. 197–198°, could be isolated by crystallization in 40–50% yield. The infrared spectrum of this compound contained bands at 1760 (enol acetate), 1730–1740 (esters), and 1640 cm.$^{-1}$ (olefin). These results as well as the elemental analysis, n.m.r. spectrum (see Experimental), and mode of formation are in agreement with structure II for the adduct; the 16β-II configuration proposed for the ring juncture is based solely on the known preference for 16α- attack shown by other addition reactions[5] of 16-dehydro steroids.

Dehydrogenation of the new cyclohexadiene ring of the adduct II was accomplished in 69% yield[6] by treatment with chloranil[7] in refluxing chlorobenzene or simply by boiling in nitrobenzene.[7] The aromatic product III could be crystallized from hexane, cyclohexane, or isopropyl alcohol. In each case, the product melted with evolution of gas within the range 120–130°. The crystals from isopropyl alcohol showed weak hydroxyl absorption in the infrared at 3600 cm.$^{-1}$ and gave an elemental analysis which checked well for one-half molecule of isopropyl alcohol of crystallization. Similarly, a n.m.r. spectrum[8] of the product from cyclohexane crystallization included a sharp singlet at 8.57 (6H) indicating a half mole of solvent of crystallization. Another noteworthy feature of this spectrum was evident in the high field methyl resonance region where two sharp singlets (3H each) were found at 8.91 and 8.98, respectively. The latter absorption peak, present also in the spectrum of the adduct II, may be assigned to the C-19 angular methyl group.[9] The C-18 methyl resonance which in most steroids appears at *higher* field[9] must, in this case, be identified with the *lower* field resonance line. This extreme deshielding of the C-18 methyl resonance is presumably caused by the magnetic anisotropy effect of the nearby aromatic ring.[10]

(1) (a) Presented in part at the American Chemical Society Southwest-Southeast Regional Meeting, December 7–9, 1961; (b) Paper LXIX, M. E. Wall, S. Serota, H. Kenney, and G. S. Abernethy, in press.

(2) This work was carried out under contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(3) Maleic anhydride has already been reported to undergo diene addition reactions with 20-methylene-Δ^{16}-pregnenes and with 20-acetoxy-$\Delta^{16,20}$-pregnadiene derivatives; see F. Sondheimer and R. Mechoulam, *J. Org. Chem.*, **24**, 106 (1959), and references therein cited.

(4) R. B. Moffett and D. I. Weisblat, *J. Am. Chem. Soc.*, **74**, 2183 (1952).

(5) (a) D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951); (b) J. Romo, M. Romero, C. Djerassi, and G. Rosenberg, *ibid.*, **73**, 1528 (1951); (c) H. Hirschmann, E. B. Hirschmann, and M. A. Daus, *ibid.*, **74**, 539 (1952); (d) D. Gould, F. Gruen, and E. B. Hershberg, *ibid.*, **75**, 2510 (1953); (e) G. P. Mueller and B. Riegel, *ibid.*, **76**, 3686 (1954); (f) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *ibid.*, **78**, 3158 (1956); (g) J. Romo, *Tetrahedron*, **3**, 37 (1958); (h) R. H. Mazur and J. H. Cella, *ibid.*, **7**, 130 (1959); (i) P. F. Beal and J. E. Pike, *J. Org. Chem.*, **26**, 3887 (1961).

(6) A reasonable yield of dehydrogenation product was also obtained from the amorphous epimer mixture remaining after crystallization of the adduct II (see Experimental).

(7) L. M. Jackman in "Advances in Organic Chemistry," Vol. II, R. A Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960.

(8) The n.m.r. spectra were taken in methylene chloride solution on a Varian Associates HR-60 spectrometer using tetramethylsilane as an internal standard (τ = 10.0). We thank Wallace Lawrence of the Chemstrand Research Laboratories for running these spectra.

(9) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, Chap. 7.

Treatment of the tetraester III with sodium methoxide in dry methanol resulted in the methanolysis of both acetyl groups and production of the phenolic diester 3-alcohol IV, m.p. 258–261°, in 77% yield. The infrared spectrum contained rather widely separated ester bands at 1720 and 1705 cm.$^{-1}$, respectively, as well as alcohol and phenol hydroxyl absorption. Well defined but different ultraviolet spectra were obtained by measurement in neutral solution ($\lambda_{max}^{CH_3OH}$ 220 and 261 mμ, 27,700 and ε 9650) and in alkaline solution ($\lambda_{max}^{1\ N\ NaOCH_3}$ 244 and 306 mμ, 22,600 and ε 11,000) in agreement with the presence of an ionizable phenolic chromophore.

The dihydroxy diester IV was found to react smoothly under conventional Oppenauer oxidation conditions producing the corresponding conjugated 3-ketone V in 88% yield. The presence of a conjugated ketone in this compound was confirmed by the infrared spectrum (ν_{max}^{Nujol} 1695 cm.$^{-1}$) but was not immediately evident in ultraviolet spectrum ($\lambda_{max}^{CH_3OH}$ 266 mμ, ε 34,500) (Fig. 2). It is apparent, however, that this spectrum represents the absorption contribution of the aromatic chromophore as well as the conjugated ketone chromophore. The absorption component due to the 3-keto-Δ^4 system was roughly assessed by running a "spectrum" of the conjugated ketone V against a solution of the 3-hydroxy compound IV (in identical concentration) as a "blank." This resulted in a symmetrical tracing in the region above 220 mμ (where isolated double bond absorption is negligible; the curve had a maximum at 242 mμ (ε 18,200) as expected for the Δ^4-3-ketone chromophore.

The pentacyclic steroid derivatives reported here have been submitted to the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, for biological evaluation.

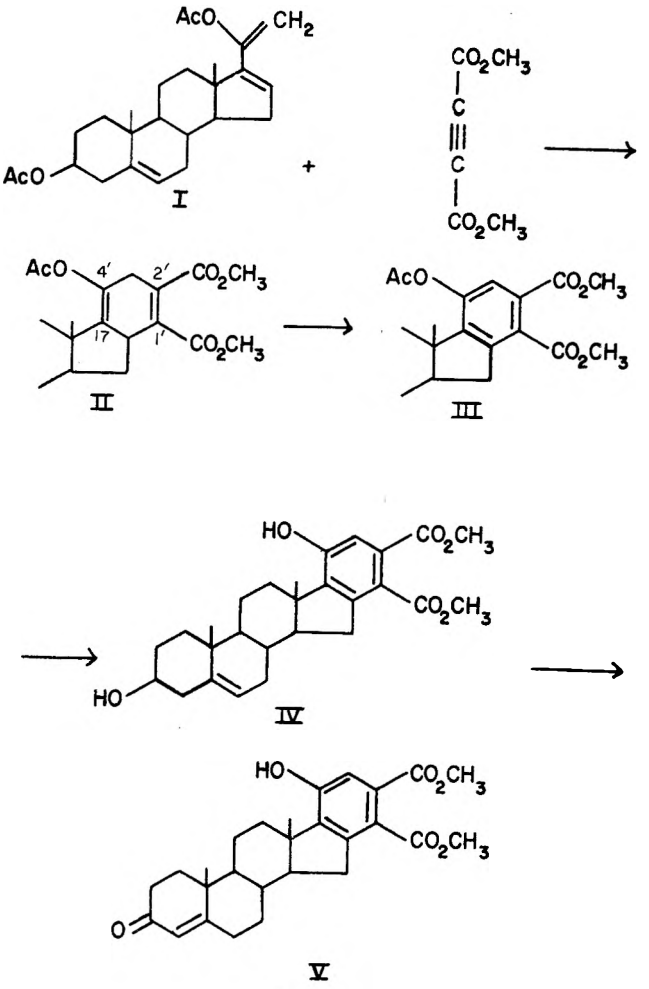

Figure 1

Experimental[11]

3β-20-Diacetoxypregna-5,16,20-triene (I).—The enol acetylation of 3β-acetoxypregna-5,16-dien-20-one was conveniently carried out on a large scale by a modification of Moffett and Weisblat's procedure.[4] A solution of 15 g. of *p*-toluenesulfonic acid monohydrate and 100 g. of the prior ketone in 2 l. of redistilled isopropenyl acetate was heated so as to cause slow distillation of solvent through an insulated Claisen head. Removal of acetone formed in the reaction was facilitated by passing a very slow stream of dry nitrogen through the system. The nitrogen flow was stopped after 6 hr., by which time 150 ml. of solvent had been collected and the temperature of the reaction mixture reached 100°. Slow distillation was continued for a final period of 1.5 hr. The acid catalyst was then neutralized by adding 8.0 ml. of pyridine, with swirling, to the cooled reaction mixture. Precipitated salt was removed by filtration through Celite. Evaporation of solvent at reduced pressure left a partly crystalline residue which was triturated with warm heptane and again freed of solvent. The resulting crystalline solid was dissolved in a minimum volume of benzene and passed slowly through a column containing 200 g. of Florisil. The early eluates (devoid of starting material by infrared determination) were freed of solvent and the solid residue was then recrystallized from methylene chloride–heptane, giving 74.3 g. (66%) of the enol acetate as colorless prisms, m.p. 137–142°. Further recrystallization from methylene chloride–methanol raised the m.p. to 143–145° without causing any change in the infrared spectrum; Moffett and Weisblat report m.p. 144–146° for this compound.[4]

Dimethyl 3β,4'-Dihydroxy-16α-(16,17-butanoandrosta-1',4',5-triene)-1',2'-dicarboxylate Diacetate[11] (II).—A solution of 8.50 g. (0.059 mole) of dimethylacetylene dicarboxylate and 23.23 g. (0.0583 mole) of 3β,20-diacetoxypregna-5,16,20-triene (I) in 350 ml. of dry benzene was heated under reflux for 16 hr. Removal of solvent at reduced pressure and crystallization of the residue from methanol gave 13.60 g. (43%) of the adduct II, m.p. 193–196°. An analytical sample, prepared by further crystallization from the same solvent, had m.p. 197–198°, $[\alpha]_D$ −85°; ν_{max} 1730–1740 (3-acetate and methyl esters), 1760 (enol acetate), and 1640 cm.$^{-1}$ (olefin). The n.m.r. spectrum showed singlet methyl resonances at 9.05 (C_{13}-CH_3), 8.96 (C_{16}-CH_3), 8.00 (C_2-OAc), 7.87 (C_4'-OAc), and 6.29 and 6.24 τ (methyl esters).

Anal. Calcd. for $C_{31}H_{40}O_8$: C, 68.86; H, 7.68. Found: C, 68.60; H, 7.45.

By concentrating original methanolic mother liquors, an additional crystalline but wide melting fraction (5.80 g., 18%, m.p. approx. 180–190°) could be obtained. This material, as well as the final amorphous residue (12.05 g.), gave an infrared spectrum which was nearly identical with that of the pure isomer (m.p. 197–198°) except in the region 1130–1150 cm.$^{-1}$.

Dimethyl 3β,4'-Dihydroxy-(16,17-butanoandrosta-1',3',5,16-tetraene)-1',2'-dicarboxylate Diacetate (III). A. Nitrobenzene Method.—A 5.9-g. sample of the adduct II, dissolved in 50 ml. of nitrobenzene, was heated to boiling and slowly distilled for 35 min. Most of the solvent was then removed at reduced pressure and below 55° using a rotary evaporator. The viscous, colored residue was dissolved in methylcyclohexane and adsorbed onto a column containing 100 g. of Florisil and prepared in the same solvent. The column was washed with 10% benzene in methylcyclohexane (200 ml.) and 20% benzene in methylcyclohexane (150 ml.) until elution of residual nitrobenzene was nearly complete. The reaction product was then eluted with benzene (500 ml.) and 10% ether in benzene (300 ml.). Crystallization from cyclohexane gave 4.44 g. (69%) of the aromatization product III, m.p. 120–125°, with evolution of gas. The n.m.r. spectrum included an intense, sharp singlet at 8.57 (C_4'-OAc) and 6.15 τ

(11) Melting points were obtained using a Kofler hot stage and are uncorrected. Optical rotations were measured at 25° in chloroform and infrared spectra were run in carbon disulfide except where noted. The pentacyclic derivatives are named as in paper LXIX (ref. 1b).

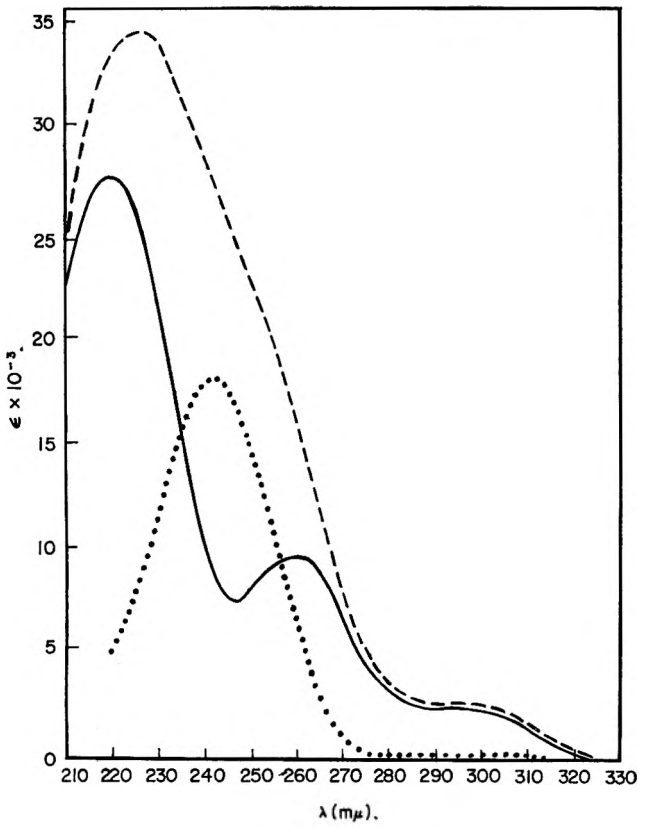

Fig. 2.—Absorption spectra of dimethyl 4′-hydroxy-(16,17-butanoandrosta-1′,3′,4,16-tetraene)-3-one-1′,2′-dicarboxylate (V), – – – –; dimethyl 3β,4′-dihydroxy-(16,17-butanoandrosta-1′,3′,5,16-tetraene)-1′,2′-dicarboxylate (IV), ———; V, run against IV as a "blank", ...

(methyl esters). A sample was recrystallized from isopropyl alcohol giving colorless plates, m.p. 125–130°, with evolution of gas; $[\alpha]_D$ −88°; ν_{max} 1760 (phenolic acetate), 1735–1720 (3-acetate and methyl esters), 1583 (aromatic), and 3600 cm.$^{-1}$ (weak, isopropyl alcohol of crystallization).

Anal. Calcd. for $C_{31}H_{38}O_8 \cdot 0.5\ C_3H_8O$: C, 68.64; H, 7.45. Found: C, 68.77; H, 7.49.

B. Chloranil Method.—The amorphous C-16 epimer mixture remaining after crystallization of adduct II (see preceding) was freed carefully of solvent by conversion to a dry foam and warming *in vacuo*. A 9.80-g. sample of this material and 5.0 g. of chloranil were dissolved in 150 ml. of dry, redistilled chlorobenzene and heated under reflux for 16 hr. Solvent was then removed at reduced pressure; residue was taken up in benzene, washed with saturated aqueous sulfur dioxide, then with cold dilute sodium hydroxide, and finally with water until neutral. Dried (magnesium sulfate) benzene solution was decolorized by passage through 100 g. of Florisil. Benzene eluates were combined, concentrated, and the residue crystallized from isopropyl alcohol, yielding 5.72 g. (56%) of plates, m.p. 124–128° dec., identical with the aromatization product III prepared as described previously.

Dimethyl 3β,4′-Dihydroxy(16,17-butanoandrosta-1′,3′,5,16-tetraene)-1′,2′-dicarboxylate (IV).—The aromatization product III (34.3 g.) was dissolved in 1300 ml. of methanol (freshly distilled from magnesium methoxide) containing sodium methoxide (from 3.57 g. of sodium). The solution was allowed to stand at 25° for 54 hr. under a nitrogen atmosphere. A 10-ml. portion of glacial acetic acid was then added followed by 200 ml. of water. About 1 l. of solvent was then removed at reduced pressure leaving a colorless crystalline sludge. The solid was collected and washed with 50% methanol–water; drying overnight at 50° *in vacuo* gave 21.0 (77%) of phenolic product, m.p. 250–255°. A sample of this material, further purified by two recrystallizations from acetone, had m.p. 258–261°, $[\alpha]_D^{CHCl_3}$ −107°; ν_{max}^{Nujol} 3460 (3-OH), 3150 (phenolic OH), 1720 and 1702 cm.$^{-1}$ (methyl esters); $\lambda\lambda_{max}^{CH_3OH}$ 219 (30,800), 258 (10,300), 294 mμ (inflection, ε 2810); $\lambda\lambda_{max}^{1\ N\ NaOCH_3}$ 244 (22,600), 306 mμ (ε 11,000).

Anal. Calcd. for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.16; H, 7.64.

Dimethyl 4′-Hydroxy-(16,17-butanoandrosta-1′,3′,4,16-tetraene)-3-one-1′2′-dicarboxylate (V).—A solution of 5.0 g. of the 3-alcohol IV and 50 ml. of cyclohexanone in 200 ml. of dry toluene was distilled until about 10 ml. of solvent was collected. A solution of 5.0 g. of aluminum isopropoxide in 50 ml. of toluene was added and the reaction mixture heated under reflux in a nitrogen atmosphere for 2 hr. About 100 ml. of toluene was then removed by distillation. The cooled reaction mixture was treated with ice (*ca.* 100 g.) and 150 ml. of cold 5% hydrochloric acid. The precipitated product was found to be very poorly soluble in the common organic solvents but could be extracted with three 200-ml. portions of 10% isopropyl alcohol in chloroform. The combined organic extracts were washed with dilute sodium bicarbonate, then water, and dried over sodium sulfate. The solution was concentrated, diluted with hot hexane, and the crystalline product collected. The conjugated ketone V (4.40 g., 88%) had m.p. 315–317°. The material was inserted in a Soxhlet thimble and continuously extracted with the solvent mixture toluene–chloroform–isopropyl alcohol (3:1:1); this resulted in recrystallization but caused no change in melting point. The product had $[\alpha]_D^{pyridine}$ −25°; ν_{max}^{Nujol} 1695 (conj. ketone), 1720 and 1730 (ester), and 3350 cm.$^{-1}$ (phenolic OH); $\lambda_{max}^{CH_3OH}$ 224 (35,900), 294 mμ (inflection, ε 2770); $\lambda\lambda\ 1_{max}^{1\ N\ NaOCH_3}$ 244 (38,300), and 306 mμ (ε 11,400). An ultraviolet spectrum of the conjugated ketone V was rerun in methanol using a solution of the 3-hydroxy compound IV (in identical concentration) as a "blank." The resulting tracing showed a single maximum at 241 mμ (ε 15,000).

Anal. Calcd. for $C_{27}H_{32}O_6$: C, 71.66; H, 7.13. Found: C, 71.40; H, 7.19.

Synthesis of Compounds Containing Carbon–Mercury and Carbon–Tin Bonds[1,2]

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Received December 26, 1962

The attempted preparation of compounds containing both carbon–tin and carbon–mercury bonds was reported in 1926.[3] Later investigation of the reaction indicated a stepwise degradation of the aryl or alkyl tin compound by the monosubstituted or inorganic mercury compound.[4] In the present investigation, the degradation of the substituted tin compounds was prevented by using disubstituted mercurials. This paper describes the synthesis of the tributyltin salt of

TABLE I

TRISUBSTITUTED TIN HALO ESTERS

Compound	M.p., °C.	Calcd. Sn	Found Sn	Yield,[a] %
Tri-*n*-butyl iodoacetate	68	25.1	25.5	50–60
Tri-*n*-propyltin iodoacetate	75	29.5	29.7	50–60
Tri-*n*-butyltin iodopropionate	61	24.3	24.3	50–60
Tri-*n*-butyltin bromoacetate	64	27.8	29.0	50–60
Tri-*n*-propyltin bromoacetate	73	30.8	30.9	50–60

[a] Crystallized from petroleum ether.

(1) Portions of this work were reported at the Northwest Regional Meeting of the American Chemical Society, Pullman, Wash., June, 1962. Scientific paper no. 2280, Washington Agricultural Experiment Stations, Pullman, Wash. Project 1525.

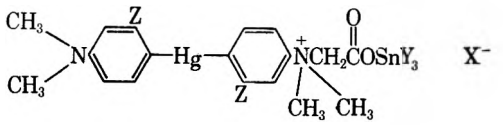
(2) Supported in part by medical and biological research funds, initiative 171, State of Washington.

(3) R. F. Chambers and P. C. Scherer, *J. Am. Chem. Soc.*, **48**, 1054 (1926).

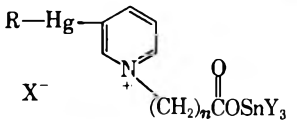
(4) A. N. Nesmeyanov and K. H. Kocheshkov, *Ber.*, **67**, 317 (1934).

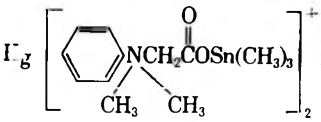
TABLE II

QUARTERNARY AMMONIUM COMPOUNDS



X	Y	Z	M.p., °C.[a]	Calcd. Hg	Calcd. Sn	Calcd. I	Found Hg[b]	Found Sn[c]	Found I[d]	Yield, %
I	n-C_4H_9	H	168–170	21.9	13.0	13.9	21.6	12.7	13.8	52
Br	n-C_4H_9	H	155–157	23.1	13.7	..	23.1	13.3	..	72
I	n-C_4H_9	CH_3	145–148	21.3	12.6	..	20.8	12.3	..	84
I	n-C_4H_9	Cl	161	20.4	12.0	..	20.6	11.8	..	50
I	n-C_3H_7	H	168	23.0	13.6	..	22.6	13.2	..	51
Br	n-C_3H_7	H	165	24.3	14.4	..	23.6	14.3	..	70



X	Y	n	R	M.p., °C.	Calcd. Hg	Calcd. Sn	Calcd. I	Found Hg[b]	Found Sn[c]	Found I[d]	Yield, %
I	n-C_4H_9	1		110–112	24.2	14.3	..	23.9	14.7	..	75
I	n-C_3H_7	1	same	124	25.4	15.1	..	24.8	15.5	..	75
I	n-C_4H_9	2	same	137	23.8	14.1	..	23.7	13.6	..	71
I	n-C_4H_9	1		120	24.2	14.3	..	24.5	14.5	..	65
				143	..	20.9	22.3	..	21.0	22.3	87

[a] Uncorrected, with decomposition. [b] Using Whitton's apparatus. [c] Kochesckov's procedure (K. A. Kochesckov, "Investigation in the Field of Organotin Chemistry," J. G. A. Luijten and G. J. M. vander Kerk, Ed., Tin Research Institute, Middlesex, England, 1955, p. 83). [d] Fusion with sodium hydroxide and sodium carbonate followed by Winkler's titration (L. W. Winkler, "Volumetric Analysis," Vol. 3, I. M. Kolthoff and R. Belcher, Ed., Interscience Publishers, Inc., New York, N. Y., 1957, p. 247).

(carboxymethyl)[p-(p-dimethylaminophenylmercuri)-phenyl]dimethylammonium iodide (1) and related compounds.

Experimental

Table I lists trisubstituted tin halo esters prepared by heating the organic tin oxide or hydroxide[5] with the calculated amount of iodoacetic acid, β-iodopropionic acid, or bromoacetic acid.[6,7]

Mercuribis-4-dimethylaniline and derivatives,[8] mercuribis-3-pyridine,[9] and 3-pyridylmercuribenzene[10] were prepared by known procedures.

Synthesis of I and other compounds (Table II) resulted when the calculated amount of mercuribis-4-dimethylaniline or other base and a slight excess of a trisubstituted tin halo ester were heated with stirring to 110° for 15 min. in a beaker in an oil bath. The mixture quickly melted, then set to a paste. After cooling, the pasty mass was transferred to a small mortar and ground with diethyl ether. The somewhat granular material was transferred to a paper thimble in an ASTM Method D147 extraction apparatus; more ether was added; and extraction was continued for at least 4 hr. An insoluble yellow powder remained in the thimble. Other compounds were prepared in exactly the same manner, except that heating was limited to 70° for 10 min. with mercuribis-3-pyridine or 3-pyridylmercuribenzene. Heating the compounds with solvents for recrystallization resulted in the formation of gum. However, near saturated solutions of I in butyrolactone or dimethyl sulfoxide, on dilution with water, yielded a product with unchanged melting point and mercury analysis.

Approximate solubility of several of the compounds was determined by machine shaking with the solvent at room temperature for 16 to 24 hr. After filtration, the solution was analyzed for mercury.[11] The compounds prepared were rather insoluble; the water solubility tended to be the reverse of alcohol solubility (Table III). The alcoholic solutions of mercuribis-3-pyridine quaternary ammonium compounds frequently precipitated on standing. When sufficient material was available, the mercury analysis of the precipitate and the original material was the same. One per cent aqueous sodium sulfide caused no separation of black mercuric sulfide on standing a week with satu-

TABLE III

APPROXIMATE SOLUBILITY IN MG./ML. OF REPRESENTATIVE COMPOUNDS

Compound	Solvent: Water	Solvent: Ethanol
I[a]	3.3	8.3
II[b]	28.6	1.2
III[c]	8.4	5.3
IV[d]	1.8	0.4

[a] Tri-n-butyltin salt of (carboxymethyl)[p-(p-dimethylaminophenylmercuri)phenyl]dimethylammonium iodide. [b] Tri-n-butyltin salt of 1-(carboxymethyl)-3-(3-pyridylmercuri)pyridinium iodide. [c] Tri-n-butyltin salt of 1-(carboxymethyl)-3-(phenylmercuri)pyridinium iodide. [d] Bis(trimethyltin) salt of (mercuridi-p-phenylene)bis[(carboxymethyl)dimethylammonium iodide].

(5) The trisubstituted tin bases were furnished by R. J. Zedler of the Metal and Thermit Corporation, New York, N. Y.

(6) G. S. Sasin, *J. Org. Chem.*, **18**, 1142 (1953).

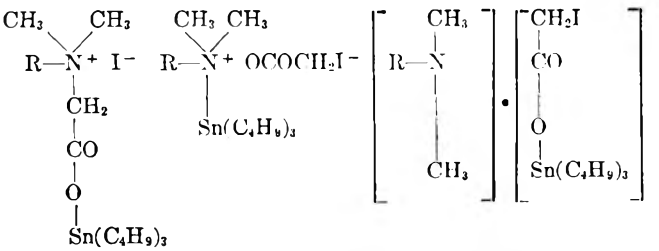
(7) H. H. Anderson, *ibid.*, **22**, 147 (1957).

(8) F. C. Whitmore, "Organic Compounds of Mercury," Chemical Catalogue Company, New York, N. Y., 1921, p. 365.

(9) C. D. Hurd and C. J. Morrissey, *J. Am. Chem. Soc.*, **77**, 4658 (1955).

(10) A. N. Nesmeyanov and I. F. Lutsenko, *J. Gen. Chem. USSR.*, **11**, 382 (1941).

(11) V. L. Miller and F. Swanberg, Jr., *Anal. Chem.*, **29**, 391 (1957).



A B C

R = mercurated base

Fig. 1.—Possible structural formulas.

rated aqueous I or IV but II precipitated mercuric sulfide, instantly, and III on standing 12 to 24 hr.

Trimethyltin iodoacetate reacted with both dimethylamino groups of mercuribisdimethylaniline. The other tin halo esters combined with only one. Several attempts to add a second tri-*n*-butyl- or propyltin halo ester or methyl iodide failed.

The compounds prepared are believed to be the iodide of the quaternary ammonium base (Fig. 1A). Figure 1B represents a substituted acetate of the quaternary ammonium base. Figure 1C represents the addition of the tri-*n*-butyltin iodoacetate as a double salt of a tertiary base as suggested by Kraus and Greer[12] for the addition of trimethyltin salts to bases such as pyridine or aniline. The latter two compounds should be obtainable with esters or salts other than the bromoacetic or iodoacetic ester. However, when the chloroacetate, acetate, or iodide reacted at 100° with mercuribis-4-dimethylaniline, the only identifiable compounds obtained were the starting materials. Feigl's test[13] for iodide was positive. It is recognized that no rigorous proof of the proposed structure of I and analogous products has been possible; however, it does seem that the fact that several similar pairs of compounds do react to yield products with compositions which indicate that corresponding types of reactions must have occurred in the several instances gives substantial justification to the proposed structure.

(12) C. A. Kraus and W. N. Greer, *J. Am. Chem. Soc.*, **45**, 3708 (1923).

(13) F. Feigl, "Spot Tests, Inorganic Applications," Elsevier Publishing Company, Amsterdam, 1954, p. 248.

Temperature Dependence of Stereochemistry of Complex Metal Hydride Reductions

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Although appreciable attention recently has been focused on the effect of solvent and reagent composition on the stereochemistry of reduction by complex metal hydrides,[1] little data appear in the literature on temperature effects on stereochemistry when other variables are held constant. Vail and Wheeler[2] have recently observed minor changes in the relative amounts of 3α- and 3β-cholestanols when reductions of 3-cholestanone were performed with various reducing agents and solvents at several temperatures. The general trend was toward increasing amounts of axial alcohol at higher temperature.[2] We wish to report results on the temperature dependence of product stereochemistry, utilizing conformationally pure ketones, in which case increased temperature may result in either an increase or decrease in the relative amount of axial alcohol, although both cases actually involve greater proportions of the major product at low temperature (an enthalpy effect).

The table shows some typical results of reduction of 3,3,5-trimethylcyclohexanone (I) (a hindered ketone) and 4-*t*-butylcyclohexanone (II) (an unhindered ketone) by excess lithium aluminum hydride and sodium borohydride (>one mole of reducing agent/mole of ketone) in various solvents, each combination of reagent and solvent being studied at several temperatures. The molar ratios of the complex metal hydride to the ketone were not kept constant, but it is felt that this has no effect on the stereochemistry since Haubenstock and Eliel[1] have shown that the stereochemistry of reductions of 3,3,5-trimethylcyclohexanone with lithium aluminum hydride in either diethyl ether or tetrahydrofuran is independent of the proportion of reactants and order of addition. Entries 5a–d likewise show that this also applies in pyridine. Eliel and Haubenstock have also shown that the relative proportion of ketone and reducing agent does not affect the stereochemical result in the reductions with sodium borohydride. It can be seen that I gives substantially greater amounts of axial alcohol (the major product) at lower temperatures, whereas there is a slight decrease in per cent axial (the minor product) when reduction of II is performed at lower temperatures, as was observed with 3-cholestanone.[2] These data are rationalizable according to the earlier views of Dauben, Fonken, and Noyce[3] on "steric approach control" and "product development control" and by assuming that the transition state for reduction of unhindered ketones (*e.g.*, II) does *not* resemble reactants but is well along the reaction coordinate toward product,[4] thus leading mainly to equatorial alcohol. This latter view is supported by several recent studies of borohydride reduction of unhindered ketones where linear-free energy relationships are obeyed[5,6] with highly positive ρ values being observed (+2.6 for *p*-substituted acetophenones[5] and +2.65 for 2- and 3-substituted fluorenones[6]). Hindered ketones, on the other hand, reach the transition state earlier ("steric approach control"), thus leading to a predominance of *exo*-attack.

The present work provides further examples of the effect of temperature and solvent on the stereochemistry of reduction of cyclic ketones. A practical aspect of the data is the indication that greatest stereoselectivity in the reduction of hindered ketones to axial alcohols can be achieved in good solvating media[1] at low temperature.

Experimental

In all the complex metal hydride reductions the ketone (approximately 7 mmoles) was dissolved in 25 ml. of the indicated solvent (Table I), protected from the atmosphere, and cooled in a bath to the desired temperature. A molar excess of the complex metal hydride was then added in powdered form to the system and stirred for 15–30 min. with a magnetic stirrer, except for the sodium borohydride reductions in isopropyl alcohol which were stirred approximately 48 hr.

All reductions run at 0° or higher were essentially complete in the reduction period (less than 1% unchanged ketone),

(1) H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962).

(2) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).

(3) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(4) M. G. Coombe and H. B. Henbest, *Tetrahedron Letters*, 404 (1961).

(5) H. Kwart and T. Takeshita, *ibid.*, **84**, 2833 (1962).

(6) G. G. Smith and R. P. Bayer, *Tetrahedron*, **18**, 323 (1962).

TABLE I

COMPLEX METAL HYDRIDE REDUCTIONS OF 3,3,5 TRIMETHYLCYCLOHEXANONE (I) AND 4-*t*-BUTYLCYCLOHEXANONE (II)

Entry	Reagent	Solvent	Temp., °C.	Molar ratio, metal hydride to ketone I	% Axial alcohol from I (normalized)	% Unreduced ketone I	Molar ratio, metal hydride to ketone II	% Axial alcohol from II (normalized)	% Unreduced ketone II
1[a]	$LiAlH_4$	Et_2O	30	1.1[a]	55[a]	2.6[a]	1.2	8	<1
2	$LiAlH_4$	Et_2O	0	1.3	58	<1	1.2	7.5	<1
3	$LiAlH_4$	Et_2O	−40	1.1	61.5	<1	1.0	5	2.6
4	$LiAlH_4$[b]	C_5H_5N	27	1.0	71	<1	1.1	11.5	<1
5a	$LiAlH_4$	C_5H_5N	0	1.05	75	<1	1.7	10.5	<1
[b]	$LiAlH_4$	C_5H_5N	0	0.77	74	1.3	...	...	..
[c]	$LiAlH_4$	C_5H_5N	0	0.50	76	0.8	...	...	..
[d]	$LiAlH_4$	C_5H_5N	0	0.30	76	41.3	...	...	..
6	$LiAlH_4$	C_5H_5N	−40	1.05	83	<1	1.1	8.5	30
7	$LiAlH_4$	THF	65	0.38[a]	74[a]	7[a]	...	...	...
8	$LiAlH_4$	THF	27	1.2	76.5	<1	1.2	8	<1
9	$LiAlH_4$	THF	0	1.3	82	<1	2.0	7.5	<1
10	$LiAlH_4$	THF	−40	1.1	87.5	<1	2.0	4.0	<1
11	$NaBH_4$	CH_3OH	27	1.2	80.5	<1	1.2	20	<1
12	$NaBH_4$	CH_3OH	0	1.3	86	<1	2.0	16.5	<1
13	$NaBH_4$[c]	CH_3OH	−40	1.2	98	<1	1.3	12.0	2
14	$NaBH_4$[d]	CH_3OH	−70	1.2	98	27.4	...	...	...
15	$NaBH_4$	*i*-C_3H_7OH	27	1.4	57.5	<1	1.4	12.5	<1
16	$NaBH_4$	*i*-C_3H_7OH	0	1.4	62.0	<1	1.5	13.0	<1

[a] Results taken from ref. 1. [b] There is no opportunity for lithium tetrakis(N-dihydropyridyl)aluminate to play a significant role in these reductions since it is slowly formed under these conditions and reduces dialkyl ketones only with great difficulty (P.T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.*, **83**, 3537; **84**, 1756 (1962)). The present reductions were accomplished within a few minutes by addition of lithium aluminum hydride to pyridine solutions of I and II. [c] Although $NaBH(OCH_3)_3$ may be involved at 0° and 27°, there was very little hydrogen evolution at −40° and none at −70°, so one may consider solvated sodium borohydride to be the major reducing species. [d] Since large amounts of ketone remain unchanged under these conditions it is conceivable that some reduction might occur during work-up. This possibility was shown to be extremely remote since a semiquantitative kinetic run at −75°, using the usual work-up for each aliquot taken, showed that good second-order kinetics were obeyed ($k_2 = 6.7 \times 10^{-4}$ l./mole-sec.) when the data were treated by the method of Brown, *et al.*, *Tetrahedron*, **1**, 214 (1957).

whereas several of the reductions at −40° did not proceed to completion in the allotted time. When the reducing agent was lithium aluminum hydride, the excess hydride was neutralized with methanol at the temperature at which the reduction was run before continuing with the work-up. The reaction mixtures were then poured into a mixture of ice, water, and ether and acidified with dilute hydrochloric acid. The crude product was taken up in ether, washed with sodium bicarbonate solution, saturated salt solution, and dried over anhydrous sodium sulfate. The ether solution was concentrated and the mixtures of *cis*- and *trans*-3,3,5-trimethylcyclohexanols and *cis*- and *trans*-4-*t*-butylcyclohexanols were analyzed by gas–liquid partition chromatography using an F & M Model 300 programmed temperature–gas chromatograph. Peak areas were calculated from the product of the peak height and half-height width.

Synthetic mixtures of the pure *cis*- and *trans*-3,3,5-trimethylcyclohexanols, as well as mixtures of the alcohols and I were prepared and analyzed by gas chromatography. Since experimental and calculated results agreed within ±1%, no correction factors were used. The separation was carried out on a 5-ft. column freshly prepared using 20% by weight of the benzene extract from commercial "Tide" detergent on Chromosorb P. Helium flow rate was approximately 120 ml. per min. and the temperature was programmed from 90° at a rate of 4.6° per minute. The ketone had a retention time of 7.67 min., the *trans* alcohol 10 min., and the *cis* alcohol 12.67 min.

Synthetic mixtures of pure *cis*- and *trans*-4-*t*-butylcyclohexanols were prepared and analyzed by gas chromatography in the same manner. The experimental results agreed with the calculated results within 1% in the absence of 4-*t*-butylcyclohexanone up to 20% of the ketone present in the mixture and within 2–3% up to 40% of the ketone in the mixture, the ketone partially masking the *cis* alcohol when it is present in large amounts. The separation was carried out on the same 5-ft. "Tide" column using a flow rate of approximately 200 ml. per min. The temperature was programmed from 90° at 4.6° per min. The retention time of the ketone was 13.5 min., that of the *cis* alcohol 14.67 min., and that of the *trans* alcohol 16.67 min.

The crude product mixtures from the hydride reductions were analyzed in the previous manner. The only peaks observed were those corresponding to the ether solvent, which immediately flashed off, the two alcohols and, in some cases where the reduction was incomplete, the ketones. In the table the yields of axial alcohols are normalized to 100%.

Acknowledgment.—We wish to thank the National Science Foundation for support of this work. We are also grateful to Professor E. L. Eliel for samples of *cis*- and *trans*-4-*t*-butylcyclohexanol and *cis*- and *trans*-3,3,5-trimethylcyclohexanol.

The Preparation of Certain Cyclopolymethylenecyclosiloxanes

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The hydrolysis of organosilicon dihalides generally results in the formation of a mixture of cyclic and linear organopolysiloxanes with the latter predominating. A survey reveals that usually the hydrolysis involves the use of dialkyl, diaryl, or alkyl–aryl substituted dichlorosilanes. Siloxane polymers resulting from the hydrolysis of 1,1-dichloro-1-silacyclobutane and 1,1-dichloro-1-silacyclopentane have been described by Hersch.[1] This paper records the preparation and characterization of four crystalline polymers of the type $[(CH_2)_xSiO]_y$ where x is 4 or 5 and y is 3 or 4.

(1) J. M. Hersch, U. S. Patent 2,464,231 (1949).

Experimental

Tetracyclopentamethylenecyclotetrasiloxane.—To a vigorously stirred suspension of 20.7 g. (0.85 g.-atom) of magnesium powder in 400 cc. of anhydrous diethyl ether was added, dropwise, a mixture of 34.1 g. (0.20 mole) of silicon tetrachloride and 92.0 g. (0.40 mole) of 1,5-dibromopentane. After a few milliliters of the mixture had been added, the reaction was initiated using a small crystal of iodine. After addition, the mixture was heated for 3 hr. after which it was left standing overnight. Hydrolysis was effected by the cautious addition of 200 ml. of a 10% hydrochloric acid solution and the ether layer dried over anhydrous calcium chloride.

Distillation at low pressures yielded 17.5 g. of material, principally 1,5-dibromopentane. Using a steam heated condenser, a viscous oil was obtained of which three fractions were collected: (1) b.p. 156–169°; (2) b.p. 173–187°; (3) b.p. 198–200° (0.07 mm.). Fractions 1 and 2 crystallized at room temperature while the viscous oil in fraction 3 required longer time. The crystals from fractions 1 and 2 were recrystallized from hot 95% ethanol giving a white product, 3.6 g., m.p. 71–73°.

Anal. Calcd. for $C_{20}H_{40}O_4Si_4$: C, 52.58; H, 8.82; Si, 24.59; mol. wt., 457. Found: C, 53.17; H, 8.78; Si, 24.09; mol. wt., 452.

Infrared absorption: strong, 2910, 2855, 1068, 783 cm.$^{-1}$; medium, 1446, 1398, 1199, 1177 cm.$^{-1}$; weak, 1460, 1343, 1290, 1268, 1003, 856, 769 cm.$^{-1}$.

Tricyclopentamethylenecyclotrisiloxane.—Similarly, 33.3 g. (0.19 mole) of 1,1-dichloro-1-silacyclohexane in 250 ml. of anhydrous ether, was treated with 38.1 g. (2.12 moles) of crushed ice. The mixture was vigorously stirred and maintained at reflux for 1 hr. The ether layer was then washed with 50 ml. of water and again stirred at reflux with 50 ml. of a 5% solution of potassium hydroxide for an additional hour. The ether layer was washed once with 50 ml. of a 1% hydrochloric acid solution and twice with water, then dried over calcium chloride. Vacuum distillation, after release of the ether, yielded a material which crystallized in the condenser. This material, recrystallized from hot 95% ethanol, gave 2.4 g. of white crystals, m.p. 92–94°. The pot residue probably contained higher polycyclic compounds including the tetramer, as indicated by infrared data.

Anal. Calcd. for $C_{15}H_{30}O_3Si_3$: C, 52.58; H, 8.82; Si, 24.59; mol. wt., 343. Found: C, 52.99; H, 9.12; Si, 24.16; mol. wt., 335.

Infrared absorption: strong, 2910, 2850, 1016, 1000, 784 cm.$^{-1}$; medium, 1445, 1398, 1175, 905 cm.$^{-1}$; weak, 1460, 1341, 1289, 1267, 1197, 855, 765 cm.$^{-1}$.

Tricyclotetramethylenecyclotrisiloxane and Tetracyclotetramethylenecyclotetrasiloxane.—In similar manner, 20 g. (0.82 g.-atom) of magnesium powder suspended in 400 ml. of anhydrous ether was treated with 34 g. (0.20 mole) of silicon tetrachloride and 86 g. (0.40 mole) of 1,4-dibromobutane. After working up as before, and evaporation of the ether, 2.2 g. of a solid precipitated. This was filtered and recrystallized from hot heptane–octane mixture as fine white crystals, m.p. 199–201°, tricyclotetramethylenecyclotrisiloxane.

Anal. Calcd. for $C_{12}H_{24}O_3Si_3$: C, 47.95; H, 8.05; Si, 28.03; mol. wt., 301. Found: C, 48.18; H, 7.94; Si, 27.95; mol. wt., 292 (Rast).

Infrared absorption: strong, 2940, 2865, 1408, 1074, 1034, 1010 cm.$^{-1}$; medium, 1454, 1249, 855, 739, 705 cm.$^{-1}$; weak, 1307, 1190, 1157, 907, 788 cm.$^{-1}$; shoulder, 1467 cm.$^{-1}$.

The remaining oil was distilled yielding 1,4-dibromobutane, b.p. 61–64° (5.4 mm.), and an uncharacterized silicon-containing liquid, b.p. 43–52° (5.4 mm.), showing Si–H infrared absorption. Further distillation yielded a solid, 2.8 g., m.p. 114–116°, tetracyclotetramethylenecyclotetrasiloxane.

Anal. Calcd. for $C_{16}H_{32}O_4Si_4$: C, 47.95; H, 8.05; Si, 28.03; mol. wt., 401. Found: C, 48.17; H, 8.23; Si, 28.25; mol. wt., 415 (Rast).

Infrared absorption: strong, 2950, 2875, 1076, 1065 cm.$^{-1}$; medium, 1455, 1410, 1249, 1014, 855, 704 cm.$^{-1}$; weak, 1310, 1192, 1155, 817, 790, 740, 672 cm.$^{-1}$; shoulder, 1468, 1065 cm.$^{-1}$.

This synthesis was repeated by treating 31.0 g. (0.20 mole) of 1,1-dichloro-1-silacyclopentane in ether with 38.0 g. (2.10 moles) of crushed ice. After an hour of reflux, 95 ml. of a 5% potassium hydroxide solution was added and refluxing continued for another hour. The ether layer was then washed several times with 50-ml. portions of water and dried over anhydrous calcium chloride. Evaporation of ether gave 0.8 g. of a crystalline solid, m.p. 199–201°, and a second solid, m.p. 115–116°. Infrared data were identical on the products prepared by these two methods.

Infrared absorption data were obtained using a Perkin-Elmer Model 21, linear in wave number, spectrophotometer equipped with sodium chloride optics. Solution spectra were recorded, using carbon tetrachloride and carbon disulfide, to cover 4000–1300-cm.$^{-1}$ and 1300–650-cm.$^{-1}$ regions, respectively. All samples were run in a 0.08-mm. fixed thickness salt cell, uncompensated. Sample concentrations were as follows: 250 mg. of solute per 2.5 ml. of carbon tetrachloride and 50 mg. of solute per 2.5 ml. of carbon disulfide, with the exception of tricyclotetramethylenecyclotrisiloxane where solubility difficulties made it necessary to use approximately 95 mg. of sample per 2.5 cc. of carbon tetrachloride.

Preparation of Ornithine from Methyl 2,5-Diazidovalerate

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2,5-Dichlorovaleric acid is an attractive starting material for the synthesis of ornithine (2,5-diaminovaleric acid) because it can be prepared from carbon tetrachloride and ethylene followed by dehydrohalogenation, chlorination, and hydrolysis.[1-3] Direct ammonolysis of 2,5-dichlorovaleric acid gives the ring closed products proline and 2-tetrahydrofuramide[4] with no evidence for ornithine formation. In order to avoid these products, some source of nitrogen incapable of undergoing ring closure reactions is desirable for the synthesis of ornithine.

We have found that sodium azide displaces both chloro groups in methyl 2,5-dichlorovalerate to form methyl 2,5-diazidovalerate. Reduction followed by hydrolysis gave ornithine in 63% yield based on methyl 2,5-dichlorovalerate.

$$ClCH_2CH_2CH_2CH(Cl)COOCH_3 + NaN_3 \xrightarrow{(CH_3)_2SO_4} N_3CH_2CH_2CH_2CH(N_3)COOCH_3$$

$$N_3CH_2CH_2CH_2CH(N_3)COOCH_3 \xrightarrow[2.\ H_2O\text{–}HCl]{1.\ H_2\text{–}Pd\ C} H_2NCH_2CH_2CH_2CH(NH_2)COOCH_3 \cdot HCl$$

Methyl 2,5-dichlorovalerate was prepared using three moles of methanol and 2,2-dimethoxypropane[5] in the presence of Dowex 50-H^+. The reaction of methyl 2,5-dichlorovaleric acid and sodium azide goes smoothly in dimethyl sulfoxide at 60–65° and is 97.5% complete after five hours. Reduction of crude[6] methyl 2,5-di-

(1) R. Joyce, W. Hanford, and J. Harmon, *J. Am. Chem. Soc.*, **70**, 2529 (1948).

(2) A. Nesmejanov, V. Kose, and R. Friedlina, *Dokl. Akad. Nauk, SSSR*, **103**, 109 (1955).

(3) For other routes to ornithine see D. M. Greenberg, "Amino Acids and Proteins," Charles C Thomas, Publisher, Springfield, Ill., 1951, p. 153; S. Akabori, Y. Itumi, and T. Okuda, *Nippon Kagaku Zasshi*, **77**, 490 (1956); *Chem. Abstr.* **52**, 8958*h* (1958); A. Nesmejanov, *et al.*, *Chem. Tech.*, **9**, 139 (1957).

(4) R. A. Strojny, H. C. White, and E. J. Strojny, *J. Org. Chem.*, **27**, 1240 (1962).

(5) N. Lorette and J. Brown, *ibid.*, **24**, 261 (1959).

(6) Methyl 2,5-diazidovalerate is a distillable liquid, b.p. 85–93° (0.3 mm.). The analysis of the distillate was low in nitrogen, perhaps because of loss of nitrogen during distillation.

azidovalerate with hydrogen and 5% palladium on charcoal at 0–25° and atmospheric pressure was followed by hydrolysis to yield ornithine hydrochloride.

Experimental

Methyl 2,5-Dichlorovalerate.—A mixture of 2,5-dichlorovaleric acid (27.4 g., 0.16 mole), methanol (15.4 g., 0.48 mole), 2,2-dimethoxypropane (50 g., 0.48 mole), and a catalytic amount of dry, powdered Dowex 50-H^+ was stirred at room temperature for 20 hr. and heated at 40–60° for 24 hr. After removal of the catalyst by filtration, distillation of the brown solution gave 18.1 g. (61% yield) of ester, b.p. 72–73° (1 mm.). Vapor phase chromatography showed one peak and a trace impurity.

Anal. Calcd. for $C_6H_{10}O_2Cl_2$: C, 38.94; H, 5.45; Cl, 38.32. Found: C, 39.34; H, 5.67; Cl, 38.69.

DL-Ornithine Hydrochloride.—Methyl 2,5-dichlorovalerate (9.40 g., 0.05 mole) was added to a mixture of 50 ml. of dimethyl sulfoxide and 13.0 g. (0.20 mole) of sodium azide and stirred for 5 hr. at 60–65°. Water was added and the orange solution extracted with ether. An aliquot of the total aqueous portion was found to contain 97.5% of the theoretical amount of inorganic chloride on titration with silver nitrate. The ether solution was washed, dried, and evaporated under reduced pressure to yield a bright yellow liquid, presumably methyl 2,5-diazidovalerate.[6]

This product was taken up in 50 ml. of 95% ethanol and placed in a reduction flask equipped with a stirrer, a sintered glass sparger, and a gas outlet tube. One gram of 5% palladium on charcoal suspended in 50 ml. of ethanol was added. With ice cooling, hydrogen was bubbled in for 2 hr. A small amount of fresh catalyst and 8 ml. of concentrated hydrochloric acid were added and reduction allowed to continue for 1 hr. with ice cooling and 4 hr. at room temperature. Filtration, evaporation, and refluxing with 40 ml. of 5 *N* hydrochloric acid for 4 hr. yielded a brown solution which was evaporated and redissolved in water. Passage through a column containing 70 g. of Dowex 50-H^+ and washing with water until the eluate was chloride-free followed by elution with ammonia gave, on evaporation, a basic oil containing 65% of the theoretical amount of ornithine by hydrochloric acid titration. Addition of hydrochloric acid to pH 3.8 and evaporation gave a tan-colored oil which, on trituration with absolute methanol, yielded 5.8 g. (63% of theory) of DL-ornithine hydrochloride. An 85% recovery of white crystals containing 98.2% of the theoretical amount of chloride ion was obtained on recrystallization from water–ethanol. Comparison of our product with an authentic sample of DL-ornithine hydrochloride showed them to possess identical infrared and n.m.r. spectra and identical R_f values on paper chromatography of 0.03 in collidine–water (125:44) and 0.09 in *n*-butyl alcohol–acetic acid–water (40:10:50).

Hydrogen Bonding in Pyrrylmethenes[1]

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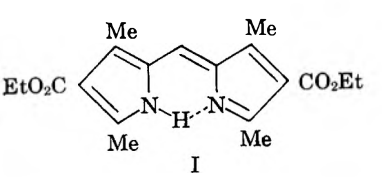
Some time ago Vestling and Downing[3] presented infrared spectral evidence for hydrogen bonding in 2,2′-(3,3′,5,5′-tetramethyl-4,4′-diethoxycarbonyl)dipyrrylmethene (I) and in the 3,4′,5-trimethyl-3′,4-diethoxycarbonyl-5′-bromo analog (II), both in carbon tetrachloride. The absence of dilution studies prevented a decision between intermolecular hydrogen bonding and an intramolecular bonding as presented for I. A proposal of the latter type has been made



I

independently by Brunings and Corwin[4] from other considerations and such structures have been assumed[5] *a priori*, although in fact this had not been established at

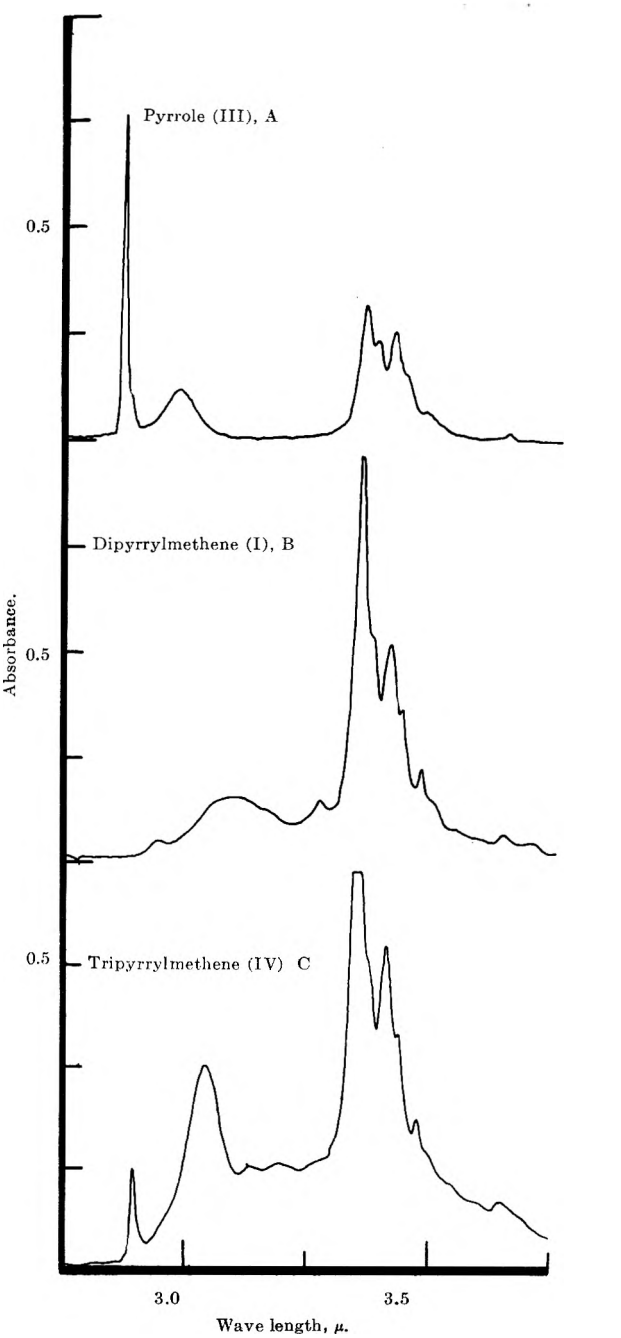


Fig. 1.—Infrared spectra in carbon tetrachloride. Letters (A, B, and C) refer to solutions marked in Table I.

(1) This work was supported in part by a PHS grant, C-6255, from the National Cancer Institute and presented for the most part at the American Petroleum Institute Symposium on Chemistry and Properties of Petroleum Type Sulfur and Nitrogen Compounds, Laramie, Wyo., July 19, 1962.

(2) National Science Foundation Undergraduate Participant (NSF-G21628).

(3) C. S. Vestling and J. R. Downing, *J. Am. Chem. Soc.*, **61**, 3511 (1939).

(4) K. J. Brunings and A. H. Corwin, *ibid.*, **66**, 337 (1944).

(5) *Cf.*, A. Albert, "Heterocyclic Chemistry," The Athlone Press, University of London, London, 1959, p. 144.

TABLE I

Compound	Molarity × 10²	Alkyl —Stretch. vib.— λ, μ	Alkyl —Stretch. vib.— A	Type of NH stretch. vib. —Free— λ, μ	—Free— A	—Free— A/A_Alk	—Intermol. assoc.— λ, μ	—Intermol. assoc.— A	—Intermol. assoc.— A/A_Alk	—Intramol. assoc.— λ, μ	—Intramol. assoc.— A	—Intramol. assoc.— A/A_Alk
Pyrrole (III)	2.954[a]	3.413	0.260	2.875	0.765	2.9	2.987	0.123	0.47			
	2.265	3.413	.196	2.875	.610	3.1	2.982	.064	.33			
	1.482	3.415	.133	2.875	.440	3.3	2.980	.034	.26			
	1.133	3.412	.096	2.874	.343	3.6	2.978	.019	.20			
Dipyrrylmethene (I)	1.479[b]	3.411[d]	.518							3.098[d]	0.158	0.31
	1.121	3.416	.399							3.099	.117	.29
	0.740	3.413[d]	.259							3.101	.080	.31
	.560	3.415	.207							3.097	.062	.30
Tripyrrylmethene (IV)	1.252	3.415[d]	.808	2.896[d]	.271	0.34	3.045[d]	.512	.63	3.138[d]	.259	.32
										3.199[d]	.267	.33
	1.242[c]	3.413	.789	2.896	.250	.32	3.043	.504	.64	3.141	.262	.33
										3.201	.269	.34
	0.913	3.416	.575	2.896	.214	.37	3.046	.369	.64	3.142	.191	.33
										3.206	.198	.34
	.621	3.417	.393	2.895	.168	.43	3.047	.244	.62	3.142	.126	.32
										3.207	.130	.33
	.457	3.415	.293	2.895	.140	.48	3.046	.170	.58	3.139	.090	.31
										3.214	.093	.32

[a] Refers to A in Fig. I. [b] B in Fig. I. [c] C in Fig. I. [d] Uncorrected, see Experimental.

the time the study reported upon here was undertaken.[6]

The spectra of carbon tetrachloride solutions of 2,4-dimethyl-3-ethoxycarbonylpyrrole (III) (Fig. 1 and Table I), which is related to I, shows free and associated NH absorption bands[7] at 2.874–2.875 and 2.977–2.987 μ, respectively. The maximum of neither band follows Beer's law[8] and that of the first shows a relative absorbance increase with dilution, whereas that of the second shows a relative absorbance decrease as seen in Table I. This is as would be expected for intermolecular association of the pyrrole. In striking contrast the spectra of solutions of methene I show no free NH and only a broad absorption with maxima at 3.097–3.101 μ at all concentrations. Accordingly, the hydrogen bonding in I, in carbon tetrachloride, is indeed intramolecular. This is presumably the case for 2,2′-(3,4′,5-trimethyl-3′,4-diethoxycarbonyl-5′-bromo)dipyrrylmethene (II) and other 2,2′-dipyrrylmethenes.

The infrared absorption spectra of solutions of 2,2′,-2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-triethoxycarbonyl)tripyrrylmethene (IV) (see Fig. 1 and Table I) show a free NH band at 2.895–2.896 μ, that which is apparently an intermolecular associated NH band at 3.043–3.047 μ, and absorption with maxima at 3.133–3.142 and 3.201–3.214 μ, which could be due to intramolecular association. This would be compatible with a structure wherein two of the rings are associated as shown for dipyrrylmethene (I) and the NH of the third ring is left free for involvement in intermolecular association.

(6) While this note was being written the abstract of the paper by L. P. Kuhn and G. C. Kleinspehn appeared, Abstracts of Papers, 142nd National Meeting, of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 842. These workers report that in all 2,2′,-dipyrrylmethenes studied by them an N–H . . . N band is presen. [see *J. Org. Chem.*, **28**, 721 (1963)]. Since submitting the manuscript, G. M. Badger, R. L. N. Harris, R. A. Jones, and J. M. Sasse, *J. Chem. Soc.*, 4329 (1962), using a calcium fluoride prism, have defined the intramolecular hydrogen-bonded NH stretching vibration in such compounds as 3.021–3.100 μ in carbon tetrachloride. Our compound I is described as absorbing at the longer wave length and an intermolecular association band was stated as not observed for the methenes examined in dilute or concentrated solutions.

(7) N. Fuson, M. L. Josien, R. L. Powell, and E. Utterback, *J. Chem. Phys.*, **20**, 145 (1952).

(8) Obedience with this law is shown in a constant value for the relative absorbance, A/A_{Alk}.[9] A plot of A_{Alk} as a function of concentration gives a straight line for each compound listed in Table I.

(9) *Cf.*, L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 13, *et. seq.*

Upon dilution the relative absorbance of the free NH vibration band increases noticeably. However, a change of any magnitude in the relative absorbance of the intermolecular association band is found only upon comparing the two more dilute solutions. This is understandable upon consideration of the relative areas of the two bands; a small change in the intensity of the broad intermolecular association band is accompanied by a much larger change in the intensity of the narrow free NH band (see Fig. 1). The solubilities of the dipyrrylmethene (I) and the tripyrrylmethene (IV) in carbon tetrachloride are much less than that of the pyrrole (III). Consequently the upper limit of concentration that could be used for the methenes is less than that for the pyrrole. Although the most concentrated solutions listed in Table I for none of the three compounds corresponds to a saturated solution, those for the methenes are concentrations judged to be as high as could be readily handled without concern for separation of the solute from the solution. With all three compounds the accuracy of measurement of the low broad absorbances for the associated NH bands, especially at low concentrations, defines an additional restriction.

Experimental

Infrared absorption data were obtained with a Beckman IR-4 double beam spectrophotometer using a lithium fluoride prism and a compensating cell containing solvent in the reference beam. A fixed path length cell, 0.9787 mm., was used for the pyrrole solutions, and a variable path length cell, 3.1045 mm., was used for the solutions of the di- and tripyrrylmethene. Both types of cells were equipped with sodium chloride windows. Measurements were made using a scanning speed of 0.17 μ/min. and an instrument slit width of 0.23 mm. at 3.000 μ (spectral band width, 0.075 μ), which was automatically varied with the wave length according to the select control device of the instrument. The absorption bands of water at 2.856 μ and of polystyrene film at 3.3026 and 3.507 μ were used for calibration of the wave length. The precision of such measurements is ±0.005 μ. Because of particular circumstances the calibration could not be applied to certain measurements in Table I and these are designated *d*.

Freshly distilled carbon tetrachloride was used as a solvent. Erroneous results were observed with methene I when this was not done.

Melting points were determined with a Fisher-Johns or a Kofler apparatus and are uncorrected.

2,4-Dimethyl-3-ethoxycarbonylpyrrole (III), m.p. 75.0–75.2° (lit.[10] m.p. 75–76°), was prepared by the hydrolysis of 2,4-dimethyl-3,5-diethoxycarbonylpyrrole and decarboxylation of the resulting carboxylic acid as described by Knorr.[10]

2,2′-(3,3′,5,5′-Tetramethyl-4,4′-diethoxycarbonyl)dipyrrylmethene (I) was synthesized through the condensation of 7.80 g. of 2-formyl-3,5-dimethyl-4-ethoxycarbonylpyrrole and 6.68 g. of 2,4-dimethyl-3-ethoxycarbonylpyrrole in the presence of 4.66 ml. of 48.3% hydrobromic acid in alcohol. A solution of the pyrrole in 50 ml. of absolute ethanol was added dropwise to a stirred, hot solution of the aldehyde and acid in 150 ml. of absolute alcohol during a period of 30 min. and the resulting mixture was refluxed for an additional 40 min. The mixture was cooled in an ice bath and 12.1 g. of the crude hydrobromide was collected. After two recrystallizations from a mixture of chloroform and cyclohexane 11.1 g. (65%) of the purified methene hydrobromide was obtained as red crystals, having a blue reflex, m.p. 212.0–213.5° dec. Portions of the purified methane hydrobromide in chloroform were shaken with an excess of ammonia in the same solvent. After filtering the resulting mixtures and evaporating the solvent, the residues were combined. The product was dissolved in a little chloroform and chromatographed on a column of Woelm alumina (nonalkaline, activity grade II). The middle fraction of the bright yellow ether eluate therefrom was collected, the solvent was evaporated, and the residue rechromatographed as before. Crystallization of the chromatographed product from acetone yielded beautiful, long, red needles of the methene (I), m.p. 186.8–188.1° dec. (lit.[11] m.p. 190°).

2,2′,2″-(3,3′,3″,5,5′,5″-Hexamethyl-4,4′,4″-triethoxycarbonyl)tripyrrylmethene (IV) was synthesized by the permanganate oxidation of the corresponding tripyrrylmethane[12] in different runs. In a typical case the methene, m.p. 215.0–216.5° dec. (lit.[12] m.p. 210.7–211.6°), was obtained in a yield of 63%.

Acknowledgment.—We are especially indebted to Dr. Norman E. Albert for suggestions and assistance with certain phases of this investigation.

(10) L. Knorr, *Ann.*, **236**, 322 (1886).

(11) A. H. Corwin and K. J. Brunings, *J. Am. Chem. Soc.*, **64**, 2106 (1942).

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A New Synthesis of Methyl Aryl Sulfones

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Methyl aryl sulfones have been prepared by several methods[1–4] all of which have limitations. We have now found a new approach involving heating of an aromatic compound with methanesulfonic anhydride.

$$RH + (CH_3SO_2)_2O \longrightarrow RSO_2CH_3 + CH_3SO_3H$$

The data, summarized in Table I, indicate the scope of this procedure. It is evident that the CH_3SO_2 group enters primarily in the *para* position, although toluene also forms considerable *ortho* isomer. The structures indicated for new compounds were not proved, but for those derived from 1,4-xylene and from 1,2,4,5-tetramethylbenzene (compounds 3 and 6), only one structure is possible if no rearrangement is assumed during reaction.

This procedure also has limitations under the conditions used. Use of pure reagents, especially with polymethylated benzenes, obviated tar formation, as did also use of fresh methanesulfonic anhydride, which deteriorates upon standing. Use of tetrachloroethylene as reaction solvent at reflux (b.p. 121°) generally gave a much cleaner reaction than employing an excess of the compound treated, as did also reduction of the standard reaction time of sixteen hours in a number of cases, as indicated in Table I. Less reactive and more volatile compounds, such as toluene and chlorobenzene, require longer periods of reaction. The following compounds did not react: 1,2-dichlorobenzene, phenyl benzoate, phenyl methanesulfonate, triphenyl phosphate, 2-nitroanisole, and 2-methoxybenzoic acid. Although anisole reacted normally, phenetole gave a good yield of phenyl methanesulfonate, as did also phenol and phenyl acetate. Intractable tars resulted from 1,2-xylene, 1,2,4-trimethylbenzene, pentamethylbenzene, phenoxyacetic acid, thioanisole, 2-methylanisole, and 3-methylanisole. Naphthalene, ethylbenzene, diphenyl oxide, and 2-phenylanisole appeared to react, but pure products could not be isolated. Infrared analysis of the product made from naphthalene showed it to comprise largely a mixture of the α- and β-methylsulfonyl derivatives. Where applicable, however, the present method appears simple and conveni-

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(2) A. Schoeberl and A. Wagner, "Houben-Weyl Methoden der Organischen Chemie," 4th Ed., Vol. IX, Thieme, Stuttgart, 1955, p. 227 ff.

(3) L. Field and R. D. Clark, *J. Org. Chem.*, **22**, 1129 (1957).

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TABLE I. METHYL ARYL SULFONES

No.	Compound reacted	Substituted methanesulfonyl-benzene formed	Reflux time, hr.	Yield, %[a]	M.p., °C. Lit.	M.p., °C. Found[d]	% Sulfur Theor.	% Sulfur Found
1	Toluene	2- and 4-Methyl	20	53[b]	88[e]	88	18.8	18.8
2	1,3-Xylene	2,4-Dimethyl	16	75	55[f]	56	17.4	17.5
3	1,4-Xylene	2,5-Dimethyl	8	42	[g]	45	17.4	17.5
4	1,2,3-Trimethylbenzene	3,4,5-Trimethyl	16	82[c]	[g]	121	16.2	16.6
4a	1,2,3-Trimethylbenzene	2,3,4-Trimethyl			[g]	97	16.2	16.3
5	1,3,5-Trimethylbenzene	2,4,6-Trimethyl	8	75	130[f]	131	16.2	16.4
6	1,2,4,5-Tetramethylbenzene	2,3,5,6-Tetramethyl	4	60	[g]	133	15.1	15.1
7	Chlorobenzene	4-Chloro	24	10	98[f]	97	16.6	16.7
8	Biphenyl	4-Phenyl	16	40	145[h]	144	13.8	13.8
9	Anisole	4-Methoxy	16	70	120[i]	120	17.2	17.3
10	4-Methylanisole	2-Methoxy-5-methyl	16	20	87[j]	86	16.0	15.9
11	1,3-Dimethoxybenzene	2,4-Dimethoxy	8	50	[g]	105	14.8	15.1

[a] Average yields of fair quality crude. [b] Over half 2-isomer by infrared analysis. [c] Total for two isomers. [d] Uncorrected. [e] The 4-isomer of ref. 4. [f] J. Troeger and C. Budde, *J. prakt. Chem.*, (2) 66, 149 (1902). [g] New compound. [h] A. Mangini, L. Ruzzier, and A. Tundo, *Bull. Sci. fac. chim. ind. Bologna*, 14, 81 (1956); *Chem. Abstr.*, 52, 19446 (1958). [i] Ref. 6. [j] D. T. Gibson and S. Smiles, *J. Chem. Soc.*, 2391 (1923).

ent and, in some cases, gives good yields where established methods give poor yields or no product at all. Thus, 1,3,5-trimethyl-benzene yields 10% or less of the methylsulfonyl compound by the Friedel–Crafts procedure[4] or by heating the hydrocarbon with methanesulfonic acid,[5] and anisole forms only phenyl methanesulfonate by the Friedel–Crafts approach.[4]

Experimental

Typical Procedure.—Anisole (6.0 g., 0.056 mole), methanesulfonic anhydride (9.0 g., 0.052 mole) (used as obtained from Distillation Products Industries) and tetrachloroethylene (50 ml.) were refluxed briskly for 16 hr. The reaction mixture was extracted with two 25-ml. portions of warm water to remove methanesulfonic acid and unchanged anhydride. The aqueous extracts were then combined, cooled, and extracted with ether to recover any dissolved product. The ether extract and the tetrachloroethylene solution of product were combined and evaporated to constant weight on a steam bath in a stream of air. The crude product solidified upon cooling and stirring. It was recrystallized from *n*-butyl alcohol or from hot water. A mixture melting point with material prepared by an alternative procedure[6] showed no depression.

The compounds in Table I have infrared spectra consistent with the structures indicated. The sulfone group showed absorption at 1160 to 1120 and at 1350 to 1300 cm.$^{-1}$ and the ether grouping at 1270 to 1230 cm.$^{-1}$.

(5) M. S. Grant and W. J. Hickinbottom, *J. Chem. Soc.*, 2520, (1959).

(6) C. M. Suter and H. L. Hansen, *J. Am. Chem. Soc.*, **54**, 4101 (1932).

Communications TO THE EDITOR

Metallic Ion Effect in Mono- *vs.* Dialkylation of Dipotassio Acetylacetone with Alkyl Halides[1]

Sir:

Although dipotassio acetylacetone (I, M = K) previously has been alkylated with molecular equivalents of several alkyl halides to form the corresponding monoalkyl derivatives II,[2,3] the formation also of the dialkyl derivative III has been observed only with *n*-octyl bromide.[3]

$$\underset{\text{I}}{CH_3COCHCOCH_2M}\quad\quad\underset{\text{II}}{CH_3COCH_2COCH_2R}$$

$$\underset{\text{III}}{RCH_2COCH_2COCH_2R}$$

A more thorough study of such reactions has now revealed that dialkylation generally accompanies monoalkylation of dipotassio I (M = K) and, more significantly, that disodio acetylacetone (I, M = Na) undergoes almost exclusively monoalkylation.

The dialkali salts I (M = K or Na), prepared from acetylacetone and two molecular equivalents of the corresponding alkali amide in liquid ammonia,[2,3] were treated during ten–twelve minutes with approximately molecular equivalents of methyl, *n*-butyl, and *n*-octyl halides.

Although the mono- and dibutylation products and especially the mono- and dimethylation products are difficult to separate by distillation, the mixtures were readily resolved by vapor phase chromatography. However, the mono- and dioctylation products were separated easily by distillation as described elsewhere.[3] The results are summarized in Table I, in which yields are given for duplicate runs. The dialkylation yields are calculated on the basis of the stoichiometry shown in Scheme A.

TABLE I

ALKYLATIONS OF DIALKALI SALTS I WITH ALKYL HALIDES TO FORM MONO- AND DIALKYLATION PRODUCTS OF II AND III

Dialkali salt I, M	Alkyl Halide	II Yield, %	III Yield,[a] %
Potassium	Methyl iodide	35, 46	26, 18
Sodium	Methyl iodide	59, 65	<1, <4
Potassium	*n*-Butyl bromide	43, 53	16, 14
Sodium	*n*-Butyl bromide	67, 73	<1, <1
Potassium	*n*-Octyl bromide	51, 57	14, 14
Sodium	*n*-Octyl bromide	66, 79	<2, <2

[a] Yield calculated based on the stoichiometry shown in Scheme A.

The identities of the monobutylation, monooctylation, and dioctylation products were established as described previously.[3] The identities of the monomethylation (from sodio experiment) and dibutylation products were established by comparison of their copper chelates with authentic samples.[4,5] The dimethylation product was compared by v.p.c. with authentic 3,5-heptanedione.[5] In all three cases monoalkylation had occurred at the 1-position and dialkylation at the 1,5-positions of 2,4-pentanedione. Incidentally, previous studies[3,6] of the alkylation of unsymmetrical β-diketones indicated that the isomeric 1,1- and 1,3-dialkylation products IV and V, respectively, would not be expected.

$$\underset{\text{IV}}{R_2CHCOCH_2COCH_3}\quad\quad\underset{\text{V}}{RCH_2COCHCOCH_3}\ (\text{R})$$

Table I shows that a substantial amount of dialkylation was obtained in each example involving the dipotassio salt of I, while little or none was obtained when the disodio salt was employed. The significance of these results is twofold. First, the alkylation of the sodio salt must clearly be recommended for most

(1) Supported in part by the National Science Foundation (NSF-G14527).

(2) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

(3) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **25**, 158 (1960).

(4) J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 284 (1945).

(5) J. T. Adams and C. R. Hauser, *ibid.*, **66**, 1220 (1944).

(6) T. M. Harris and C. R. Hauser, *ibid.*, **81**, 1160 (1959).

(7) S. D. Work and C. R. Hauser, *J. Org. Chem.*, **28**, 725 (1963).

synthetic purposes. Second, these observations have considerable theoretical significance. Although metallic cation effects have been observed before in the acylation[7] and aldol-type condensation[8] of β-diketone dianions, this represents the first observation of such an effect in alkylation reactions. The previously observed[7,8] cation effects involved ionization of the carbonyl reagent by the dianion. The present effect appears to involve a proton transfer between dianion I and alkylation product IIa (Scheme A).

$$\mathrm{I} + \mathrm{RX} \longrightarrow \underset{\mathrm{IIa}}{\mathrm{CH_3COCHCOCH_2R}} \quad (1)$$

$$\mathrm{I} + \mathrm{IIa} \rightleftharpoons \underset{\mathrm{IIb}}{\mathrm{MCH_2COCHCOCH_2R}} + \mathrm{CH_3COCHCOCH_3} \quad (2)$$

$$\mathrm{IIb} + \mathrm{RX} \longrightarrow \mathrm{RCH_2COCHCOCH_2R} \quad (3)$$

SCHEME A

The difference in the results obtained with potassium and with sodium might be explained on the basis that the ratio of the rates of alkylation (step 1) to proton exchange (step 2) is somewhat less with the potassio salts (M = K) than with the sodio salts (M = Na). This permits a significant build up of potassio IIb, which undergoes alkylation (step 3). This hypothesis is supported by the observation that with potassium, but not with sodium, the rate of addition of the alkyl halide affects the ratio of mono- and dialkylation observed. Thus, when *n*-butyl bromide was added to I (M = K) over a few seconds, considerably less dialkylation was observed than when the halide was added over two hours. In contrast, with disodio acetylacetone (I, M = Na) no more than a trace of the dialkylation product could be observed even when the *n*-butyl bromide was added over a two-hour period. Further study of this effect is in progress.

(8) R. J. Light and C. R. Hauser, *J. Org. Chem.* **26**, 1716 (1961).
(9) National Science Foundation Cooperative Fellow, 1961–1962; James B. Duke Fellow, 1962–1963.

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Hydrogenation of Aromatics with Complex Metal Catalysts

Sir:

The preparation of hydrogenation catalysts by the borohydride reduction of transition metal salts[1] or by the aluminum trialkyl reduction of organic soluble metal salts[2] has been described recently. Both of these catalyst systems are effective for the hydrogenation of olefins, the latter presumably by addition of transition metal hydrides to the double bond followed by hydrogenolysis of the resultant transition metal alkyl. We now wish to report the facile hydrogenation of aromatic nuclei by transition metal complex catalysts. For such systems, the hydride addition mechanism is probably not valid.

TABLE I

HYDROGENATION OF AROMATICS WITH COMPLEX NICKEL CATALYSTS[a]

	Temp., °C.	Time, hr.	Products	Yield, %
Benzene	150–190	0.2	Cyclohexane	100
o-Xylene	150	3.7	*cis*-1,2-Dimethylcyclohexane	65.5
			trans-1,2-Dimethylcyclohexane	34.5
Phenol	150–160	0.2	Cyclohexanol	92.1
			Cyclohexanone	5.2
Pyridine	150–174	3	Piperidine	98
Dimethyl terephthalate	200	3.5	Dimethyl hexahydroterephthalate	100
Dimethyl phthalate	150	0.4	Dimethyl hexahydrophthalate	100
Naphthalene	210	18	Tetralin	84
			Decalin	13

[a] Initial pressure, 1000 p.s.i., 0.3–5.0 mole % nickel.

When triethyl aluminum is added to nickel(II) 2-ethylhexanoate dissolved in a noncomplexing organic solvent such as heptane or benzene, an exothermic reaction occurs with the evolution of a gas which is greater than 95% ethane. The ultimate amount of gas evolution and the highest catalytic activity occurs at aluminum:nickel ratios of 3–4:1. The black reaction mixture is not separated by ultracentrifugation and is neither pyrophoric nor paramagnetic. This solution is an extremely effective catalyst for the hydrogenation of aromatics. For example, addition of 1000 p.s.i. of hydrogen to a benzene solution containing 0.3 mole % nickel gave complete hydrogenation in one-fifth hour, temperature increasing from 150–190°. In comparison, hydrogenation of benzene with a like amount of nickel as 49% nickel on kieselguhr required eight hours under the same conditions. The hydrogenation of other aromatics is given in Table I. In general, the hydrogenations (Table I) proceed more readily than the reported[3] hydrogenations with Raney nickel or other supported nickel catalysts. Surprisingly, nitrobenzene or *p*-nitrophenol, so readily reduced by Raney or supported nickel catalysts, are relatively inert to hydrogenation with the present complex nickel catalysts. Other transition metal complex catalysts can be prepared similarly. Catalytic activity toward benzene hydrogenation decreases in the order Ni $\geq$ Co > Fe > Cr > Cu.

Catalytic activity is very dependent on the associated anion or other electron donors present. While any carboxylate salt gives active catalysts, it is most convenient to use the soluble 2-ethylhexanoates or commercially available naphthenates. Halides give poor catalysts and the hydrogenation of benzene is

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(2) M. F. Sloan, A. S. Matlack, and D. S. Breslow, reported at 14th Delaware Science Symposium, Delaware Section of the American Chemical Society, University of Delaware, Newark, Del., February 23, 1963.
(3) (a) H. Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wis., 1937; (b) H. A. Smith, in "Catalysis," Vol. V, P. H. Emmett, Ed., Reinhold Publishing Co., New York, N. Y., 1957, p. 175.

poisoned by triphenylphosphine. A similar sensitivity to electron donors has been reported in the oligomerization behavior of dienes with soluble nickel(0) catalysts.[4]

We do not believe the active catalyst is the free metal, but rather the metal hydride whose existence would be fleeting at the temperatures employed or a zero-valent metal π-complex solubilized by organic ligands. In support of the latter, Wilke[5] has reported that reaction of nickel acetylacetonate and aluminum trialkyls in the presence of 1,5-cyclooctadiene gives the stable crystalline complex, *bis*-1,5-cyclooctadiene nickel(0).

(4) G. Wilke, *Angew. Chem.*, **75**, 10 (1963).
(5) G. Wilke, B. Bogdanovic, P. Heimbach, M. Kroner, and E. Muller, *Advan. Chem. Ser.*, **34**, 137 (1962).

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